Dosimetric effects of Onyx embolization on Gamma Knife arteriovenous malformation dose distributions

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OBJECTIVE Patients with arteriovenous malformations (AVMs) treated with Gamma Knife radiosurgery (GKRS) subsequent to embolization suffer from elevated local failure rates and differences in adverse radiation effects. Onyx is a common embolic material for AVMs. Onyx is formulated with tantalum, a high atomic number ($Z = 73$) element that has been investigated as a source of dosimetric uncertainty contributing to the less favorable clinical results. However, prior studies have not modeled the complicated anatomical and beam geometries characteristic of GKRS. This study investigated the magnitude of dose perturbation that can occur due to Onyx embolization using clinically realistic anatomical and Gamma Knife beam models.

METHODS Leksell GammaPlan (LGP) was used to segment the AVM nidus and areas of Onyx from postcontrast stereotactic MRI for 7 patients treated with GKRS postembolization. The resulting contours, skull surface, and clinically selected dose distributions were exported from LGP in DICOM-RT (Digital Imaging and Communications in Medicine—radiotherapy) format. Isocenter locations and dwell times were recorded from the LGP database. Contours were converted into 3D mesh representations using commercial and in-house mesh-editing software. The resulting data were imported into a Monte Carlo (MC) dose calculation engine (Pegasos, Elekta Instruments AB) with a beam geometry for the Gamma Knife Perfexion. The MC-predicted dose distributions were calculated with Onyx assigned manufacturer-reported physical constants (MC-Onyx), and then compared with corresponding distributions in which Onyx was reassigned constants for water (MC-water). Differences in dose metrics were determined, including minimum, maximum, and mean dose to the AVM nidus; selectivity index; and target coverage. Combined differences in dose magnitude and distance to agreement were calculated as 3D Gamma analysis passing rates using tolerance criteria of 0.5%/0.5 mm, 1.0%/1.0 mm, and 3.0%/3.0 mm.

RESULTS Overall, the mean percentage differences in dose metrics for MC-Onyx relative to MC-water were as follows; all data are reported as mean (SD): minimum dose to AVM = -0.7% (1.4%), mean dose to AVM = 0.1% (0.2%), maximum dose to AVM = 2.9% (5.0%), selectivity = 0.1% (0.2%), and coverage = -0.0% (0.2%). The mean percentage of voxels passing at each Gamma tolerance were as follows: 99.7% (0.1%) for 3.0%/3.0 mm, 98.2% (0.7%) for 1.0%/1.0 mm, and 52.1% (4.4%) for 0.5%/0.5 mm.

CONCLUSIONS Onyx embolization appears to have a detectable effect on the delivered dose distribution. However, the small changes in dose metrics and high Gamma passing rates at 1.0%/1.0 mm tolerance suggest that these changes are unlikely to be clinically significant. Additional sources of delivery and biological uncertainty should be investigated to determine the root cause of the observed less favorable postembolization GKRS outcomes.

<http://thejns.org/doi/abs/10.3171/2016.6.GKS161502>

KEY WORDS AVM; stereotactic radiosurgery; embolization; Gamma Knife

THE primary goal in the management of cerebral arteriovenous malformations (AVMs) is to eliminate the risk of intracranial hemorrhage, which is responsible for the most serious neurological complications

of the disorder. The risk of hemorrhage in untreated AVMs is estimated to be in the range of 2.2%–4.0% per year, with a total mortality rate due to a hemorrhage in the range of 23%–29%.^{4,19,30} The most effective way to eliminate this

ABBREVIATIONS AVM = arteriovenous malformation; DTA = distance to agreement; GKRS = Gamma Knife radiosurgery; LGP = Leksell GammaPlan; MC = Monte Carlo; NBCA = *N*-butyl cyanoacrylate; STL = stereolithography.

SUBMITTED June 9, 2016. **ACCEPTED** June 29, 2016.

INCLUDE WHEN CITING DOI: 10.3171/2016.6.GKS161502.

risk is by obliteration of the AVM nidus through one or a combination of strategies including microsurgery, radiosurgery, and embolization.^{9,33,40,45,57}

Stereotactic radiosurgery, particularly Gamma Knife radiosurgery (GKRS), has gained a prominent role in the management of cerebral AVMs due to its high obliteration rate, low complication rate, and minimally invasive nature relative to microsurgery.^{24,34,46,47} Obliteration rates with the Gamma Knife are related to prescription dose; at a prescription dose of 25 Gy, AVM obliteration occurs approximately 60%–80% of the time. The obliteration rate decreases as the prescription dose to the nidus is decreased or the nidus volume is increased.⁴⁸

Embolic Agents and Potential Effects on Delivered Dose Distribution

Embolization of AVMs is also playing an increasingly important role, often as an adjuvant treatment to radiosurgery or microsurgery, with the goal to reduce the nidus volume of large AVMs and minimize the risks of any intranidal aneurysms and arteriovenous fistulas.^{1,11,14,15}

Unfortunately, in a small subset of patients, GKRS fails to result in complete obliteration of the AVM nidus, prolonging the risk of hemorrhage and, in most cases, necessitating retreatment of the AVM.⁵⁶ Several published series report on potential causes for failure in radiosurgical treatment for cerebral AVMs. A common theme is that prior embolization may be an important prognostic factor; however, the specific reasons for this lower obliteration rate remain unclear.^{10,12,14,20,28,41}

Historically, the most commonly used agent was *N*-butyl cyanoacrylate (NBCA), which is a fast-polymerizing liquid adhesive.^{17,54} This agent has been reported to be difficult to use due to unpredictability of the flow and speed of polymerization.⁵³ More recently, Onyx (Covidien), a less-adhesive, more slowly polymerizing agent, has gained prominence. Onyx is an ethylene vinyl alcohol copolymer dissolved in dimethyl sulfoxide^{49,52} (Table 1). Onyx comes in 2 basic viscosities: Onyx 18 (18 centistokes) and Onyx 34 (34 centistokes).

The tantalum component of Onyx exists to make the material radio-opaque when injected through a microcatheter under fluoroscopy guidance.⁵³ Tantalum is a transition metal with the relatively high atomic number 73. For comparison, titanium, which is an often-studied interface metal commonly used in biocompatible implants, has atomic number 22 and is considered a “high-Z” material relative to soft tissue (effective $Z = 5$ –8) or bone (effective $Z = 14$).¹⁸ Whereas the presence of tantalum is an asset for visualization under fluoroscopy, it is a liability for CT imaging. The high-Z tantalum causes significant image artifact at typical kilovoltage CT energies (Fig. 1 left). However, investigation has found that Onyx creates a signal void, but little image distortion, on T1-weighted MRI (Fig. 1 right).³⁹

To minimize the risk of future bleeding, a vital aspect of AVM radiosurgery is to completely cover the nidus with a minimum biologically effective dose. Even the smallest underdose of the nidus can leave the patient at significant risk.^{16,43} Several studies have proposed that the presence of

TABLE 1. Onyx formulation and material composition (as a percentage of weight)

Component Name	Purpose	Weight Composition by %, Onyx 18/Onyx 34
Ethylene vinyl alcohol copolymer	Embolic material	3.2:4.2
Dimethyl sulfoxide	Solvent for delivery into bloodstream	58.2:57.6
Tantalum ($Z = 73$)	Radiographic visualization	38.6:38.2

high-Z materials such as tantalum (or Lipiodol in the case of NBCA) might distort the delivered radiosurgical dose distribution, potentially causing underdosing of the nidus and preventing subsequent obliteration.^{1,21,26,37,44} However, these studies were conducted either with a single treatment beam irradiating from 1 direction, or using simple target geometries. In clinical practice using GKRS, the target is a nidus of intricate morphology, which when embolized has a complex mixture of embolic material and blood. The beam geometry is likewise complex, with a total number of beams = $192 \times$ number of isocenters (for a Perfexion model Gamma Knife assuming no sectors are blocked).²³ Thus, prior studies may not have adequately modeled the complicated anatomical and beam geometries characteristic of GKRS.

This study investigated the magnitude of dose perturbation that can occur due to Onyx embolization by using clinically realistic anatomical and Gamma Knife beam models and a Monte Carlo (MC) approach. Our hypothesis is that although tantalum is a high ($Z = 73$) atomic number material that can cause dosimetric effects, under realistic clinical geometries used in GKRS, any effects will be minimal and will not significantly perturb the delivered dose distribution.

Methods

Identification of Patients With AVMs Embolized With Onyx

We conducted a review of Gamma Knife treatment records at the University of Virginia. We looked for patients with AVMs or dural arteriovenous fistulas that were treated with both GKRS and prior embolization using Onyx between 2007 and 2012. Our search was restricted to patients treated later than July 2007, because these radiosurgery procedures were performed on the Gamma Knife Perfexion and therefore have imaging and treatment plans readily available. Twenty-five patients were identified. Ten patients were randomly selected for inclusion in the study. The clinical treatment plans and stereotactic MR images for each patient were located in Leksell GammaPlan (LGP; version 10.1, Elekta Instrument AB). Three patients were excluded because of our inability to visualize the nidus and/or Onyx on postcontrast MRI, leaving 7 patients in the study. The study was approved by the institutional review board at the University of Virginia.

FIG. 1. CT and MR appearances of Onyx embolization. **Left:** A CT scan of the brain showing extreme artifact caused by the tantalum used to make Onyx radio-opaque. **Right:** An MR image of the same area of the brain showing Onyx as a signal dropout, along with residual nidus as a mixed pattern of enhancement.

Contouring of AVM Nidus and Onyx

For each of the 7 patients, contours of the nidus and Onyx embolization were created within LGP on postcontrast stereotactic MRI (3D postcontrast T1-weighted gradient-echo MR; 1.0 × 1.0 × 1.3-mm voxels) used for treatment planning. Contours were created by a neurosurgeon, with review by a medical physicist and a neuroradiologist.

The nidus was identified as an area of complicated, mixed-contrast texture, and was correlated to coregistered digital subtraction angiography acquired as part of the treatment planning process. Onyx was identified as a flow void in the general vicinity of the nidus (Fig. 2).³⁹

Contour-to-Mesh Conversion Procedure

The nidus, Onyx, and outer skull contours, as well as the planned dose distributions, were exported in DICOM-RT (Digital Imaging and Communications in Medicine–radiotherapy) format using the functionality built into LGP. The contours were converted into a mesh representation using a multistep procedure (Fig. 3).

Contour Conversion to Mesh Format

Functionality within 3D Slicer (www.slicer.org)⁸ was used to convert the skull, nidus, and Onyx contour stacks to a 3D mesh representation (Fig. 4). Once conversion was complete, each mesh was exported from 3D Slicer in stereolithography (STL) file format (3D Systems).

In certain cases, meshes have a very large number of vertices and faces (this is especially true of skull meshes) and take up more memory than the Elekta MC system can handle. A freeware product called MeshLab (ISTI-CNR) was used to perform a decimation of these meshes to reduce the memory footprint while maintaining topological consistency. A quadric edge collapse decimation algo-

FIG. 2. Representative slices through the MR image of each of the 7 patients included in the study, along with the corresponding nidus (pink) and Onyx (blue) contours. PI = prescription isodose; Rx = prescription.

FIG. 3. Procedure for exporting, processing, and converting patient data for subsequent MC simulation. **a:** Dose and contour export from LGP. **b:** Mesh creation from contours. **c:** Mesh simplification and smoothing. **d:** Mesh topology repair to ensure closed surfaces. **e:** Mesh conversion to raw triangle format. **f:** Extraction of transform between stereotactic to imaging coordinates. **g:** MC simulation.

rithm¹³ within MeshLab was applied to reduce the number of faces by a factor of 10.

Meshes created with 3D Slicer have terracing artifacts due to the fact that they were created from contour stacks, with 1 contour per slice, and MR slice thicknesses that are of a non-negligible thickness. A smoothing step was thus used to diminish the terracing artifact on nidus and Onyx meshes.⁵¹

Finally, a second postprocessing step was applied that identifies and repairs meshes to ensure topological closure, which is a requirement for the subsequent MC analysis. For this step, a commercial product called netfabb (netfabb GmbH) was used. Meshes in STL format are imported into netfabb. The software then analyzes the meshes and indicates whether there are defects to be corrected; if so, it applies the corrections.

Completed meshes were re-exported into STL file format and converted into a raw, American Standard Code for Information Interchange (ASCII)–triangle format accepted by the Elekta MC system, using custom software created in the Python programming language.

Coordinate Transformation Determination

The MC analysis requires knowledge of the transformation between the stereotactic coordinate space used by the Gamma Knife planning system and the imaging (DICOM) coordinate space. This transformation information is stored in 4×4 matrix form in the Gamma Knife treatment planning system and was extracted using a custom structured query language (SQL) query.

Monte Carlo Analysis

The completed skull, Onyx, and nidus meshes, as well as the coordinate transformation matrix, were used as inputs into the subsequent MC simulations. The MC simulations were performed using a calculation engine developed at the manufacturer (Pegasos, Elekta Instrument AB) and an associated geometry interface (Hermes, Elekta Instrument AB) (Fig. 5). Predicted radiosurgical dose distributions in the presence of Onyx (MC-Onyx) were obtained by MC simulation assuming physical constants of water for brain and nidus structures, and manufacturer-reported physical constants of Onyx for the Onyx contour. These were compared with the dose distributions obtained by setting all structures to the physical constants for water (MC-water), which are similar to the assumptions used by the TMR 10–based treatment algorithm in LGP.⁵⁵

The dose distributions MC-Onyx and MC-water were compared via a variety of dose metrics, including minimum/mean/maximum dose to the nidus, prescription isodose volume, selectivity index (TV_{PIV}/PIV), coverage index (TV_{PIV}/TV), and gradient index (PIV_{half}/PIV), where PIV is the prescription isodose volume, TV_{PIV} is the volume of nidus covered by the prescription isodose volume, and PIV_{half} is the volume of the isodose surface that is one-half of the prescription isodose.^{31,32} All dose metrics were calculated in terms of percentage isodoses (i.e., percentage of maximum dose). As a gross measure of the overall dosimetric difference between MC-Onyx and MC-water, 3D local Gamma passing rates were determined for 3.0 mm/3.0%, 1.0 mm/1.0%, and 0.5 mm/0.5% passing crite-

FIG. 4. Conversion of contour stacks into a 3D mesh representation using 3D Slicer.

ria.²⁵ MATLAB (version R2015a, MathWorks) was used for analysis of all dose metrics.

Results

Overall, MC determined that dosimetric differences between MC-Onyx and MC-water were small (Table 2). The largest difference in dose metrics was the maximum dose to the nidus, with a mean (standard deviation) difference of 2.9% (5.0%). All other dose-metric differences were less than 1.0%. The Gamma passing rates were 52.1% (4.4%), 98.2% (0.7%), and 99.7% (0.1%) for 0.5%/0.5 mm, 1.0%/1.0 mm, and 3.0%/3.0 mm, respectively (Table 3). Close inspection of the results in some cases shows some minor shifts in isodose curves, especially at higher isodose levels (i.e., 70%–90%), between MC-Onyx and MC-water (Fig. 6).

Discussion

Our results suggest that there are detectable differences in dose distribution caused by the presence of Onyx. However, the magnitude and location of the differences suggest that they are not likely to be clinically significant in terms of obliteration probability. Close inspection of the MC-calculated distributions for MC-Onyx and MC-water show that many of the differences are in high-isodose regions near or inside of the Onyx. This is further supported by the somewhat larger difference in maximum nidus dose between MC-Onyx and MC-water (2.9% mean dif-

ference) compared with the other dose metrics, which are all less than 1.0% mean difference. It should be noted that the maximum dose to the nidus is a point dose that can be highly sensitive to effects such as calculation grid alignment and resolution (0.5 mm in this study).

Our study applies the concept of Gamma analysis to provide a measure of the global match between 2 dose distributions by combining a distance to agreement (DTA) criterion and a voxel-by-voxel dose-difference criterion.²⁵ A given voxel “fails” the Gamma analysis if it lies outside of the specified DTA and/or dose-difference criterion. The percentage of voxels that fail the Gamma analysis can be used as a global measure of the similarity of 2 distributions. Our results show a sharp rise in Gamma passing rates, from a mean of 52.1% at the 0.5 mm/0.5% (DTA/dose) criterion to 98.2% at 1.0 mm/1.0%. These results suggest that if one considers the approximate overall uncertainty of a radiosurgery procedure (i.e., approximately 1.0 mm uncertainty), then the difference between MC-Onyx and MC-water distributions are not likely to be clinically significant. We believe that the smaller passing rates at the more stringent 0.5 mm/0.5% criterion probably reflect contouring and grid resolution uncertainties, as well as distortions in dose caused by the Onyx embolization.

Prior Work

It has long been recognized that a significant amount of scattered radiation can result from the introduction of

FIG. 5. MC simulation of GKRS for embolized AVMs. **Left:** Gamma Knife Perfexion geometry model used for phase-space generation (Hermes, Elekta Instrument AB). **Right:** MC simulation for 1 patient showing AVM nidus and Onyx within LGP dose matrix along with sample simulated particle trajectories.

high-atomic-number (high-Z) materials into a megavoltage photon beam.^{6,42} This has also been shown to be true at low-Z–high-Z interfaces, such as that between tissue and metal implants.^{7,27,29,36,38,50}

Several investigators have attempted to quantify the probable effect that the high-Z components of embolic materials would have on the delivered dose distribution. Andrade-Souza et al. conducted a study involving NBCA using a single 5-MV photon beam irradiating a block of solid water with embedded wells of embolic material, sandwiched with radiochromic film in a solid-water phantom. They found a 10%–15% dose reduction downstream of the embolic material relative to solid water, which varied with the concentration of Lipiodol.² Roberts et al. performed a

similar set of measurements at 6-MV and 16-MV beam energies. At 6 MV, they found 97% beam transmission relative to water, and a 1% interface enhancement.³⁷ Mamaloui-Hunter et al. created a simplified model of a Gamma Knife beam geometry using ray tracing. They estimated the effective linear attenuation coefficient of Onyx at ⁶⁰Co energy from observed CT Hounsfield numbers at 120- to 140-kV energies. At ⁶⁰Co energies, they found a 0.2% dose reduction per beam and a < 0.01%–0.2% overall reduction in dose at the center of an Onyx target.²⁶ Labby et al. calculated linear attenuation coefficients for NBCA with added Lipiodol, and with and without added tantalum. They found that at 6-MV photon energies, the dosimetric error would remain < 1% for emboli up to 1.1-cm thick.²¹

The majority of these interface studies used a unidirectional experimental setup. A single beam (typically from a linear accelerator or ⁶⁰Co unit) was used to perpendicularly irradiate the interface and measure the dose distortion. However, GKRS uses a large number of cross-firing beams to help spread incident energy and achieve a characteristically steep dose gradient. The results of our study show that although localized dose effects can occur (especially within regions of Onyx), the high Gamma Index passing

TABLE 2. MC-determined dosimetric differences between MC-Onyx and MC-water*

Dosimetric Parameter	% Difference MC-Water vs MC-Onyx, Mean (SD)
Nidus, min dose	−0.7 (1.4)
Nidus, mean dose	0.1 (0.2)
Nidus, max dose	2.9 (5.0)
Rx isodose vol	−0.1 (0.3)
Coverage (TV _{PIV} /TV)	−0.0 (0.2)
Selectivity (TV _{PIV} /PIV)	0.1 (0.2)
Gradient index (PIV _{half} /PIV)	−0.0 (1.5)

PIV = prescription isodose volume; PIV_{half} = volume of the isodose surface that is one-half of the prescription isodose; Rx = prescription; TV_{PIV} = volume of nidus covered by the prescription isodose volume.

* MC-water is the reference. Coverage, selectivity, and gradient index calculations based on Paddick (2000) and Paddick and Lippitz (2006).

TABLE 3. Voxel passing rates of 3D Gamma analysis*

Gamma Passing Rate Criteria (dose difference [%]/DTA [mm])	% Passing Rate, Mean (SD)
0.5:0.5	52.1 (4.4)
1.0:1.0	98.2 (0.7)
3.0:3.0	99.7 (0.1)

* Comparison between MC-Onyx and MC-water dose distributions.

FIG. 6. Example case showing differences between MC-Onyx and MC-water dose distributions. **Upper:** LGP-calculated dose distribution overlaid on T1-weighted MR image with Onyx (blue) and nidus (pink) contoured. **Lower:** MC-water (solid lines) and MC-Onyx (dotted lines) isodose curves from an axial plane corresponding to the slice in the upper panel. The curves show minor areas of disagreement, mainly at high isodose lines (such as the 70% isodose line).

rate at traditional radiosurgery tolerances (98.2% passing at 1.0 mm/1.0% tolerance) and the similar selectivity and coverage metrics (mean differences of 0.1% and -0.0% , respectively) suggest that these effects tend to be equalized over a typical Gamma Knife treatment geometry and are not likely to be clinically significant. These findings support the conclusions of Mamalui-Hunter et al., who similarly investigated a Gamma Knife beam geometry.²⁶

Alternative Causes of Poor Stereotactic Radiosurgery Results

Pollock et al. found that incomplete angiographic defi-

nition of the nidus was the most common reason for incomplete obliteration, with recanalization of prior embolization playing an important role.³⁵ Gallina et al. similarly cited inaccurate target definition and recanalization of a previously embolized nidus, as did Kwon et al.^{12,20} Bauer et al. presented a case study demonstrating volume loss within an Onyx embolus and subsequent nidus recanalization.³ Flickinger et al. concluded that along with marginal dose, target definition significantly affects outcome, and this is made more difficult by prior embolization.¹⁰ Buis et al. investigated the effect of intraobserver variation in target definition on outcome and found that patients with prior embolization had larger variations in target delineation.⁵

Other factors cited by these studies as causes of treatment failure include “radiobiological resistance,” incomplete nidus definition due to obscuring hematomas, and intentional partial radiation of the target. However, it should be noted that not all studies investigating postembolization radiosurgery have found a negative effect on the probability of obliteration. A study published by our own institution investigated the clinical effect of embolization on subsequent stereotactic radiosurgery obliteration probability and found no statistically significant difference, albeit with a relatively small patient cohort.²²

Study Limitations

Limitations of our study include a small number of patients, uncontrolled variability in contour morphology and nidus/Onyx distance, contouring uncertainty of both the nidus and Onyx, and uncertainty in the clinically achieved concentration of tantalum within the nidus (i.e., the concentration of tantalum can vary depending on the Onyx/blood mixture achieved upon injection). We believe that a strength of our approach is the use of actual clinical data, including the clinical morphology of the AVM nidus and Onyx and a clinical beam setup, when making comparisons. Our results thus far support the prior results of Mamalui-Hunter et al., who used a similar Gamma Knife beam geometry and a more regular Onyx target.²⁶ Further work will include simulations on a larger patient cohort, determination of the dependence of any dose perturbation on the concentration of tantalum in the sample, and correlation of dose metrics to the probability of nidus obliteration.

Conclusions

The high-Z tantalum component of Onyx appears to have localized, detectable effects on the delivered dose distribution as calculated by MC simulation. However, the small changes in dose metrics and high Gamma passing rates at 1.0%/1.0 mm tolerance suggest that these changes are unlikely to be clinically significant to the dose distribution as a whole. Additional sources of delivery and biological uncertainty should be investigated to determine the root cause of the observed less favorable postembolization GKRS outcomes.

Acknowledgments

We thank Emin Faruk Kececi, PhD, for his work on aspects of

this project not directly related to this manuscript, including phantom design and construction.

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Disclosures

This work was funded by a grant from Elekta Instrument AB. Mr. Lundin and Dr. Nordström are employees of Elekta Instrument AB. Dr. Schlesinger received clinical or research support (includes equipment or material) for this study from Elekta Instrument AB.

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Conception and design: Schlesinger, Nordström, Lundin, Sheehan. Acquisition of data: Schlesinger, Nordström, Lundin. Analysis and interpretation of data: Schlesinger, Nordström, Lundin, Sheehan. Drafting the article: Schlesinger. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Schlesinger. Study supervision: Schlesinger.

Supplemental Information

Previous Presentations

This paper was presented at the 18th International Leksell Gamma Knife Society Meeting, Amsterdam, The Netherlands, May 15–19, 2016.

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