Multistage stereotactic radiosurgery for large cerebral arteriovenous malformations using the Gamma Knife platform

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Purpose: Radiosurgery is an established technique to treat cerebral arteriovenous malformations (AVMs). Obliteration of larger AVMs ($> 10\text{--}15\text{ cm}^3$ or diameter $> 3\text{ cm}$) in a single session is challenging with current radiosurgery platforms due to toxicity. We present a novel technique of multistage stereotactic radiosurgery (SRS) for large intracranial arteriovenous malformations (AVM) using the Gamma Knife system.

Materials/Methods: Eighteen patients with large ($> 10\text{--}15\text{ cm}^3$ or diameter $> 3\text{ cm}$) AVMs, which were previously treated using a staged SRS technique on the Cyberknife platform, were retrospectively selected for this study. The AVMs were contoured and divided into 3–8 subtargets to be treated sequentially in a staged approach at half to 4 week intervals. The prescription dose ranged from 15 Gy to 20 Gy, depending on the subtarget number, volume, and location. Gamma Knife plans using multiple collimator settings were generated and optimized. The coordinates of each shot from the initial plan covering the total AVM target were extracted based on their relative positions within the frame system. The shots were regrouped based on their location with respect to the subtarget contours to generate subplans for each stage. The delivery time of each shot for a subtarget was decay corrected with ^{60}Co for staging the treatment course to generate the same dose distribution as that planned for the total AVM target. Conformality indices and dose–volume analysis were performed to evaluate treatment plans.

Results: With the shot redistribution technique, the composite dose for the multistaged treatment of multiple subtargets is equivalent to the initial plan for total AVM target. Gamma Knife plans resulted in an average PTV coverage of $96.3 \pm 0.9\%$ and a PITV of 1.23 ± 0.1 . The resulting Conformality indices, $V_{12\text{Gy}}$ and R_{50} dose spillage values were 0.76 ± 0.05 , 3.4 ± 1.8 , and 3.1 ± 0.5 respectively.

Conclusion: The Gamma Knife system can deliver a multistaged conformal dose to treat large AVMs when correcting for translational setup errors of each shot at each staged treatment. © 2017 American Association of Physicists in Medicine [<https://doi.org/10.1002/mp.12455>]

Key words: arteriovenous malformation, Gamma Knife, stereotactic radiosurgery

I. INTRODUCTION

Radiosurgery is an effective treatment for small cerebral arteriovenous malformations (AVM). Total nidus obliteration is

achieved in 70–95% of patients at 3–5 yr^{1–4} for small AVMs ($< 10\text{--}15\text{ cm}^3$ or diameter $< 3\text{ cm}$). Obliteration of larger AVMs ($> 10\text{--}15\text{ cm}^3$ or diameter $> 3\text{ cm}$) has been challenging using radiosurgery⁵ and other treatment modalities.⁶

Radiation dose must be decreased with increasing lesion volume to prevent toxicity of surrounding normal tissue, consequently limiting rates of successful obliteration.⁷

Several centers have pursued a multistaged, spatially fractionated approach for the treatment of large AVMs using a Gamma Knife treatment platform (Elekta, Stockholm, Sweden).^{8,9} It is hypothesized that increased radiation dose reduces the intracranial hemorrhage risks for large AVMs by improving obliteration rates, and normal tissues adjacent to the total target but away from the staged target subvolume undergo sublethal radiation repair prior to the next stage. Staging AVM treatments by segmenting the total AVM into subvolumes treated as separate targets over a period of several months permits a more potent obliterative dose than could be delivered to the entire volume in a single fraction.

The previously reported Gamma Knife multistage treatment technique has several limitations. With this technique, a separate plan is created for each treatment stage making it difficult to assess the cumulative dose distribution to the total AVM before the final staged treatment. This limits the design of an optimal comprehensive plan. Also, the interval between each staged treatment can be several months, requiring an MRI and Angiogram acquisition for each treatment. The anatomy changes relative to the frame, complicating contouring and the dose prescription, and each angiogram has its independent risk of stroke. With geometric miss, there may be a higher hemorrhage risk of a partially treated AVM. To avoid these limitations, we developed a practical multistage radiosurgery technique using the Cyberknife delivery platform and treatment planning system¹⁰ to assess the cumulative dose of entire staged course before the first staged treatment and reducing stage intervals from 1/2 to 4 weeks. With recent advances to the Gamma Knife platform, such as ICON systems, it may be possible to implement more accurate multistage technique with the Gamma Knife system for the treatment of large AVMs.

2. MATERIALS AND METHODS

This study was approved by the institutional review board and conducted in accordance with institutional guidelines. Eighteen patients diagnosed with large ($25.8 \pm 17.6 \text{ cm}^3$) localized cerebral AVMs shown in Table I, which were previously treated with a multistaged SRS technique on the Cyberknife platform,¹⁰ were selected for this retrospective study. The composite prescription dose ranged from 15 Gy to 20 Gy covering more than 95% of the total AVM volume.

2.A. Target localization

Patients were immobilized and imaged using a 16-slice Brilliance Big Bore CT scanner (Philips Healthcare, Andover, MD, USA) without contrast to be used as the primary image set. A custom-built angiogram localization frame was attached to the head immobilization system and a contrast CT scan and orthogonal Angiogram images were acquired with

the patient in the identical position. A T1-weighted MRI image was acquired with gadolinium contrast for improved target definition. A target volume was obtained by contouring the overlapped target outline projection areas from both AP and lateral angiograms. Additional information from the contrast CT and MRI datasets was also used to contour the final AVM nidus. Depending on the target size and shape, each AVM was manually divided into 3–8 sub-targets with approximately equal volumes.

2.B. Technique for splitting the total AVM

The staged planning technique for large AVM is presented as follows. First, the treatment plan is designed with the prescription dose to cover the total AVM target volume. Shots are divided among each subtarget depending on the center of each shot as shown in Fig. 1(a). If the center of a shot is within a sub-target, then it becomes associated with the corresponding subtarget's staged plan. If the center of a shot is outside the total target area, the shot becomes associated with the subtarget staged plan with the closest minimum distance between the shot center to the weighted center of the subtarget. The cumulated dose distribution of all the staged treatments should be identical to the original plan for the total target.

To simulate this approach, we combine the MRI image of a Gamma Knife frame with the MRI image of each patient (Fig. 2). The MRI image set with the frame was input into the Leksell Gamma Knife Planning (LGP) system. Treatment planning was performed on the total AVM target area with an identical prescription dose (15–20 Gy) used in the previous Cyberknife staged treatment planning work.¹⁰ The coordinates of each shot are extracted from the planning file of the LGP system and analyzed with in-house software. The shots are resorted and the substage plan is generated by grouping shots within the subtarget region. As each substage plan will be delivered in consecutive stages, the treatment times for each shot are decay adjusted for ⁶⁰Co to generate the same dose prescribed on the original planning day. The Perfexion version of Leksell Gamma Knife has the ability to generate composite shots which combine different collimator sizes with eight bands of sources. In this work, composite plans using shots with multiple collimator sizes as well as plans using single collimator sizes with spherical shots are evaluated to verify the robustness of multistage planning technique.

2.C. Treatment planning

Although it is possible to reposition the Gamma Knife frame on the patient's skull with reference markers for each stage, the setup error may reach 5 mm in translations and 3 degrees in rotation with frame repositioning on an anthropomorphic skull phantom in a simulated situation. The ⁶⁰Co Sources in each of eight radial sections can only be collimated to 4 mm, 8 mm, 16 mm, or block out.

TABLE I. Patient statistics.

Patient no.	Age at therapy	Gender	Total AVM volume (cm ³)	Stages number	Prescription dose (Gy)	Subtarget volume (cm ³)	Treatment duration	Treatment scheme (stages/week)
1	51	M	44.8	8	18	5.6 ± 2.0	7/10/15–8/4/15	2 stages/week
2	14	F	14	8	18	1.8 ± 0.4	4/20/15–5/6/15	2 stages/week
3	13	M	13.1	3	18	4.4 ± 1.0	10/24/14–11/7/14	1 stage/week
4	16	M	12.4	3	18	4.1 ± 0.4	5/16/14–5/30/14	1 stage/week
5	29	M	15.8	4	18	4.0 ± 1.4	8/20/13–9/17/13	1 stage/week
6	19	M	14.1	4	15	3.5 ± 0.8	7/13/12–8/10/12	1 stage/week
7	8	F	10.7	6	18	1.8 ± 0.1	7/11/12–8/08/12	1 stage/week
8	47	F	65.8	8	16	8.2 ± 1.4	2/25/12–4/4/12	1 stage/week
9	22	M	67	6	16	11.2 ± 0.4	1/20/12–2/22/12	1 stage/week
10	12	F	21.3	4	18	5.3 ± 2	1/25/12–2/15/12	1 stage/week
11	50	M	15.3	3	20	5.1 ± 0.9	12/09/11–12/21/11	1 stage/week
12	20	F	17.7	3	18	5.9 ± 0.4	10/26/11–11/09/11	1 stage/week
13	27	M	24	4	18	6.0 ± 2.5	4/13/11–7/15/11	1 stage/month
14	26	M	26.3	7	18	3.8 ± 1.2	5/25/11–7/13/11	1 stage/week
15	19	M	16.3	3	18	5.4 ± 1.1	1/12/11–3/23/11	1 stage/month
16	59	M	25.1	5	18	5.02 ± 1.5	11/05/10–3/09/11	1 stage/month
17	37	M	17.4	3	20	5.8 ± 2.3	4/17/09–6/17/09	1 stage/month
18	62	F	42.7	3	16	14.2 ± 1.2	10/29/08–1/07/09	1 stage/month
Mean	29.5	–	25.8	4.7	17.7	–	–	–
SD	17.2	–	17.6	1.9	1.3	–	–	–

Combined collimation in a single section is not available. Therefore, the shape of each shot cannot be changed to compensate the rotational error in all three axes. Therefore, we developed a procedure to compensate the translational setup error based on the MRI image registration and the coordinate transform of the center of each shot for each staged treatment based on the optimal 3D coordinate transform¹¹ as follows.

2.C.1. Shot coordinate conversion from frame to DICOM coordinates

A treatment plan as described in Section 2.B is created for the total AVM and split it into multiple stages. The coordinate system for the Gamma Knife frame [X as shown in Fig. 3(a)] can be defined by the four cross-sectional points *ABCD* of the linear mark on the frame with the position $P(x_b, y_b, z_i)$ ($i = A, B, C$ or D) in the DICOM coordinate system and $P(a_b, b_b, c_i)$ ($i = A, B, C$ or D) in the *X* coordinate system. The center of each planned shot in the *X* coordinate system, which is used by the planning system to place the shots, is recorded as $S(a, b, c)$. Then, the centroids of the *X* and DICOM coordinates are determined to remove the translation between two coordinates.

$$\begin{aligned} centroid_X &= 1/4 \sum_i^{A,B,C,D} P(a_i, b_i, c_i) \\ centroid_{DICOM} &= 1/4 \sum_i^{A,B,C,D} P(x_i, y_i, z_i) \end{aligned} \quad (1)$$

The rotation matrix between the *X* and DICOM coordinate systems is

$$R = VU^T \quad (2)$$

Where matrix *V* and *U* are from the Singular Value Decomposition (*SVD*) in Eq. (3) from the covariance matrix, *H*, which is obtained with Eq. (4).

$$[U, S, V] = SVD(H) \quad (3)$$

$$H = \sum_i^{A,B,C,D} [P(a_i, b_i, c_i) - centroid_X] * [P(x_i, y_i, z_i) - centroid_{DICOM}]^T \quad (4)$$

Therefore, the optimal transformation matrix is:

$$M = \begin{bmatrix} R & t \\ 0 & 1 \end{bmatrix} \quad (5)$$

where *t* is the translation between coordinates as follows:

$$t = -R * centroid_X^T + centroid_{DICOM}^T \quad (6)$$

For each shot, the optimal converted coordinates in the DICOM system are determined as:

$$S(x, y, z, 1)^T = M * S(a, b, c, 1)^T \quad (7)$$

2.C.2. Shot coordinate conversion from DICOM to frame coordinates

The first staged treatment can be delivered when the frame is still attached in its original position to the patient. The

FIG. 1. Multistage SRS of large AVM using Gamma Knife. (a) Shots are divided among two stages depending on the center location of each shot. (b) Example dose distribution for each staged treatment of individual sub-targets.

frame is re-positioned with the help of skin marks as close as to the original position to achieve optimal position of shots as determined from the initial plan on the total AVM. Errors may occur during the frame repositioning process. Therefore, a new MR image is taken and registered with the original planning MR image in Velocity™ (Varian Medical System, Palo Alto, CA, USA) as shown in Fig. 3(b).

The coordinate system for the Gamma Knife frame in the new MR image of k th stage is X_k , and defined by the four cross-section points A_k, B_k, C_k , and D_k of the linear marks on the frame with the position of $P_k(x_{ki}, y_{ki}, z_{ki})$ ($i = A_k, B_k, C_k$, or D_k) in the same DICOM coordinate system from image registration. These four point coordinates $P_k(a_{ki}, b_{ki}, c_{ki})$ ($i = A_k, B_k, C_k$, or D_k) in the X_k system are equal to $P(a_i, b_i, c_i)$ ($i = A, B, C$, or D) in the X coordinate system. We can use the coordinate transformation Eq. (7) presented in Section 2.C.1 to obtain the transformation matrix between X_k and DICOM coordinates as follows:

$$S_k(x_k, y_k, z_k, 1)^T = M_k * S_k(a_k, b_k, c_k, 1)^T \quad (8)$$

Where $S_k(x_k, y_k, z_k)$ is the center of each planned shot in the DICOM coordinates system, and $S_k(a_k, b_k, c_k)$ is the center of each planned shot in the X_k coordinate system. M_k is the transformation matrix between the k th staged treatment frame matrix, X_k , and the DICOM coordinates. Therefore, the shot coordinates in the new frame system are:

$$S_k(a_k, b_k, c_k, 1)^T = M_k^{inv} * S_k(x_k, y_k, z_k, 1)^T \quad (9)$$

FIG. 2. Simulation of Gamma Knife treatment by combining an image of the Gamma Knife frame and an MRI image for a Cyberknife treatment. (a) Gamma Knife frame MRI image. (b) Patient MRI image. (c) Combined Gamma Knife frame and patient MRI images.

Where M_k^{inv} is the inverse matrix of M_k . As shown in Fig. 3(b), the center of each shot is the same as the original plan location in DICOM coordinates (e.g., $S_k(x_k, y_k, z_k, 1)^T = S(x, y, z, 1)^T = M * S(a, b, c, 1)^T$ as of Eq. (7) for corresponding shots, where M is the optimal transformation matrix from the Gamma Knife frame coordinate system, X , to DICOM coordinates at the planning stage and $S(a, b, c)$ is the

FIG. 3. Shots repositioned to compensate for translational setup errors. (a) Original plan for entire AVM target. (b) Setup error after repositioning the patient in the next staged treatment. Shots are repositioned to compensate for translational setup errors depending on the image registration.

center position of each shot in frame coordinate, X , for k th stage at the first day when plan was completed. The new shot coordinates in the new Gamma Knife frame system of k th stage are:

$$S_k(a_k, b_k, c_k, 1)^T = M_k^{inv} * M * S(a, b, c, 1)^T \quad (10)$$

These coordinates can be placed manually into the Gamma Knife treatment planning system along with the weight of each shot and corrected shot time. With this method, translational errors between k th stage and planning are corrected, but the rotational error cannot be corrected.

In summary, the planned coordinates of each shot were extracted from Gamma Knife treatment planning system then split according to the subtarget contour using a custom program. After compensation for translational setup errors of each shot as described in the previous section, the coregistered frame coordinates are then manually entered into the Gamma Knife treatment planning system for delivery to the patient.

2.D. Dose volume characteristics

For this study, the dose conformity index recommended by the RTOG for radiosurgery (PITV; ratio of total volume receiving the prescription dose or greater to that of the target volume), the Paddick conformity index (CI), the R_{50} (ratio of the volume receiving 50% of the prescription dose or greater to the target volume), and the $V_{12\text{ Gy}}$ (ratio of volume receiving 12 Gy or greater to the volume of the whole brain) indices were used to evaluate the final PTV and normal tissue dose coverage. For planning purposes the PITV was kept as low as achievable and constrained to be less than 2.0.

2.E. Residual rotational error analysis

The rotational error will occur when repositioning the patient with the markers on the frame. Our technique is able to compensate for the translational error during repositioning. To estimate the dose distribution difference induced by residual rotational errors, a systematic analysis was performed for the total AVM target. To simulate this planning technique in the extreme case, a random 5 mm translation combined with rotations of $\pm 1^\circ$, $\pm 3^\circ$, and $\pm 5^\circ$ in all three axes of the Gamma Knife frame images were generated before merging with the patient MR image set. The technique in Section 2.C.2 was used to compensate the translation position errors for each shot. Dose distributions were compared between the original planned dose on the total AVM and that resulting from residual rotational errors from the coordinate transform.

2.F. Phantom study for ICON system

The Leksell Gamma Knife[®] Icon[™] is a novel image guided radiosurgery system which integrates the Gamma Knife Perfexion delivery system with Cone Beam CT (CBCT), providing increased workflow flexibility with planning on frameless images and subsequent frameless dose delivery. With the help of the ICON system, the patient can be repositioned to the original planned position with minimal intrafraction position errors, making it attractive for staged AVM treatments.

As shown in Figs. 4(a) and 4(b), an anthropomorphic phantom with accurately aligned EBT3 Gafchromic[™] film (Ashland, Lexington, KY, USA) is used to evaluate the accuracy in the ability to deliver a multistage plan to large AVM targets. The simulated target is approximately 3 cm in

diameter and split into three stages. The plan for entire AVM target was delivered as a reference without any setup errors as shown in Fig. 4(c). Staged plans were then delivered to the phantom with random setup errors to simulate real treatment conditions [Fig. 4(d)–4(f)]. A flat panel scanner, Epson Expression 10000XL (Seiko Epson Corp., Nagano, Japan), was used to scan the film. RIT V6.4 (Radiological Imaging Technology, Inc, Colorado Springs, CO, USA) was used to compare dose differences between staged deliveries to the reference.

3. RESULT AND DISCUSSION

As discussed in the methods section, the entire treatment workflow was successfully commissioned for the treatment of large AVMs using the Gamma Knife delivery platform and treatment planning systems. Based on quality assurance testing, stereotactic localization of the each shot center within

the AVM target in the multistage treatment is achievable within 1 mm.

This novel treatment delivery technique is beneficial in that the radiation oncologist and physicist can design the final dose distribution for the entire AVM on the first day before any dose delivery. Then this ‘total’ dose distribution is simply broken up into subsequent staged plans so that the cumulative dose matches that of the ‘total’ dose distribution. Physicians have the freedom to split the total AVM target in any subtarget combinations. This is advantageous for designing a conformal dose distribution to the target volume and avoiding excess dose to adjacent normal structures, such as the optic nerves and brain stem.

Table II shows the parameters used for planning and evaluation for the eighteen patients of this study. Dose distributions were optimized to achieve approximately 95% PTV coverage with a PITV conformity index as low as achievable.

FIG. 4. Phantom study of the ICON system. (a) Irradiation with the ICON frameless system. (b) Anthropomorphic phantom with film. (c) Irradiation for entire AVM target to be used as the reference dose distribution. (d) First stage irradiation (e) Cumulative dose distribution from the first and second stages with random setup errors. (f) Cumulative dose distribution from all stages with random setup errors.

TABLE II. Summary of dosimetric analysis.

Patient no.	Total AVM volume (cc)	Stages number	Prescription dose (Gy)	Coverage (%)			CI			PITV			V _{12Gy} (%)			R ₅₀		
				CK	GK comp	GK sphere	CK	GK comp	GK sphere	CK	GK comp	GK sphere	CK	GK comp	GK sphere	CK	GK comp	GK sphere
1	44.8	8	18	96.2	96.3	96.5	0.63	0.64	0.69	1.48	1.44	1.36	7.84	7.49	6.76	3.75	3.35	3.00
2	14	8	18	95.6	96.5	96.5	0.82	0.76	0.77	1.12	1.22	1.21	1.92	2.25	1.86	3.04	3.39	2.74
3	13.1	3	18	96.6	97.7	97.9	0.75	0.72	0.71	1.25	1.33	1.34	2.44	2.16	2.39	4.13	3.57	4.17
4	12.4	3	18	95.3	96.1	96.4	0.78	0.73	0.70	1.16	1.27	1.33	1.95	2.00	1.80	3.97	3.84	3.42
5	15.8	4	18	95.7	96.4	96.9	0.77	0.75	0.76	1.19	1.23	1.24	2.97	2.80	2.43	3.94	3.80	3.07
6	14.1	4	15	95.9	96.2	95.2	0.70	0.75	0.76	1.31	1.23	1.19	1.82	1.79	1.57	3.94	3.83	3.22
7	10.7	6	18	98.6	97.8	98.3	0.82	0.76	0.71	1.18	1.26	1.35	1.95	2.02	1.85	3.89	3.83	3.36
8	65.8	8	16	95.8	96.3	96.1	0.86	0.82	0.84	1.07	1.14	1.11	7.37	7.51	7.12	2.49	2.31	2.17
9	67	6	16	95.5	96.2	95.2	0.88	0.84	0.82	1.04	1.10	1.11	7.23	7.40	6.97	2.79	2.77	2.64
10	21.3	4	18	95.4	95.2	96.5	0.84	0.81	0.80	1.09	1.12	1.17	3.21	3.30	3.06	3.16	3.18	2.87
11	15.3	3	20	95.0	95.5	96.5	0.85	0.83	0.70	1.07	1.10	1.33	2.32	2.46	2.57	3.04	3.13	3.25
12	17.7	3	18	95.9	95.7	95.9	0.82	0.79	0.78	1.12	1.16	1.18	2.41	2.81	2.48	2.95	3.54	3.03
13	24	4	18	96.5	95.0	95.8	0.72	0.80	0.75	1.30	1.12	1.22	3.99	3.05	3.28	4.02	2.97	3.21
14	26.3	7	18	95.3	95.8	95.4	0.60	0.68	0.71	1.50	1.35	1.29	4.65	4.31	3.65	4.58	3.65	3.58
15	16.3	3	18	96.1	96.1	97.0	0.67	0.74	0.71	1.38	1.24	1.32	3.09	2.73	2.46	4.29	4.00	3.54
16	25.1	5	18	96.1	95.3	96.2	0.76	0.83	0.77	1.21	1.10	1.16	4.27	4.15	4.02	3.31	3.21	3.05
17	17.4	3	20	96.5	95.3	95.1	0.85	0.89	0.85	1.09	1.02	1.06	2.35	2.41	2.18	2.47	2.55	2.31
18	42.7	3	16	96.1	96.4	96.0	0.87	0.84	0.85	1.06	1.10	1.08	5.09	5.30	4.97	2.95	2.76	2.65
Mean	25.8	4.7	17.7	96.0	96.1	96.3	0.78	0.78	0.76	1.20	1.20	1.23	3.71	3.66	3.41	3.48	3.32	3.07
SD	17.6	1.9	1.3	0.8	0.8	0.9	0.08	0.06	0.05	0.14	0.11	0.10	1.99	1.97	1.84	0.64	0.49	0.48

CI: ratio of target volume receiving the prescription isodose to the target volume, multiplied by the ratio of the target volume receiving the prescription isodose to the prescription isodose volume; PITV: ratio of prescription dose volume to that of target volume; V_{12Gy}: percent of brain volume receiving 12 Gy or more; R₅₀: ratio of volume receiving 50% of the prescription dose to the target volume; CK: Cyberknife plan; GK Comp: Gamma Knife composite shots plan; GK Sphere: Gamma Knife spherical shots plan.

All 18 patients achieved planning objectives in all planning methods ($96.0 \pm 0.6\%$, $96.1 \pm 0.8\%$ and $96.3 \pm 0.9\%$ for Cyberknife inverse planning, Gamma Knife with multicollimator composite shots and with spherical shots respectively). The average CI value, a measure of the compactness of the high dose distribution to an intended target and the location of the prescription isodose volume relative to the target volume, was similar for the inverse planning technique to that common for smaller AVMs using the Gamma Knife Perfection or Cyberknife systems (0.80).¹² A value close to 1.0 is expected to minimize radiation related complications. In this work, the CI is close to that of single small targets (CI at 0.78 ± 0.08 , 0.78 ± 0.06 , and 0.76 ± 0.05 for Cyberknife inverse planning and Gamma Knife with multicollimator composite shots and spherical shots, respectively) indicating that the novel planning technique that is feasible to deliver conformal dose to large target volumes.

Dose-volume effects and parameters which correlate well with normal tissue complications for the staged treatment of large-volume AVMs have yet to be determined. PITV and R_{50} represent the ratio of the 100% and 50% of prescription dose volume, respectively, relative to the target volume. As shown in Table I. All planning techniques have similar dose spread surrounding the target volume. The V_{12Gy} index has been observed to correlate with the risk of developing SRS-related imaging changes and has been used as a surrogate for normal tissue damage. The volume receiving 12 Gy is minimized in staged treatments, regardless of the number of stages used.¹³ In this work, the composite V_{12Gy} was less than 10% of the brain volume for all patients. This parameter continues to be used for plan evaluation and comparison as experience is gained in staged treatments of large AVMs.

Figure 5 shows the statistics of dose distribution difference inside the total AVM target volume for the staged treatment due to simulated residue rotational error. It is clear that the dose difference increases with increasing degree of residue rotation error. In Table III, the volume of the target having a dose difference within 3% is decreased with larger residual rotational errors (98.28%, 84.22% and 68.08% for $\pm 1^\circ$, $\pm 3^\circ$, and $\pm 5^\circ$ rotation, respectively, for a composite shot plan). The volume of the target with a dose difference within 5% (99.89%, 94.86% and 83.01% for $\pm 1^\circ$, $\pm 3^\circ$, and $\pm 5^\circ$ rotation, respectively, for a composite shot plan) indicates that rotation less than $\pm 3^\circ$ is acceptable for treatment which can be achieved with marks placed on both the patient skin and frame. A composite shot plan with variable collimator settings and a shaped dose distribution was expected to have larger dose differences with rotational errors when compared with a single collimator spherical shot plan, but interestingly, our results show that the influence is insignificant (93.8% (spherical shots) vs. 94.86% (composite shots) for $\pm 3^\circ$ rotation). The influence of shot position, target location, and skull shape on rotational errors and effects on dose differences are commendable topics for future study. The ratio of prescription dose coverage, PITV, CI, V_{12Gy} , and R_{50} between staged delivery dose to

FIG. 5. Residual rotational errors after compensation of translational setup errors depending on a rotation angle of $\pm 1^\circ$, $\pm 3^\circ$, and $\pm 5^\circ$ in (a), (b), and (c) respectively. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE III. Dose distribution difference summary.

	$\pm 1^\circ$ rotation		$\pm 3^\circ$ rotation		$\pm 5^\circ$ rotation	
	Spherical	Composite	Spherical	Composite	Spherical	Composite
Residue shot center error (mm)	0.06 ± 0.03	0.06 ± 0.04	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.02
Dose diff < 3%	95.92%	98.28%	80.5%	84.22%	67%	68.08%
Dose diff < 5%	99.25%	99.89%	93.8%	94.86%	83.31%	83.01%
Coverage ratio (staged/original)	$100.4 \pm 1.0\%$	$99.6 \pm 0.5\%$	$100.1 \pm 1.3\%$	$99.6 \pm 0.2\%$	$100.2 \pm 1.5\%$	$99.5 \pm 0.5\%$
PITV ratio (staged/original)	$100.4 \pm 2.3\%$	$98.6 \pm 1.2\%$	$100.0 \pm 2.5\%$	$98.8 \pm 0.5\%$	$100.9 \pm 2.9\%$	$99.0 \pm 0.9\%$
CI ratio (staged/original)	$100.3 \pm 0.4\%$	$100.7 \pm 0.4\%$	$100.3 \pm 0.5\%$	$100.4 \pm 0.4\%$	$99.6 \pm 0.6\%$	$100.1 \pm 0.6\%$
V_{12Gy} ratio (staged/original)	$100.3 \pm 1.5\%$	$98.9 \pm 1.2\%$	$99.9 \pm 1.6\%$	$98.9 \pm 0.5\%$	$100.5 \pm 1.9\%$	$99.2 \pm 0.9\%$
R_{50} ratio (staged/original)	$100.1 \pm 1.4\%$	$99 \pm 1.4\%$	$99.7 \pm 1.5\%$	$98.8 \pm 0.7\%$	$100.1 \pm 1.7\%$	$99.1 \pm 1.2\%$

planning dose was shown in Table III as well. There is no statistical difference in all these parameters for the staged dose delivery with the remaining rotation error after correction of translational error. The effect of rotational error on the dose distribution increases with the increase in distance to the shot center. Therefore, the high dose region which is critical to target control was less prone to impacted by random rotation error. However, systematical rotation of staged treatment should be avoided.

The ICON system can compensate for translational setup errors of each shot, but cannot compensate for rotational errors. With the frameless mask system, the maximum setup error observed with our phantom was less than 1 degree about any rotational axis and 1 mm in any translational direction. However, to simulate large rotation and translation errors up to 5 degrees and 5 mm, respectively, fixation bolts of the mask were released. A gamma passing criteria of 3% and 1 mm was used with the entire plan delivered in one session to film as the reference and a multistaged delivery with up to 5 mm in translational errors and 5 degrees in rotational errors in all directions. A gamma passing rate of $95.9 \pm 3.2\%$ was observed.

Our group has a history with staged treatment of large AVMs using the Cyberknife system.¹⁰ It is interesting to compare the Cyberknife and Gamma Knife techniques. The influence of residual setup error for each stage with the Cyberknife platform is minimized by robotic positioning compensation based on X-ray imaging. However, with our Cyberknife technique, it is cumbersome to split the monitor units for each beam for each subtarget plan and manually change it in the treatment planning system. Furthermore, once subtargets are split and each staged plan is created, it can be very difficult to change the plan if the physician wishes to change the subtarget to avoid a high dose for certain critical organs in a single stage. Although there is no method to compensate for residue rotational errors with the Gamma Knife platform, it is clear from this work that the influence of this error is insignificant for the cumulative dose to the total AVM target. Additionally, the shot splitting technique for the Gamma Knife is less cumbersome when compared to monitor unit splitting with the Cyberknife platform. Furthermore, staged plans

with the Gamma Knife technique are more easily adaptable if any changes to subtargets are requested by the physician to avoid single stage high dose to critical organs. Shots can be simply switched between subtargets.

4. CONCLUSION

The Gamma Knife system can deliver a multistaged conformal dose to treat large AVMs with the ICON systems. The Gamma Knife system can also deliver staged AVM treatments for large AVMs without these additional systems when correcting for translational setup errors. Rotational setup errors, which cannot be corrected for, have little effect on the dose distribution to the AVM target for the Gamma Knife technique. Target coverage and prescription dose conformity were shown to be similar to that of a single target, single fraction treatment.

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CONFLICT OF INTEREST

None.

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