PETITION

**Petition for Gamma Knife in the Western Portion of the State (HSAs I, II, and III)**

**PETITIONER**

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*STATEMENT OF THE PROPOSED CHANGE*

The Charlotte-Mecklenburg Hospital Authority d/b/a Atrium Health (Atrium) respectfully petitions the State Health Coordinating Council (SHCC) to create a special allocation for one gamma knife unit to meet the stereotactic radiosurgery needs of citizens in the western portion of the state (Health Service Areas I, II, and III) in the 2020 State Medical Facilities Plan (SMFP).

*BACKGROUND*

Stereotactic radiosurgery (SRS) uses many precisely focused radiation beams to treat tumors and other problems in the brain, neck, lungs, liver, spine and other parts of the body. SRS is used instead of, or in conjunction with, traditional (i.e., open) surgery due to its extreme accuracy, efficiency and outstanding therapeutic response. Gamma knife surgery is a form of stereotactic radiosurgery, primarily used for treating brain disorders.

There are currently only two providers of gamma knife services in North Carolina. Wake Forest Baptist Medical Center in Winston Salem acquired a gamma knife pursuant to Policy AC-3 and began operation in 1999. Vidant Medical Center in Greenville began operation in 2005. The procedure volume for each provider over the last eight years and the compound annual growth rates is shown in the table below. The table shows that each provider has grown volume over the period and the total procedures grew in FFY 2018.

| Facility | FFY 2011 | FFY 2012 | FFY 2013 | FFY 2014 | FFY 2015 | FFY 2016 | FFY 2017 | FFY 2018 | Compound Annual Growth Rate |
|---|---|---|---|---|---|---|---|---|---|
| Wake Forest Baptist Medical Center | 354 | 364 | 335 | 375 | 439 | 460 | 457 | 496 | 4.94% |
| Vidant Medical Center | 49 | 79 | 107 | 133 | 123 | 230 | 164 | 148 | 17.11% |
| Total | 403 | 443 | 442 | 508 | 562 | 690 | 621 | 644 | 6.93% |

*Source: State Medical Facilities Plans and Hospital License Renewal Applications.*

## TECHNOLOGY OF GAMMA KNIFE

Stereotactic radiosurgery was developed in the 1950s and was originally employed with a single beam method to treat trigeminal neuralgia patients. Gamma knife radiosurgery was subsequently developed as a dedicated tool to provide higher and more precise therapeutic doses of radiation to the brain while minimizing the impact on patients' normal brain tissues. The first gamma knife was developed in 1968 and utilized 179 cobalt sources in a hemispheric array. At the time of its introduction, imaging technology was limited to radiographs and angiography. As such, the initial indications for gamma knife surgery were primarily vascular abnormalities.

Today, gamma knife surgery is a leading treatment solution which is primarily focused on tumors in the brain. There are, however, continually expanding clinical capabilities and applications for this technology. Gamma knife is a very precise radiosurgery procedure, limiting radiation dose to healthy tissue while focusing energy on pathological tissues-allowing for the treatment of virtually all disorders in the brain with ultrahigh precision. Recent gamma knife innovations make it possible to treat patients without invasive fixation (i.e. stereotactic frames), thus enhancing patient comfort while assuring the same high level of dosing precision.

## REASON FOR REQUEST

### Demand for Gamma Knife Services

The pie chart below lists the distribution of conditions treated on gamma knives as reported by the leading gamma knife provider, Elekta, for 2017.
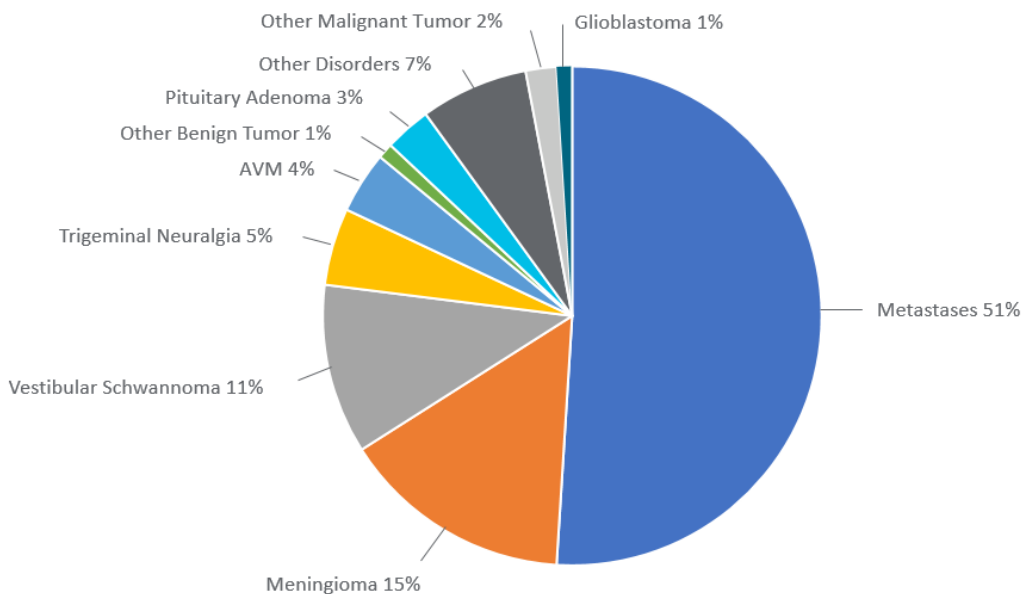


Source: Elekta, 2018

The predominant conditions treated with a gamma knife include: brain tumors (both benign and malignant-including vestibular schwannoma (acoustic neuroma)), trigeminal neuralgia and arterio-venous malformations (AVM). In 2017, these conditions comprised over 85 percent of all cases treated on gamma knives.

To demonstrate the demand for gamma knife services in North Carolina, specifically the Western portion of the state, Atrium has prepared the following analysis using the incidence rates of the predominant conditions treated with gamma knife or other radiosurgery devices. The incidence rates for each condition were multiplied by the population of the state and the relevant Health Service Areas. The percentage of each condition appropriate for gamma knife SRS was then multiplied by the resulting number of cases in each condition.

The population figures used in the calculation are from the Office of State Budget and Management for 2018. The total population of North Carolina was estimated to be 10,401,960 in July of 2018. The total population of the eastern and western regions of the state as defined by the HSA was calculated summing the respective county populations. In July 2018, the population of the western part of the state (HSA I, II and III) was 5,401,490 and the population of the eastern part of the state (HSA IV, V, and VI) was 5,000,470.

The formula used to calculate the number of potential gamma knife cases is described below using the factors for meningiomas (a common, benign brain tumor).

> Incidence rate per million [74.4] X (State population [10,401,960] / 1,000,000) X % Indicated for gamma knife [50%] = Potential radiosurgery cases [387]

Where the literature source provided a range of incidence rate, the calculations were performed for both the low and high values. As the table below indicates, using just the five most prevalent conditions the number of potential radiosurgery cases in North Carolina could be between 2,042 and 3,484 (more contemporary population-based analyses support the higher projections).

| Category | Condition | Annual Incidence (per million) | | Prevalence (per million population) | % Indicated for Gamma Knife | Potential Gamma Knife Cases in NC | |
|---|---|---|---|---|---|---|---|
| | | Low | High | | | Low | High |
| Benign Tumors | Meningioma | | 74.4 | 975 | 50% | 387 | 387 |
| | Vestibular Schwannoma | | 19 | 200 | 80% | 158 | 158 |
| Malignant Tumors | Metastases | 83 | 143 | NA | 90% | 777 | 1,339 |
| Vascular Abnormalities | Ateriovenous Malformations | 8.9 | 13.4 | 180 | 70% | 65 | 98 |
| Functional Disorders | Trigeminal Neuralgia | 126 | 289 | 700 | 50% | 655 | 1,503 |
| | | | | | TOTAL | 2,042 | 3,484 |

*Sources: Gamma Knife Radiosurgery: A Review of Epidemiology and Practice, Hamilton, T.; Kano, H; Lunsford, L.; 2014 and Epidemiology of Metastatic Brain Tumors, Fox, B., Cheung, V., Patel, A., Suki, D., and Rao, G., Epidemiology of Metastatic Brain Tumors, Neurosurgery Clinics, January 2011, Vol 22, Issue 1, Pages 1-6 .*

Using the same approach to apply the incidence rates to the HSA population results in the following table:

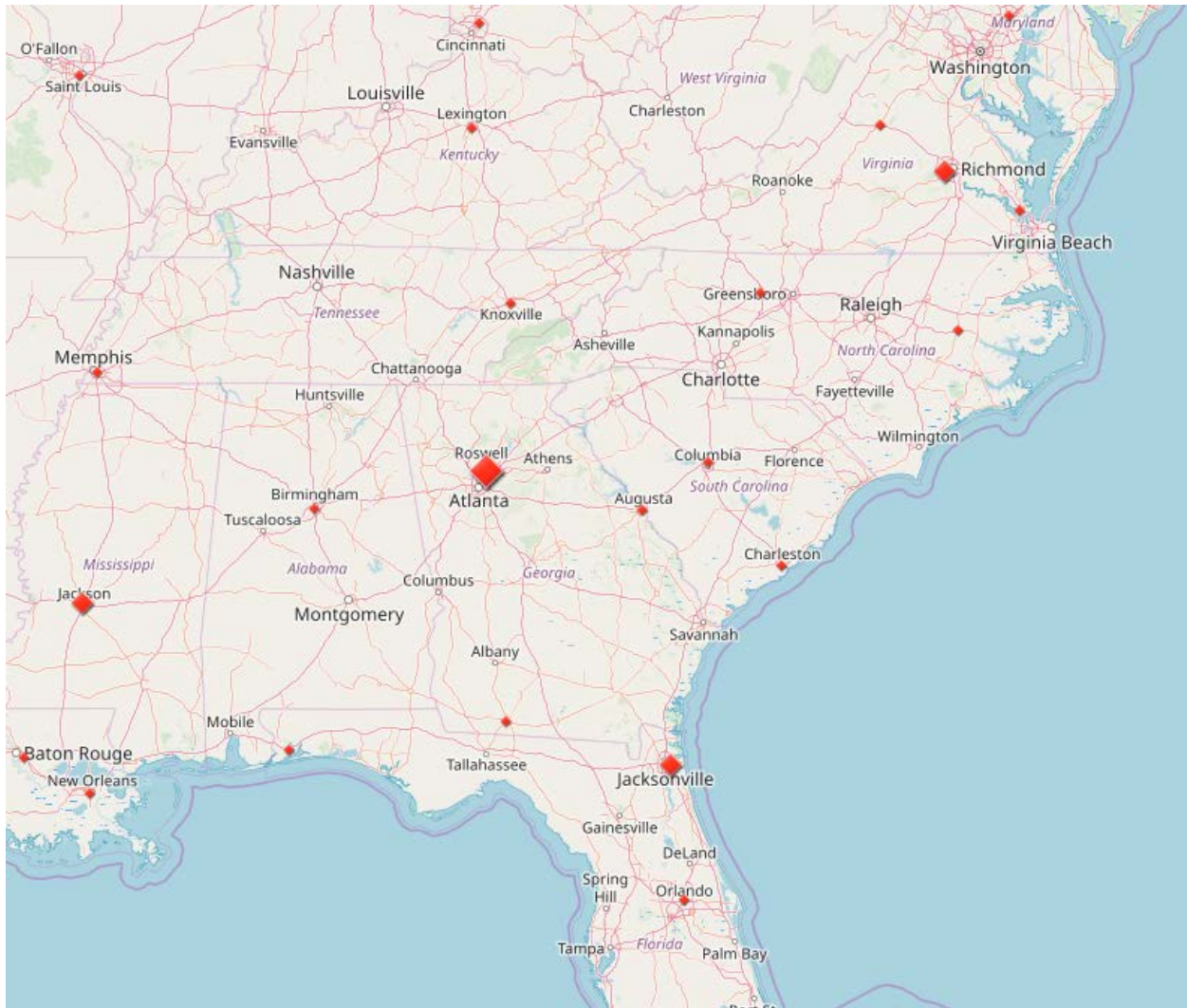| Category | Condition | HSA I, II, III Potential Gamma Knife | | HSA IV, V, VI Potential Gamma Knife | |
|---|---|---|---|---|---|
| | | Low | High | Low | High |
| Benign Tumors | Meningioma | 201 | 201 | 186 | 186 |
| | Vestibular Schwannoma | 82 | 82 | 76 | 76 |
| Malignant Tumors | Metastases | 403 | 695 | 374 | 644 |
| Vascular Abnormalities | Ateriovenous Malformations | 34 | 51 | 31 | 47 |
| Functional Disorders | Trigeminal Neuralgia | 340 | 781 | 315 | 723 |
| | TOTAL | 1,060 | 1,809 | 982 | 1,675 |

**Limited Access to Gamma Knife Services**

Currently, there are currently only two providers of gamma knife services in North Carolina. Wake Forest Baptist Medical Center in Winston Salem began operation in 1999. Vidant Medical Center in Greenville began operation in 2005. Approximately 126 hospitals and clinics nationwide have a gamma knife. The maps below show the locations of gamma knives in the US, the mid-Atlantic region and finally in North Carolina.
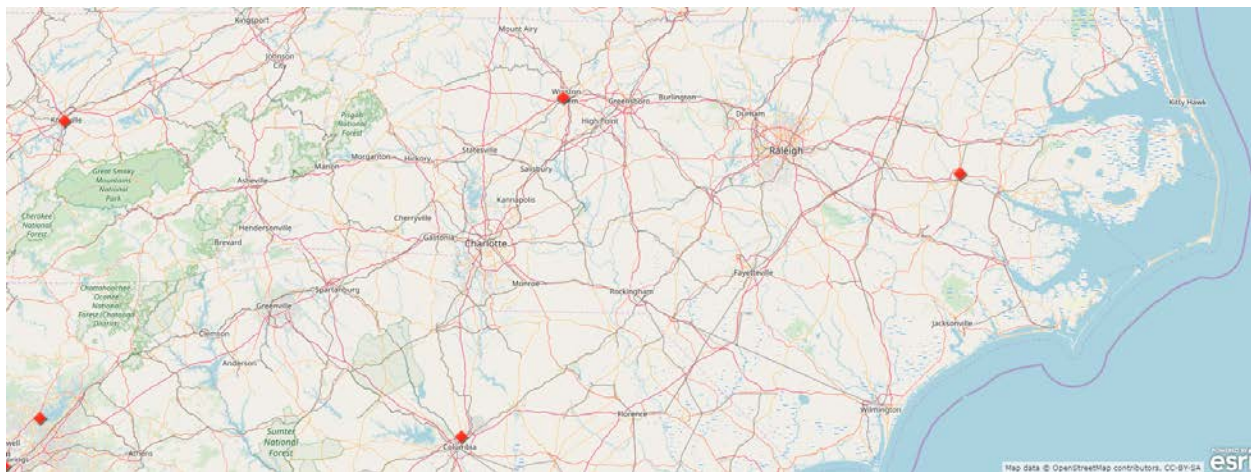
## Location of Gamma Knives
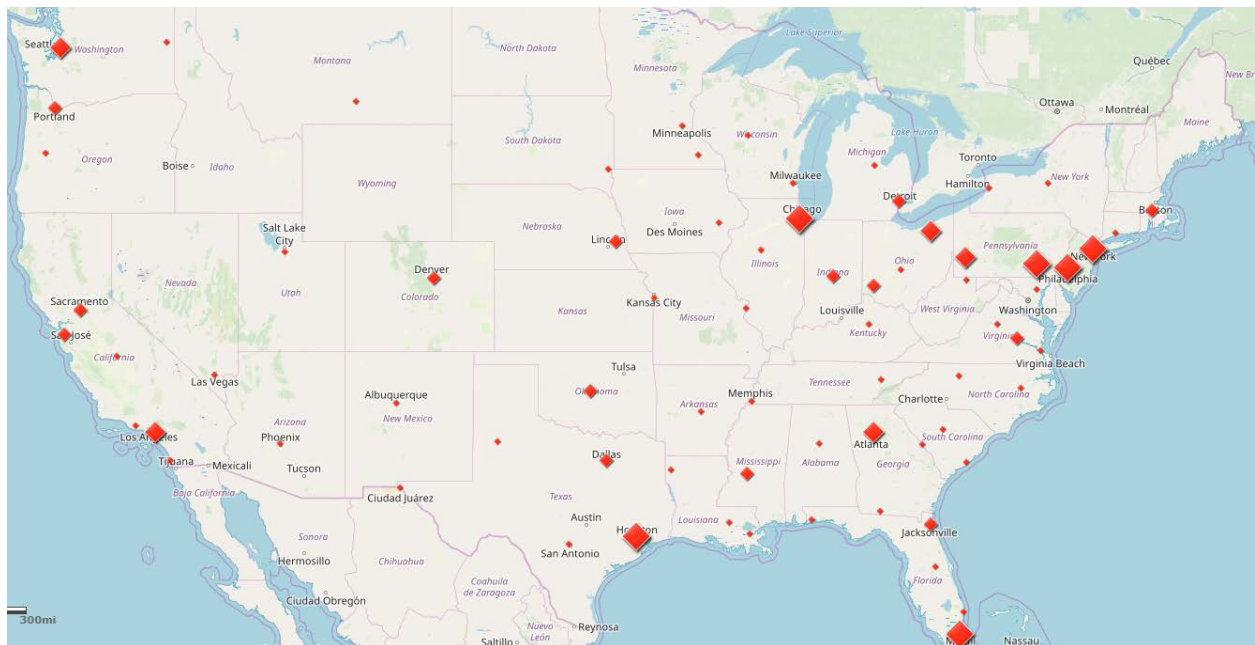


*Source: Elekta*

The larger icons above reflect the clustering of multiple gamma knives in a metropolitan area. The size of the icon is representative of the relative number of gamma knives in the area.

The map above provides a clear indication of the much higher number of gamma knives in operation in Virginia and Georgia as compared to North Carolina.

The table below shows the number of gamma knives currently in operation in each state (including Washington, D.C.) and the population per gamma knife. There are eight states that do not currently have a gamma knife. As the table indicates, North Carolina has less access to gamma knife therapy on a per population basis than 39 other states, including all of our neighboring states. In fact, North Carolina has the same number of gamma knives as South Carolina, even though NC has more than double the population.

If this petition is granted and ultimately another gamma knife unit is developed in North Carolina, the state would have 3.4 million people per gamma knife which would only elevate its population/unit ranking to 36, just below Tennessee.  Atrium realizes that a population to gamma knife ratio, taken alone, may not be sufficient to show a need for another gamma knife in North Carolina; however, it is helpful to show that the population of the state could easily support an additional gamma knife compared to national standards.

| State | Gamma Knives | 2018 Population | Population per Gamma Knife | Rank |
|---|---|---|---|---|
| DC | 1 | 702,455 | 702,455 | 1 |
| AK | 1 | 737,438 | 737,438 | 2 |
| SD | 1 | 882,235 | 882,235 | 3 |
| NE | 2 | 1,929,268 | 964,634 | 4 |
| RI | 1 | 1,057,315 | 1,057,315 | 5 |
| MT | 1 | 1,062,305 | 1,062,305 | 6 |
| PA | 11 | 12,807,060 | 1,164,278 | 7 |
| OR | 3 | 4,190,713 | 1,396,904 | 8 |
| HI | 1 | 1,420,491 | 1,420,491 | 9 |
| NJ | 6 | 8,908,520 | 1,484,753 | 10 |
| MS | 2 | 2,986,530 | 1,493,265 | 11 |
| LA | 3 | 4,659,978 | 1,553,326 | 12 |
| WV | 1 | 1,805,832 | 1,805,832 | 13 |
| WA | 4 | 7,535,591 | 1,883,898 | 14 |
| OH | 6 | 11,689,442 | 1,948,240 | 15 |
| OK | 2 | 3,943,079 | 1,971,540 | 16 |
| NM | 1 | 2,095,428 | 2,095,428 | 17 |
| GA | 5 | 10,519,475 | 2,103,895 | 18 |
| VA | 4 | 8,517,685 | 2,129,421 | 19 |
| IN | 3 | 6,691,878 | 2,230,626 | 20 |
| FL | 9 | 21,299,325 | 2,366,592 | 21 |
| SC | 2 | 5,084,127 | 2,542,064 | 22 |
| NY | 7 | 19,542,209 | 2,791,744 | 23 |
| MN | 2 | 5,611,179 | 2,805,590 | 24 |
| CO | 2 | 5,695,564 | 2,847,782 | 25 |
| TX | 10 | 28,701,845 | 2,870,185 | 26 |

| State | Gamma Knives | 2018 Population | Population per Gamma Knife | Rank |
|---|---|---|---|---|
| WI | 2 | 5,813,568 | 2,906,784 | 27 |
| AR | 1 | 3,013,825 | 3,013,825 | 28 |
| NV | 1 | 3,034,392 | 3,034,392 | 29 |
| MO | 2 | 6,126,452 | 3,063,226 | 30 |
| IA | 1 | 3,156,145 | 3,156,145 | 31 |
| UT | 1 | 3,161,105 | 3,161,105 | 32 |
| IL | 4 | 12,741,080 | 3,185,270 | 33 |
| MI | 3 | 9,995,915 | 3,331,972 | 34 |
| TN | 2 | 6,770,010 | 3,385,005 | 35 |
| CT | 1 | 3,572,665 | 3,572,665 | 36 |
| CA | 10 | 39,557,045 | 3,955,705 | 37 |
| KY | 1 | 4,468,402 | 4,468,402 | 38 |
| AL | 1 | 4,887,871 | 4,887,871 | 39 |
| NC | 2 | 10,383,620 | 5,191,810 | 40 |
| MD | 1 | 6,042,718 | 6,042,718 | 41 |
| MA | 1 | 6,902,149 | 6,902,149 | 42 |
| AZ | 1 | 7,171,646 | 7,171,646 | 43 |
| DE | 0 | 967,171 | N/A | 44 |
| ID | 0 | 1,754,208 | N/A | 45 |
| KS | 0 | 2,911,505 | N/A | 46 |
| ME | 0 | 1,338,404 | N/A | 47 |
| ND | 0 | 760,077 | N/A | 48 |
| NH | 0 | 1,356,458 | N/A | 49 |
| VT | 0 | 626,299 | N/A | 50 |
| WY | 0 | 577,737 | N/A | 51 |

*Source: US Census Bureau, Elekta.*

**Superiority of Gamma Knife SRS to Other SRS Alternatives**

Gamma knife offers advantages to the other SRS alternatives currently in use in the state. These advantages include precision in treating target tissue (tumors) with less damage to healthy tissue. In a 2016 article titled "Dosimetric characterization of hypofractionated Gamma Knife radiosurgery of large or complex brain tumors versus linear accelerator–based treatments" published in the Journal of Neurosurgery, researchers at Stanford University, University of California San Francisco and the University of Arizona School of Medicine studied the effectiveness of hypofractionated gamma knife radiosurgery versus LINAC based treatment on large or complex brain tumors. The researchers concluded gamma knife was a more effective treatment and offered the following conclusion: "When treating large or complex brain lesions via hypofractionated radiosurgery, GK better spares the normal brain and delivers higher target dose compared with LINAC-based CK/VMAT deliveries." The article is included in Attachment 1.

In a separate article by investigators from the University of Oklahoma titled "Normal Brain Sparing With Increasing Number of Beams and Isocenters in Volumetric-Modulated Arc Beam Radiosurgery of Multiple Brain Metastases" published in "Radiotherapy" in 2016, the researchers compared TrueBeam RapidArc linear accelerator based SRS to a reference gamma knife treatment. The researchers concluded "…there is further technological development needed for volumetric-modulated arc radiotherapy before similar dosimetric treatment plans could be achievable when compared to Gamma Knife radiosurgery." This article is included in Attachment 1. The significance of these findings is that approximately 20% of patients with brain metastases have between 5-10 lesions at time of diagnosis. These patients are not currently eligible for SRS on linac-based platforms due to technical and logistical issues. These patients would potentially be eligible for focused treatment using a gamma knife (see below).

*ALTERNATIVES CONSIDERED*

Under the North Carolina Certificate of Need (CON) statute, Atrium believes there are three ways to develop the needed gamma knife, and only the last, through a special allocation in the 2020 SMFP, is a reasonable alternative. The rationale for not maintaining the status quo is discussed above regarding the need for a gamma knife in the western half of the state. The other alternatives are as follows:

1. **File a petition for an additional linear accelerator (LINAC) configured to perform SRS.**
   Gamma knife is a simpler, and therefore more reliable, technology than linear accelerator SRS. It is subject to less "down time" due to technological issues. Treatment planning tends to be simplified leading to increased throughput, particularly for oligimetastases (1-4 brain lesions) which make up the vast majority of metastatic brain tumors. In addition, approximately 20 percent of patients with brain metastases have between 5 and 10 lesions

at diagnosis. These patients are not currently eligible for SRS on most LINACs but these patients could be treated on a gamma knife. LINAC based SRS typically uses a machine not dedicated for SRS, hence each treatment takes a longer period of time and there is less time dedicated to SRS treatments as these devices serve as "general use" radiation machines as well (i.e., treating other patients who require more conventional forms of radiotherapy). A dedicated SRS treatment machine would allow for increased volume of patient treatments and expand treatment indications (e.g., more than 4 brain metastases, trigeminal neuralgia, movement disorders).

The gamma knife is acknowledged as the gold standard for cranial SRS by referring physicians and is sought out by patients for its unparalleled precision in treating brain tumors. Atrium rejected this alternative because linear accelerators configured to perform SRS are not capable of providing the same level of precision and efficiency as gamma knife for patients with intracranial pathologies.

2. **File a CON to develop a gamma knife in response to a need determination in the *SMFP*.**
   This option is unreasonable as a need determination has not been published in the SMFP since 2005. There is not written methodology to determine when a gamma knife is needed in North Carolina. The SHCC has the authority to decide whether a gamma knife is needed. It is impossible to determine when such a decision could be reached. As such, Atrium rejected this alternative.

3. **Special allocation.** The currently proposed petition seeks a special allocation for one gamma knife unit in the western portion of the state. Given the shortcomings of the previous alternatives to meeting the need for gamma knife services, Atrium believes this approach is the only reasonable pathway to developing greater access to this important service.

The final alternative, a special allocation as proposed in the petition, is the only alternative that will ensure the development of gamma knife services in the western portion of the state, where access is needed. As such, Atrium believes the current petition is the most effective alternative for developing needed access to gamma knife services. As discussed above, gamma knife technology offers significant benefits for patient care. North Carolina, and the western portion of the state in particular, do not yet have adequate access to this service. Atrium estimates that there is adequate patient volume in the western portion of the state to support the need for a special allocation of a gamma knife unit as requested in this petition. Atrium believes that a special allocation in the SMFP is the only reasonable alternative to develop this service, given the deficiencies of other potential approaches.

Please note that Atrium also considered filing a petition for an adjusted need determination for the Proposed 2020 SMFP during the summer petition cycle. However, given the regional impact of this proposal on HSAs I, II, and III, Atrium believed its petition was more appropriately submitted at this time. Historically, the SHCC has reviewed petitions that have statewide or regional impacts during the spring petition cycle so that the Proposed SMFP can include the need for comment by interested parties.

## *ADVERSE EFFECTS IF PETITION IS NOT APPROVED*

As discussed above, the proposed special allocation will enable increased access to gamma knife services in the western portion of the state. Gamma knife technology offers significant benefits to patients and payors, as detailed above.

Without the approval of this petition, patients in the western portion of the state will not have adequate access to gamma knife services. As a result, patients will have an increased chance of delays in the treatment and healing process, and possibly less access to gold-standard therapies.

Atrium believes that a special allocation in the SMFP is the only reasonable alternative to develop this service, given the deficiencies of other potential approaches.

## *NO UNNECESSARY DUPLICATION*

As noted above, there are only two operational gamma knife units in North Carolina. Based on a review of data, Atrium believes that there is a demand for more than one unit in the western portion of the state and residents of this region do not have adequate access to this service. As a result, the proposed petition for a special allocation of one unit of gamma knife equipment in the western portion of the state will not result in the unnecessary duplication of health resources in the area.

## *CONFORMITY WITH THE BASIC PRINCIPLES*

The proposed petition is consistent with the basic principles of the SMFP: safety and quality, access, and value.

Safety and Quality

Gamma knife procedures are very safe and the level of precision of the radiation beams allow for less damage to normal tissues than other SRS methods. The result is better patient outcomes and fewer complications/negative outcomes.

Access

As noted above, there are only two existing gamma knife units in North Carolina and as a result the state, particularly the western portion, has inadequate access to this technology. Nearby states such as Georgia, Virginia, Florida, South Carolina and Tennessee have greater access to gamma knife services than North Carolina on a per population basis.

**Accessibility of Gamma Knife in Neighboring States**

| State | Gamma Knives | 2018 Population | Population per Gamma Knife |
|---|---|---|---|
| Georgia | 5 | 10,519,475 | 2,103,895 |
| Virginia | 4 | 8,517,685 | 2,129,421 |
| Florida | 9 | 21,299,325 | 2,366,592 |
| South Carolina | 2 | 5,084,127 | 2,542,064 |
| Tennessee | 2 | 6,770,010 | 3,385,005 |
| North Carolina | 2 | 10,383,620 | 5,191,810 |

Source: Elekta; U.S. Census Bureau.

If this petition is granted and ultimately another gamma knife unit was developed in North Carolina, the state would have 3,461,207 people per gamma knife, slightly ahead of Tennessee, but still far behind many other states.

Value

The expansion of gamma knife access will reduce treatment delays associated with alternative SRS configured linear accelerators operating at a high utilization level. Earlier treatment can often lead to lower costs and complications. Atrium estimates that there is adequate patient volume in the western portion of the state to support a gamma knife unit. This broad geography will allow a future gamma knife provider to draw sufficient volume to efficiently utilize this technology.

**SUMMARY**

In summary, Atrium believes the proposed special allocation for one gamma knife unit in the western portion of the state will provide the citizens of North Carolina with significant benefits in terms of safety/quality, access, and value and urges the SHCC to approve this petition.

# Attachment 1

# Journal Articles

# Dosimetric characterization of hypofractionated Gamma Knife radiosurgery of large or complex brain tumors versus linear accelerator–based treatments

**Peng Dong, PhD,[1,3] Angélica Pérez-Andújar, PhD,[1] Dilini Pinnaduwage, PhD,[4] Steve Braunstein, MD, PhD,[1] Philip Theodosopoulos, MD,[2] Michael McDermott, MD,[2] Penny Sneed, MD,[1] and Lijun Ma, PhD[1]**

Departments of [1]Radiation Oncology and [2]Neurosurgery, University of California, San Francisco; [3]Department of Radiation Oncology, Stanford University, Stanford, California; and [4]Department of Radiation Oncology, The University of Arizona School of Medicine and St. Joseph's Hospital and Medical Center, Phoenix, Arizona

**OBJECTIVE** Noninvasive Gamma Knife (GK) platforms, such as the relocatable frame and on-board imaging, have enabled hypofractionated GK radiosurgery of large or complex brain lesions. This study aimed to characterize the dosimetric quality of such treatments against linear accelerator–based delivery systems that include the CyberKnife (CK) and volumetric modulated arc therapy (VMAT).

**METHODS** Ten patients treated with VMAT at the authors' institution for large brain tumors (> 3 cm in maximum diameter) were selected for the study. The median prescription dose was 25 Gy (range 20–30 Gy) in 5 fractions. The median planning target volume (PTV) was 9.57 cm$^3$ (range 1.94–24.81 cm$^3$). Treatment planning was performed using Eclipse External Beam Planning V11 for VMAT on the Varian TrueBeam system, Multiplan V4.5 for the CyberKnife VSI System, and Leksell GammaPlan V10.2 for the Gamma Knife Perfexion system. The percentage of the PTV receiving at least the prescription dose was normalized to be identical across all platforms for individual cases. The prescription isodose value for the PTV, conformity index, Paddick gradient index, mean and maximum doses for organs at risk, and normal brain dose at variable isodose volumes ranging from the 5-Gy isodose volume (V5) to the 15-Gy isodose volume (V15) were compared for all of the cases.

**RESULTS** The mean Paddick gradient index was 2.6 ± 0.2, 3.2 ± 0.5, and 4.3 ± 1.0 for GK, CK, and VMAT, respectively (p < 0.002). The mean V15 was 7.5 ± 3.7 cm$^3$ (range 1.53–13.29 cm$^3$), 9.8 ± 5.5 cm$^3$ (range 2.07–18.45 cm$^3$), and 16.1 ± 10.6 cm$^3$ (range 3.58–36.53 cm$^3$) for GK, CK, and VMAT, respectively (p ≤ 0.03, paired 2-tailed t-tests). However, the average conformity index was 1.18, 1.12, and 1.21 for GK, CK, and VMAT, respectively (p > 0.06). The average prescription isodose values were 52% (range 47%–69%), 60% (range 46%–68%), and 88% (range 70%–94%) for GK, CK, and VMAT, respectively, thus producing significant variations in dose hot spots among the 3 platforms. Furthermore, the mean V5 values for GK and CK were similar (p > 0.79) at 71.9 ± 36.2 cm$^3$ and 73.3 ± 31.8 cm$^3$, respectively, both of which were statistically lower (p < 0.01) than the mean V5 value of 124.6 ± 67.1 cm$^3$ for VMAT.

**CONCLUSIONS** Significantly better near-target normal brain sparing was noted for hypofractionated GK radiosurgery versus linear accelerator–based treatments. Such a result supports the use of a large number of isocenters or confocal beams for the benefit of normal tissue sparing in hypofractionated brain radiosurgery.

http://thejns.org/doi/abs/10.3171/2016.7.GKS16881

**KEY WORDS** hypofractionation; stereotactic radiosurgery; volumetric modulated arc therapy; Gamma Knife; CyberKnife; normal tissue; oncology

GAMMA Knife (GK) radiosurgery has been the gold standard therapy for single-fraction high-dose irradiation of relatively small brain lesions (e.g., approximately < 4 cm in maximum diameter).[1,24,25] However, recent technical advancements in noninvasive platforms, such as the relocatable eXtend head frame system[13,26] and on-board kV imaging capabilities,[22] have enabled the GK to be used to perform hypofractionated radiosurgery of large and/or complex intracranial lesions that had been mostly treated with linear accelerator (LINAC)–based modalities, such as X-band CyberKnife (CK) or S-band LINACs.

Compared with LINAC-based modalities, major physical characteristics that distinguish GK include the following: 1) GK uses a narrow energy spectrum of gamma rays from Co-60 sources instead of broad-spectrum bremsstrahlung of electrons hitting high-Z targets from a LINAC; and 2) treatment of a large target via GK requires many isocenters, collectively involving thousands of beams from different directions, whereas CK typically uses nonisocentric beams of approximately 100–300 directions and traditional S-band LINACs tend to use a single isocenter with approximately 5–10 fixed beam directions and/or 1–10 rotational arc beams.

Previous investigations that compared GK treatment planning quality against LINAC-based modalities for treating sizable lesions were largely constrained by the practical consideration of the invasive metal frame required for GK treatments. However, 1 study, which characterized GK treatments of intermediate-size (2–4 cm) intracranial targets versus fan beam–based intensity modulated radiotherapy (f-IMRT) treatments, found that GK spares the normal brain tissue significantly better, spurring the concern for pediatric patients.[16]

With rapid advancements in digitally controlled LINAC delivery, such as volumetric modulated arc therapy (VMAT) via flattening filter-free beams,[18] studies have reported feasibilities of applying such treatments toward large or multiple brain lesions.[2,6,17,28] VMAT delivery can be, in theory, viewed as intensity modulated arc therapy delivery with multiple overlapping arcs in analogous f-IMRT delivery.[31,32] Therefore, the question arises as to whether VMAT delivery has overcome the normal tissue–sparing discrepancy compared with GK delivery, as found with f-IMRT delivery. This question is especially relevant for an on-board image-guided GK system for which hypofractionated image-guided treatments of large brain targets have become a turn-key solution in contrast to the previous GK systems.[9,21] As a result, the goal of our study was to investigate dosimetric capabilities of hypofractionated GK treatments of larger or complex brain tumors versus the latest LINAC-based treatments with either CK or S-band LINAC-based VMAT treatment deliveries.

## Methods

### Patient Selection

Ten patients with single cranial tumors, who were originally treated at our institution with the VMAT technique (RapidArc, Varian Oncology Systems), were selected for this study (Table 1). These VMAT cases were patients who were consecutively treated between 2014 and 2015. The median prescription dose was 25 Gy (range 20–30 Gy) in 5 fractions. The median planning target volume (PTV) was 9.57 cm[3] (range 1.94–24.81 cm[3]). The median dose coverage was 97% (range 92%–99%) for all of the cases. Patients who underwent hypofractionated treatments were largely randomly selected in terms of patient performance status, primary versus metastatic disease, target location, and nearby critical structures.

For each case, the DICOM-radiotherapy (DICOM-RT) structure sets were extracted and exported to both the GK and CK treatment planning systems (described below) by experienced users in a blinded and independent fashion, i.e., the participants planning 1 modality (e.g., GK, CK, or VMAT) were blinded to the treatment planning process and quality of the other 2 modalities when planning each case. Once completed, all of the cases were collected on a centralized system (MIM Software, Version 6) for final review and analysis.

### Treatment Planning and Delivery System

The VMAT treatment planning was performed for all of the cases via the Eclipse External Beam Planning V11 for the TrueBeam STx LINAC system (Varian Oncology Systems) equipped with a high-definition 120-leaf MLC system. The center leaf size was 2.5 mm and peripheral leaves were 5 mm. Following the general recipe of VMAT delivery, 2 arcs of isocentric full 360° coplanar beams with alternate collimator angles of 30° or 330° were used, with sections encompassing critical organs blocked when planning a treatment. The isocenter of the plan was all placed inside the individual solitary target.

Note that the use of coplanar arc beams is not mandatory for cranial VMAT treatments. However, they are adopted for patient treatments at our institution due to marginal differences observed between the coplanar technique and the noncoplanar techniques for single-target treatments, which was noted in our previous study.[6] Furthermore, Eclipse uses the progressive resolution optimizer with explicit dose-volume histogram objectives. To decrease dose spillage, the planner iteratively tunes the weighting on the normal tissue objective, which controls how dose falls off outside a defined PTV. The optimization typically took 25–35 minutes per arc. The delivery of the plan is approximately 5 minutes for 6-MV standard flattened beams or approximately half of that time for 6-MV flattening filter-free beams.[6,30]

The CK treatment planning was performed via the Multiplan V4.5 for the CyberKnife VSI System via sequential inverse optimization.[7] The system is equipped with both fixed-size cone and iris collimators with apertures varying from 5 to 60 mm and is capable of nonisocentric, noncoplanar delivery. Two fixed-size cone collimators were used for each plan to reduce delivered monitor units compared with using 1 collimator. Collimators were chosen such that 1 collimator diameter was approximately equal to the central part of the lesion and the other was small enough to cover the tumor's smallest features.

For treatment node selection, we used the default template path set for the head location: "1path_head." The CK

**TABLE 1. Physical and dosimetric characteristics of the 10 cases selected for the study**

| Case No. | Dose, Gy | No. of Fx | Target Vol, cm³ | Target Coverage, %* | PIV, cm³ | PIV₅₀, cm³ |
|---|---|---|---|---|---|---|
| 1 | 30 | 5 | 8.0 | 98 | 8.8 | 41.8 |
| 2 | 25 | 5 | 13.0 | 97 | 13.4 | 57.3 |
| 3 | 25 | 5 | 10.1 | 95 | 10.4 | 42.6 |
| 4 | 25 | 5 | 8.6 | 95 | 9.3 | 44.6 |
| 5 | 20 | 5 | 6.4 | 95 | 6.6 | 19.0 |
| 6 | 20 | 5 | 24.8 | 99 | 30.3 | 88.1 |
| 7 | 25 | 5 | 11.7 | 98 | 12.7 | 55.9 |
| 8 | 25 | 5 | 9.1 | 98 | 14.7 | 89.3 |
| 9 | 25 | 5 | 15.3 | 92 | 16.7 | 90.3 |
| 10 | 25 | 5 | 1.9 | 99 | 3.5 | 12.5 |

Fx = total number of fractions; PIV = prescription isodose volume, i.e., total isodose volume enclosed by the prescription isodose surface for the reference VMAT treatment plans; PIV₅₀ = total isodose volume enclosed by 50% of the prescription isodose surface for the reference VMAT treatment plans.
\* The target coverage was normalized to be identical across all of the treatment modalities.

system allows for 12 beam angles at each node position. Approximately 50–100 nodes and 200–250 beams were used in our plans. Several "auto-shells" were created outside the target volume to constrain the conformity and the extent of the low-dose region. Beam-reduction and time-reduction steps were used to confine the treatment time to < 40 minutes. The treatment planning optimization time was approximately < 1 hour.

The GK treatment planning was performed via the Leksell GammaPlan V10.2 for the Perfexion eXtend system.[3,13,26] Dose distribution of each shot is shaped from 192 directions through 8 sectors of independently opened or blocked collimators in the size of 4, 8, and 16 mm. Manual forward planning with the GammaPlan was performed. Treatment planning employs a compromise between tight dose gradients and treatment time because the benefit of tight dose gradients achieved by using smaller collimator sizes is offset by the long treatment time (approximately 20–30 minutes). The optimization time depends on the planner's skill and experience with the system and typically took 10–20 minutes.

### Plan Evaluation

The percentage of the PTV receiving at least the prescription dose ranged from 95% to 99% and was normalized to be identical across all of the platforms for individual cases (Table 1). The prescription isodose values were between 70% and 94% for VMAT, 47% and 69% for GK, and 46% and 68% for CK. Note that the prescription isodose values for the CK and GK treatments were selected for the purpose of matching the PTV coverage of the original VMAT treatment plans that were delivered for patient treatments. Special care was taken to ensure that any dose larger than 105% of the prescription dose was located within the PTV. The VMAT and CK systems consider low-dose spillage as a significant penalty in the

optimization process, whereas for GK all of the shots are placed manually. The dose limits to critical structures (brain, eyes, optic nerves, chiasm, brainstem, spinal cord, cochlea, and pituitary gland) were also monitored for the 3 modalities during plan generation.

The following dosimetry metrics were analyzed: 1) conformity index (CI), which is the ratio of the volume covered by the prescription isodose (V100%) to the PTV volume (VPTV) as normalized by the target volume coverage (the value is typically between 1 and 1.5 and is equal to the inverse of the Paddick CI[19]); 2) Paddick gradient index (GI), which is defined as the ratio of the 50% prescription dose isodose volume to the 100% prescription dose isodose volume;[20] and 3) dose-volume parameters, with normal brain dose at variable isodose volumes, such as 5-Gy isodose volume (V5), 10-Gy isodose volume (V10), and 15-Gy isodose volume (V15). The normal brain volume is defined as the entire brain volume excluding the PTV. Finally, paired nonparametric ANOVA tests were performed to examine the statistical significance of the differences seen across these modalities for the above dosimetric indices.

### Results

Figure 1 shows the isodose distribution for a representative case from the 3 modalities in the axial, sagittal, and coronal planes. The differences in the plans from the 3 modalities are qualitatively demonstrated in this representative case. With equivalent coverage between all techniques required at planning, the larger low-dose (< 5 Gy) volume in the VMAT cases and smaller medium-dose (approximately 10-Gy level) volume for GK and CK plans are evident in this example representation.

Figure 2A shows the distribution for the CI. The average CI was 1.18, 1.12, and 1.21 for GK, CK, and VMAT, respectively (p > 0.06). Figure 2B shows the distribution for the GI. The mean Paddick GI was 2.6 ± 0.2, 3.2 ± 0.5, and 4.3 ± 1.0 for the GK, CK, and VMAT, respectively (p < 0.002). Figure 2C details the distribution for the prescription isodose line. The average prescription isodose values were 52% (range 47%–69%), 60% (range 46%–68%), and 88% (range 70%–94%) for GK, CK, and VMAT, respectively, thus producing significant variations in the dose hot spots among the 3 platforms.

Figure 3 represents distributions for the normal brain volumes receiving a dose of 15 Gy, 10 Gy, and 5 Gy. The mean V15 was 7.5 ± 3.7 cm³ (range 1.53–13.29 cm³), 9.8 ± 5.5 cm³ (range 2.07–18.45 cm³), and 16.1 ± 10.6 cm³ (range 3.58–36.53 cm³) for GK, CK, and VMAT, respectively (p ≤ 0.03). The mean V10 values for GK and CK were similar (p > 0.13) at 18.1 ± 8.8 cm³ and 20.5 ± 10.1 cm³, respectively, both of which were statistically lower (p < 0.01) than the mean V10 value of 37.8 ± 21.0 cm³ for VMAT. Furthermore, the mean V5 values for GK and CK were similar (p > 0.79) at 71.9 ± 36.2 cm³ and 73.3 ± 31.8 cm³, respectively, both of which were statistically lower (p < 0.01) than the mean V5 value of 124.6 ± 67.1 cm³ for VMAT. Note that the whisker-box–plotted range of Figs. 2 and 3 exhibited greater variations for VMAT compared with GK or CK. Such variations were not found to cor-
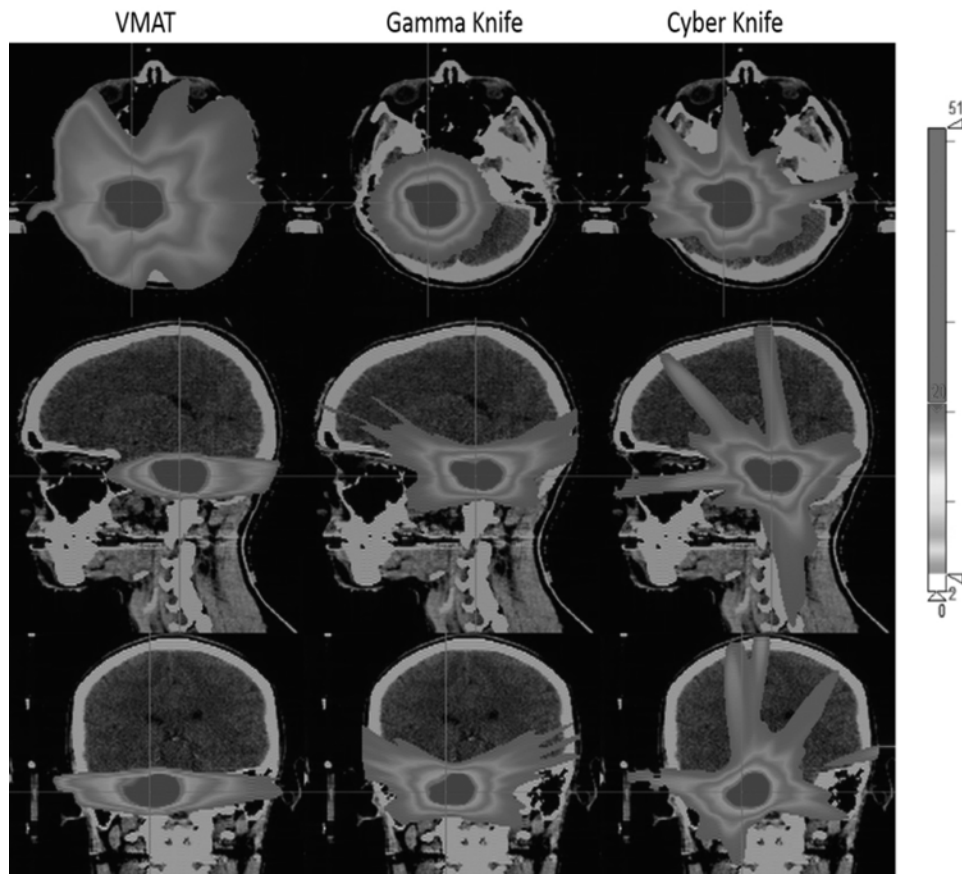
**FIG. 1.** Dose distributions of VMAT, GK, and CK plans in the axial plane (**upper**), sagittal plane (**center**), and coronal plane (**lower**) for a typical patient.

relate with the size, geometry, or location of the targets, and the effect may be contributed by the small sample size of the study.

Finally, the doses to the critical structures were all found to be within the clinical constraints and were nonremarkable for the 3 modalities (p > 0.05). Certain variations noted for small structures (such as the lens of the eye) were probably a contribution from beamlets passing through the structure, because they were not specifically constrained during planning for the current study. The beam-on time was estimated to be approximately 40 minutes, 30 minutes, and 5 minutes under a nominal dose rate of 3.0 Gy/min, 10.0 Gy/min, and 20.0 Gy/min for GK, CK, and VMAT, respectively, excluding patient setup and treatment-related quality assurance time and effort.

## Discussion

Large statistically significant differences in dose fall-off (e.g., as indicated by the GI values for equivalent target volume coverage and dose conformity) have been observed for hypofractionated radiotherapy of large brain tumors among GK, CK, and VMAT treatments. Compared with LINAC-based CK/VMAT deliveries, GK consistently produced sharper dose fall-off and better normal brain–sparing results, despite greater central tar-

get dose. Such results were in good agreement with studies that treated multiple lesions with these platforms[11,12] and an early study[16] that compared GK against f-IMRT deliveries for treatment of intermediate-sized targets, where GK was found to produce significantly sharper dose fall-off in sparing the normal brain tissue surrounding the target.

In the context of hypofractionated treatments for large brain tumors, our study has suggested that there is ample room for future technical improvements in LINAC-based as well as GK-based hypofractionated treatments. Techniques such as the effective utilization of noncoplanar arc beams via manual or broad-range optimization approaches,[4,6,29] 2-step optimizations for CK beams,[14] and optimizing sector beam–based intensity modulated GK beams[10] have all shown promise for improving the existing treatment-planning qualities of VMAT, CK, and GK, respectively. The results of the present study, which are based on default and repeatable techniques, have established a reference baseline for evaluating the aforementioned and other potential future developments.

The results of our study also point out the general fallacy of assuming that the same dose to the target periphery would produce an equivalent normal brain tissue dose from one treatment platform to another. This issue is particularly relevant for large lesion treatments because the
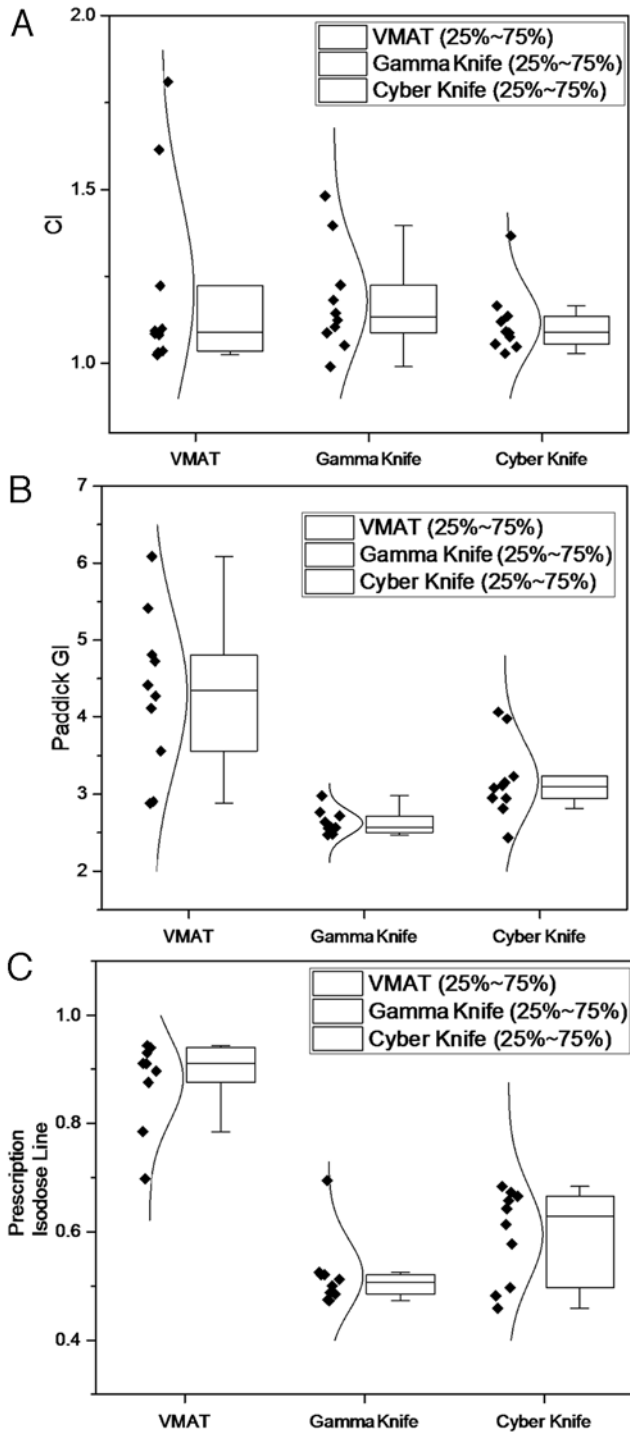
**FIG. 2.** Box-and-whisker plots for CI (**A**), GI (**B**), and prescription iso-dose (**C**) values for all of the cases planned for the GK, CK, and VMAT treatments.



**FIG. 3.** Box-and-whisker plots for normal brain V15 (**A**), V10 (**B**), and V5 (**C**).

dose to the normal brain has been found to increase steeply in a nonlinear function as the target size increases.[15] Ongoing and further clinical studies investigating the normal brain–tolerable dose for hypofractionated treatments (such as addressing the questions like what the

10-Gy or 12-Gy single-fractional equivalent doses are for different hypofractional schema, and whether biological equivalent dose-based conversion formula of our previous study[5] equating hypofractionated treatments such as 25 Gy in 5 fractions with single-fractional equivalent dose

remains valid, and so on) will ultimately help to elucidate the best dosing and fractionation practices, not only based on the dose prescribed to the target periphery but also taking into account the dose to the surrounding normal brain tissues.[8,23,27] Until such studies are completed, we caution and recommend clinical users to pay special attention to the normal brain dose and margin status in the vicinity of a large or complex brain target receiving hypofractionated radiosurgery.

## Conclusions

When treating large or complex brain lesions via hypofractionated radiosurgery, GK better spares the normal brain and delivers higher target dose compared with LINAC-based CK/VMAT deliveries.

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## Disclosures

Professor Ma is a patent holder for the University of California Regents.

## Author Contributions

Conception and design: Ma, McDermott, Sneed. Acquisition of data: Ma, Dong, Pérez-Andújar, Pinnaduwage, Theodosopoulos. Analysis and interpretation of data: all authors. Drafting the article: Ma, Dong, Pérez-Andújar, Pinnaduwage, Braunstein. Critically revising the article: Ma, Dong, Pérez-Andújar, Pinnaduwage, Braunstein. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Ma. Administrative/technical/material support: Ma, Theodosopoulos, McDermott, Sneed. Study supervision: Ma, McDermott, Sneed.

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# Normal Brain Sparing With Increasing Number of Beams and Isocenters in Volumetric-Modulated Arc Beam Radiosurgery of Multiple Brain Metastases

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## Abstract

Recent studies have reported about the application of volumetric-modulated arc radiotherapy in the treatment of multiple brain metastases. One of the key concerns for these radiosurgical treatments lies in the integral dose within the normal brain tissue, as it has been shown to increase with increasing number of brain tumors treated. In this study, we investigate the potential to improve normal brain tissue sparing specific to volumetric-modulated arc radiotherapy by increasing the number of isocenters and arc beams. Adopting a multi-institutional benchmark study protocol of planning multiple brain metastases via a radiosurgical apparatus, a flattening filter-free TrueBeam RapidArc delivery system (Varian Oncology, Palo Alto, California) was used for a volumetric-modulated arc radiotherapy treatment planning study, where treatment plans for target combinations of N = 1, 3, 6, 9, and 12 targets were developed with increasing numbers of isocenters and arc beams. The treatment plans for each target combination were compared dosimetrically among each other and against the reference Gamma Knife treatment plan from the original benchmark study. We observed that as the number of isocenters or arc beams increased, the normal brain isodose volumes such as 12- to 4-Gy on average decreased by up to 15% for all the studied cases. However, when the best volumetric-modulated arc radiotherapy normal brain isodose volumes were compared against the corresponding reference Gamma Knife values, volumetric-modulated arc radiotherapy remained 100% to 200% higher than those of Gamma Knife for all target combinations. The study results, particularly for the solitary (N = 1) metastases case, directly challenged the general notion of dose equivalence among current radiosurgical modalities. In conclusion, multiple isocenter and multiple arc beam delivery solutions are capable of decreasing normal brain irradiation exposure for volumetric-modulated arc radiotherapy. However, there is further technological development in need for volumetric-modulated arc radiotherapy before similar dosimetric treatment plans could be achievable when compared to Gamma Knife radiosurgery.

## Keywords

intensity-modulated arc therapy, stereotactic radiosurgery, brain metastases, normal tissue dose, comparison of techniques

## Abbreviations

FFF, flattening filter-free; FFP, flattening filter present; GK, gamma knife; MLC, multileaf collimator; MR, magnetic resonance; PFX, Perfexion; QUANTEC, Quantitative Analysis of Normal Tissue Effects in the Clinic; SRS, stereotactic radiosurgery; VMAT, volumetric modulated arc radiotherapy

## Introduction

Gamma Knife (GK) technology is considered a reference standard apparatus for the treatment of intracranial lesions with radiosurgery, in particular for treating brain metastases.[1-5] However, advances in linac-based delivery have enabled this technology to evolve as a potential alternative to GK for radiosurgery. More recently, volumetric-modulated arc therapy and flattening filter-free (FFF) linac designs have resulted in fast

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delivery with radiosurgical precision.[6] With minutes as opposed to hours required to deliver even complex radiosurgery dose distributions, there are major questions as to what technology is optimal and why in terms of quality and efficiency trade-off.

In order to delineate a qualitative baseline for normal brain tissue-sparing capabilities among contemporary radiosurgical apparatus, multi-institutional benchmark studies have been conducted for both solitary and multiple intracranial targets.[7-9] In the case of simple solitary target, an equivalent normal brain tissue-sparing effect was observed between GK and linac-based radiosurgery modalities, for example, robotic CyberKnife and dynamic conformal arc deliveries via conventional flattening filter present (FFP) beams. However, for multiple brain metastases, these linac-based radiosurgical treatments were found to yield significantly higher normal brain dosing compared to the reference GK Perfexion (PFX) treatments.[7,8]

Without clinical data to show that there is a consequence to these greater integral doses, it may be that the benefit of delivering therapy within minutes with volumetric-modulated arc radiotherapy (VMAT) outweighs any theoretical potential for neurocognitive damage. Our goal is not to address this issue but to examine whether we can adjust the planning technique for VMAT to reduce normal brain tissue dose exposure. One such strategy is to increase the number of arc beams or isocenters, with the rationale that as the number of the beams increases, the dose contribution from individual beams decreases. For example, if we assume for 18 equally weighted coplanar beams (10° apart covering a span of 180°) focused at the isocenter, each beam would contribute approximately 1 (or 6%) of 18 of the total summed dose at the isocenter. However, when the number of beams increases to 180 (eg, 1° spaced apart simulating a continuous arc beam irradiation), then each beam would contribute <1% of the total dose at the isocenter. Consequently, the entrance dose for the 180-beam arrangement would be significantly less than that of the 18-beam arrangement. The goal of the present study is to investigate whether more arc beams could significantly impact normal brain tissue doses for single as well as multiple brain tumors when treated with VMAT.

## Materials and Methods

Standard data sets utilized in our prior multi-institutional benchmark study were adopted for the current study.[7] This data set was created from a patient previously treated with stereotactic radiosurgery (SRS), anonymized, reviewed, and approved by the institutional review board. The data set consisted of computed tomography and magnetic resonance (MR) images with contours for a multiple brain metastases case with 12 brain tumors distributed throughout the brain. The total summed target volume was 5.4 mL, and all targets were approximately ellipsoidal in shape. A 3-dimensional rendered MR-referenced planar image showing the location and numbering of these targets is illustrated in Figure 1. Per the benchmark study protocol, 4 preset groups of target
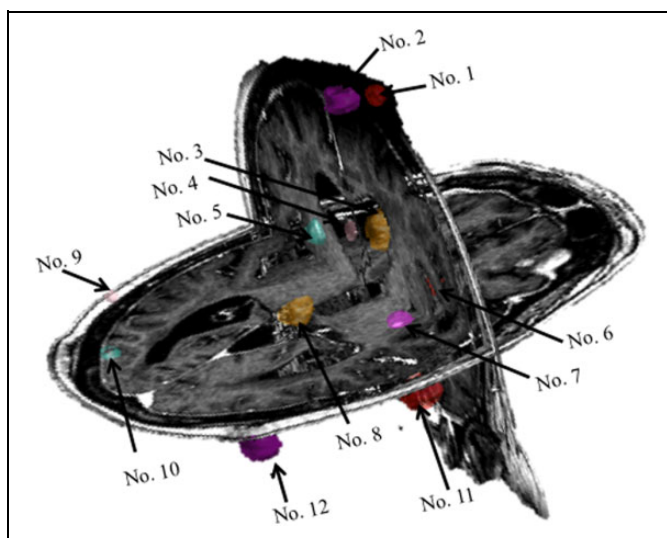


**Figure 1.** Illustration of the target location for the benchmark case: Target No. 12 was selected for N = 1 target treatment planning; Target No. [9, 11, 12][7,8] were selected for N = 3 target treatment planning; Target No. [1, 2, 8, 9, 11, 12] were selected for N = 6 target treatment planning; Target No. [1, 2, 4, 7, 8, 9, 10, 11, 12] were selected for N = 9 target treatment planning; and finally all targets were selected for N = 12 target treatment planning.

combinations (N = 3 [1.8 mL], 6 [3.1 mL], 9 [4.1 mL], and 12 [5.4 mL]) as in Figure 1 were used for VMAT treatment planning. Specifically, for the current study, a solitary target (No. 12 of Figure 1) with a volume of 1.04 mL and N = 3 target combinations was also selected for VMAT treatment planning subject to varied number of arc beam configurations, and isocenters are placed in center of mass of the metastatic lesions.

In order to systematically adjust the total number of arc beams and compare results against the reference data based on the GK radiosurgery system, as described in our previous benchmark study, the linac system of an independent manufacturer (Varian, Palo Alto, California) was adopted for VMAT treatment planning using 6 MV FFF X-ray beams with a 2.5-mm multileaf collimator (MLC) capable of delivering intensity-modulated arc beams with an output of 1400 MU/min. All VMAT (RapidArc [Varian, Palo Alto, California]) plans were calculated on a 2.5-mm grid using Eclipse Version 11 treatment planning system (Varian, Palo Alto, California). The panel inserts of Figure 2 illustrate the multiple arc beam arrangements for the current study, that is, 1-arc, 3-arc, 5-arc, and 7-arc beams for the individual target combinations (N = 1, 3, 6, 9, and 12). Following the general clinical practice of VMAT planning as recommended by the manufacturer, a 360° trans axial arc beam was included in all multiple arc beam arrangement. Plans with 3, 5, and 7 arcs were accomplished using additional non-coplanar beams with couch angles of 0°, 15°, 30°, 45°, 345°, 330°, or 315° in which half-rotation arcs were used. The collimator angle of 30° was used for 1-arc plan, and rest of the multiple arc beam plans used alternate 30° or 330° collimator angle. The gantry and collimator angles for the 1-arc, 3-arc, 5-
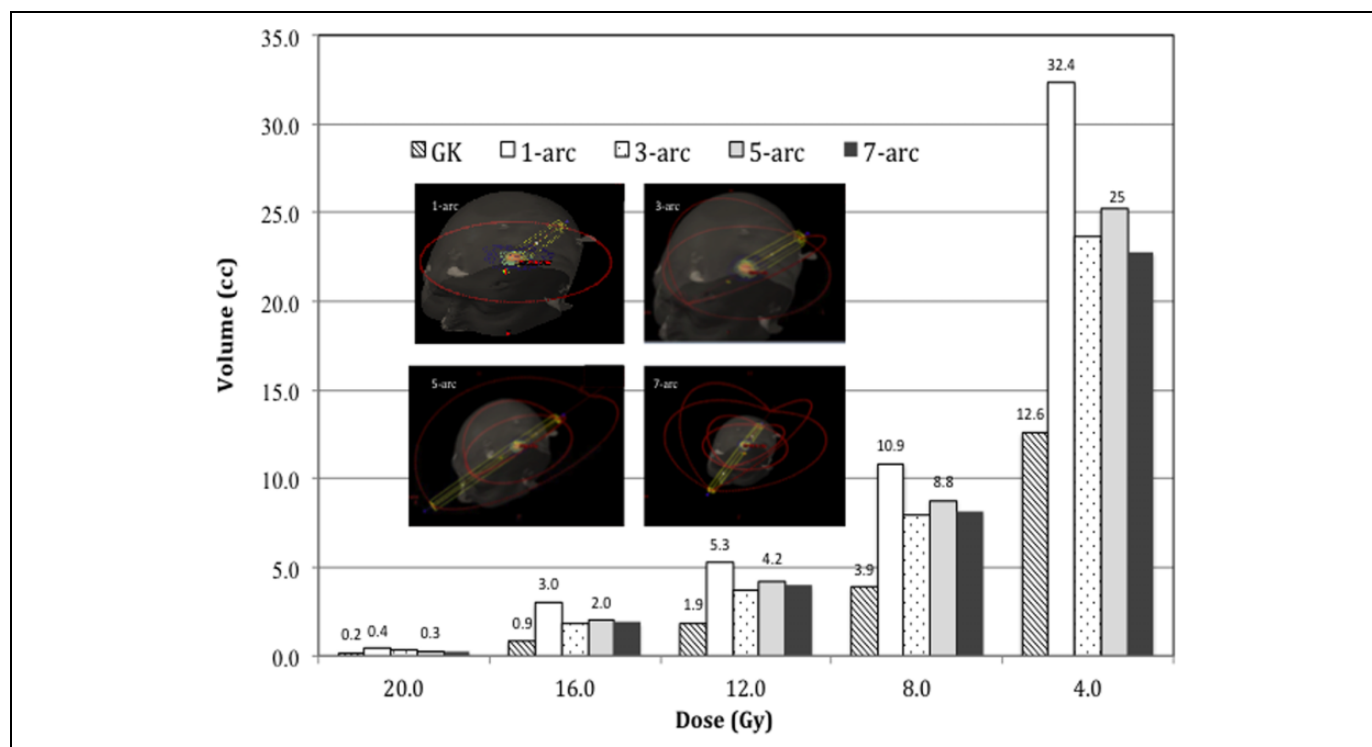
**Figure 2.** Plot of normal brain volume enclosed by different levels of isodose values for the solitary target planned with varied volumetric-modulated arc radiotherapy (VMAT) techniques, that is, 1-arc, 3-arc, 5-arc, and 7-arc configurations as illustrated in the graph.

arc, and 7-arc beam arrangements are described in the legends of Figure 2. Note that these arc beam arrangements were largely derived from the beam configurations of traditional cone-based SRS planning and previously published VMAT planning techniques[10] as well as user experiences.

All targets were prescribed 20 Gy to cover at least 99% of each individual target volume regardless of solitary or multiple targets involvement plus normal tissue constraints as stipulated in the benchmark study protocol.[7] In short, all treatment plans were developed with maximal effort to ensure clinical deliverability of these treatment plans. In another word, the goal of our study is to compare clinically feasible treatment plans for both GK and VMAT. Of note, no specific dose constraints were enforced for critical structures for VMAT plans per our previous publication.[8] However, constraints for maximum dose hot spots were ≤110% and (brain–planning target volume (ptv)), with priority of 75 to 85 were used for all VMAT plans. As a general practice, the GK treatment plans tended to posses the dose hot spots up to 200% of the prescription dose, whereas the VMAT treatment plans typically possessed the dose hot spots up to 116% of the prescription dose. This was also contributed by the hardware limitations and clinical practice considerations such as a finite number of shots for GK, and MLC leakage due to the wider jaw opening to cover combined 2 or more targets and also the limitation of MLCs to close completely between targets at different angles when single isocenter was used to plan multiple targets at the same time for VMAT delivery, and so on. Finally, the normal brain volumes at the peripheral isodose levels of 4, 8, 12, 16, and 20 Gy were compared among

each VMAT treatment plans of different arc beam combinations and also against the reference GK PFX data.

## Results

Results for the solitary target for varied arc beam combinations via FFF beams are shown in Figure 2. When compared with the 1-arc treatment plans, all multiple arc treatment plans exhibited significant decreases in the order of 20% to 30% for all the peripheral isodose volumes (ie, 16, 12, 8, and 4 Gy). Of note, similar improvements were also noted at the prescription isodose level (ie, 20 Gy), indicating higher dose conformity as more noncoplanar arc beams were used for treatment planning. However, when comparing 3-arc, 5-arc, and 7-arc treatment plans, the differences in the isodose volumes among the treatment plans were significantly less with a consistent trend of 5-arc treatment plans producing the highest peripheral isodose values, whereas the 3-arc or 7-arc treatment plans produced the lower values. Such a variation was commonly encountered as in conventional linac SRS and was mostly caused by a preconfigured gantry/couch/collimator arrangements to cover random distributions of multiple intracranial targets. However, when compared to the reference GK PFX values, all VMAT treatment plans produced remarkably higher values (approximately a factor of 2) in the peripheral isodose volumes.

The results for the multitarget VMAT treatment planning via multiple arc (eg, 3-arc, 5-arc, and 7-arc) treatment deliveries are shown in Figure 3. Note that Figure 3 is
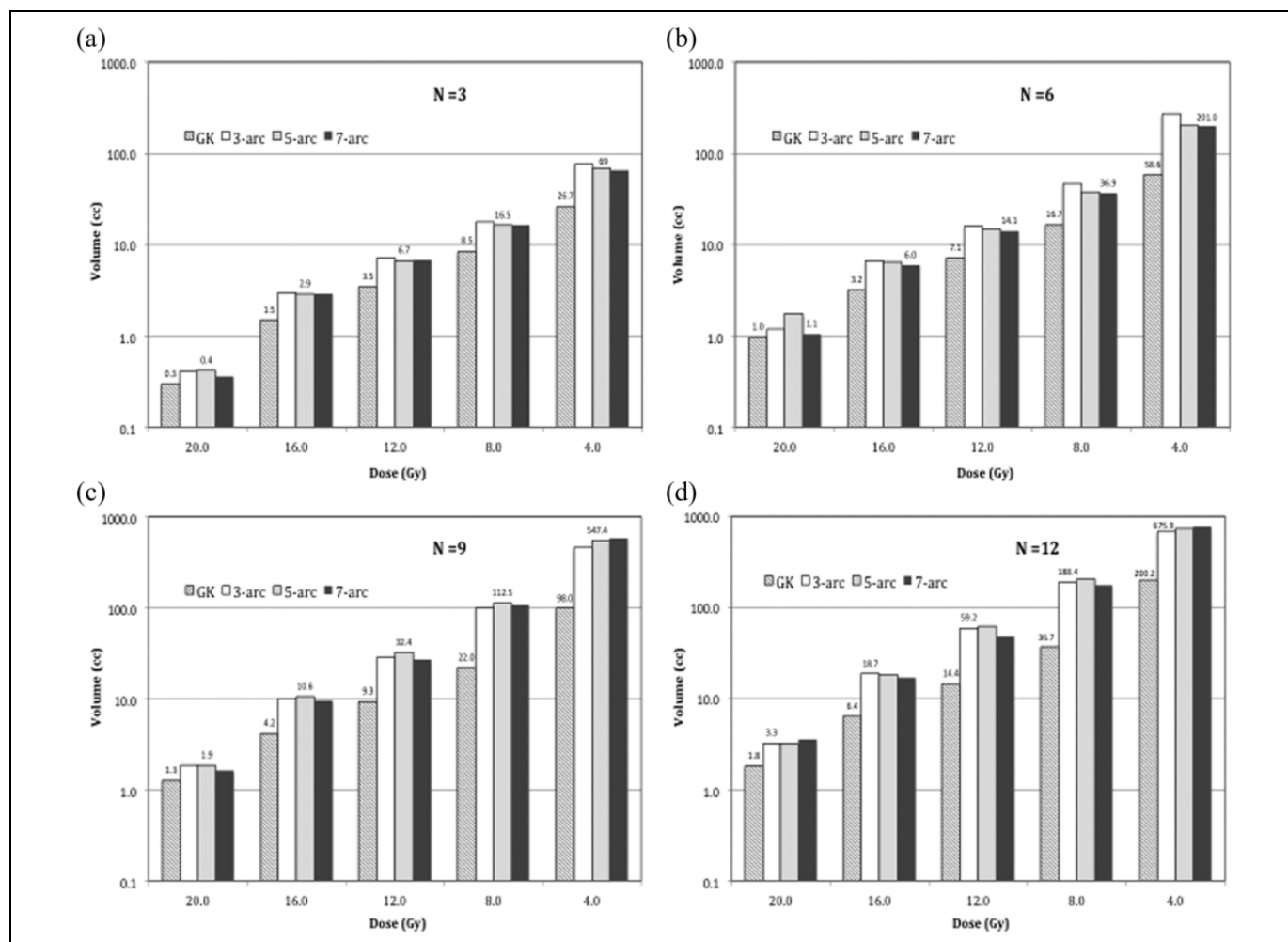
**Figure 3.** Semilogarithmic plot of normal brain volume dependence on the isodose levels for multitarget (N = 3, 6, 9, and 12) treatment planning with the multi-arc/multi-isocenter technique. Note the large discrepancy between the volumetric-modulated arc radiotherapy (VMAT) technique and the reference Gamma Knife (GK) values at the peripheral isodose volumes such as from the 12-Gy to the 4-Gy isodose levels.

plotted with a logarithmic scale to highlight the high iso-dose volumes such as differences in the 20- and the 16-Gy dose levels. Conventional 1-arc configuration was unable to produce treatment plans satisfying dose–volume constraints. For lower isodose volumes, such as the 8- or 4-Gy dose levels, the differences between the multi-isocenter multiple arc deliveries were in the range of 4.4% to 15.4% (average: 8.9% ± 3.8%) from their respective median values for all the cases. For all the VMAT results, the low isodose level volumes such as the 8- and 4-Gy isodose levels were averaged 275% ± 132% higher when compared to the reference GK PFX values. Furthermore, the 12-Gy isodose volumes and the 16-Gy isodose volumes were on average 179% ± 91% and 129% ± 40% higher than the GK PFX values, respectively. These results are in good agreement with previously reported data (9) obtained using tighter optimization constraints, whereas in the present study, clinically deliverable FFF VMAT treatment plans with a maximum dose of <116% of the prescription dose are achieved.

## Discussion and Conclusions

The peripheral dose distributions within the normal brain tissue surrounding the radiosurgery target(s) are expected to vary based on treatment technique and specifically for VMAT based on number of arcs and isocenters. In this technical report of VMAT treating brain metastatic lesions, we found that the normal brain tissue-sparing effect can be improved on the order of 5% to 10% in the peripheral 8-Gy to 12-Gy isodose volumes by increasing the number of isocenters and arc beams per routine clinical practices at our institutions. However, the magnitudes of improvements are not significant enough to overcome the differences observed between VMAT and the reference standard GK PFX treatment plans for the same lesions.

Similar levels of discrepancy were further noted for a solitary lesion planned with FFF beam-based VMAT as compared to a standard GK PFX treatment plan. Such an observation suggests that FFF beam-based VMAT of solitary intracranial lesions may be dosimetrically unique when compared to a

conventional FFP beam-based SRS for managing solitary lesions as reported in a prior study.[9]

Considering the results of the current study to those of prior, 2 essential areas emerged as key to normal brain sparing for multiple target brain SRS: (1) dose fall-off near a single target and (2) dose interplay or dose interference among neighboring targets when multiple targets are involved. The results of the current study suggest that increasing the number of isocenters or FFF-based arc beams does not significantly impact either of these 2 factors. This is likely caused by the peripheral dose characteristics of the FFF beams where narrowly collimated beamlets tend to elevate the peripheral dose compared to those of the GK PFX beams. Therefore, one potential area of improvements lies in sharpening the penumbra of the current FFF beams, as applied to VMAT, as this may directly impact these 2 factors. In fact, such an improvement has already been observed for the GK beam geometry in a prior study,[11] where adding shaped metal flattening filters to intersect individual GK beamlets was found effective in improving the normal brain sparing for majority of the cases.

Given elevated normal brain tissue dose, radiosurgery practitioners need to exercise caution in dose prescription and target margin assessment when applying the emerging technologies such as VMAT in single and multiple target intracranial SRS. Our study highlighted the relationship between the peripheral target dose and the dose to the surrounding normal brain tissues as reported previously.[8] In essence, due to steep dose fall-off surrounding a radiosurgical target, a seemingly small expansion or contraction on the prescription isodose volume can lead to large dose variations to the target periphery, thus dramatically altering the dose to the surrounding normal brain tissue.[12] As a result, care must be taken to ensure proper dose to the target first before comparing or surveying peripheral isodose volumes such as 12, 8, and 4 Gy across different treatment modalities.

The clinical implications of the low-dose irradiation of the normal brain are unknown, awaiting the results of clinical studies such as the North American Gamma Knife Consortium trial and RTOG 0933 trial results. However, animal study[13] and early data[14,15] have all pointed to a low tolerance dose and essential need to spare critical neurostem cell compartments including hippocampi in normal brain irradiation to improve neurocognitive functions of the patients. Given the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) practice guideline and known correlation between low-level isodose volumes and the treatment complications,[16-18] maximally sparing the normal brain via technical improvements is therefore highly warranted. Ultimately, clinical trials such as North American Gamma Knife Consortium will help define acceptable levels of normal brain irradiation on neurocognitive functional outcomes in managing metastatic brain tumors with SRS.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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