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Comparison of Plan Quality and Delivery Time between Volumetric Arc Therapy (RapidArc) and Gamma Knife Radiosurgery for Multiple Cranial Metastases

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Abstract

Background—Volumetric modulated arc therapy (VMAT) has been shown feasible for radiosurgical treatment of multiple cranial lesions with a single isocenter.

Objective—To investigate whether equivalent radiosurgical plan quality and reduced delivery time could be achieved in VMAT for patients with multiple intracranial targets previously treated with Gamma Knife (GK) radiosurgery.

Methods—We identified 28 Gamma Knife treatments of multiple metastases. These were replanned for multi-arc (MA) and single-arc (SA), single-isocenter VMAT (RapidArc) in Eclipse. The prescription for all targets was standardized to 18 Gy. Each plan was normalized for 100% prescription dose to 99–100% of target volume. Plan quality was analyzed by target conformity (RTOG, Paddick CI), dose fall-off (area under DVH curve), as well as the V4.5, V9, V12, and V18 isodose volumes. Other endpoints included beam-on and treatment time.

Results—Compared to Gamma Knife, multi-arc VMAT improved median plan conformity ($CI_{VMAT} = 1.14$, $CI_{GK} = 1.65$; $p < 0.001$) with no significant difference in median dose fall-off ($p = 0.269$), 12Gy isodose volume ($p = 0.500$), or low isodose spill ($p = 0.49$). Multi-arc VMAT plans were associated with markedly reduced treatment time. A predictive model of the 12Gy isodose volume as a function of tumor number and volume was also developed.

Conclusion—For multiple target SRS, 4-arc VMAT produced clinically equivalent conformity, dose fall-off, 12 Gy isodose volume, and low isodose spill, and reduced treatment time compared to GK. Due to its similar plan quality and increased delivery efficiency, single-isocenter VMAT radiosurgery may constitute an attractive alternative to multi-isocenter radiosurgery for some patients.

Keywords

Multiple metastases; radiosurgery; gamma knife; linac; plan quality; treatment efficiency; RapidArc

Introduction

Intracranial metastatic disease is discovered in an estimated 170,000 cancer patients per year.¹ Multiple cranial metastases are present in roughly 70–80% of these cases.² In recent years, the expanded availability of high-resolution imaging and improved precision of patient localization have fostered an increasingly prominent role for stereotactic radiosurgery (SRS) in the treatment of multiple intracranial metastasis cases. Gamma Knife (GK) has heretofore been the predominant modality employed for confocal treatment of multiple metastases. However, because of its high delivery efficiency³ and plan quality⁴, there has been significant interest in the viability of single-isocenter, linac-based arc therapy⁵ for multiple metastasis treatment. Previous work has found Gamma Knife superior to conformal arc-based³ multiple target SRS with regard to normal brain exposure. However, a new generation of linacs (e.g. TrueBeam STx, Novalis Tx) capable of VMAT (volumetric modulated arc therapy), coupled with improved planning strategies^{4, 6, 7} is now available. Therefore, we investigated whether improved VMAT technology and planning technique provide sufficient merit to re-evaluate this conclusion.

To assess the clinical feasibility of such an approach, we retrospectively evaluated plan quality and efficiency of treatments for consecutive patient cases at our institution who received GK therapy for multiple metastases to the brain. We then re-planned each case for different types of VMAT delivery and compared plan quality and prospective treatment efficiency. Our hypothesis was that VMAT could deliver clinically equivalent plan quality to GK with a significant increase in treatment efficiency.

Methods

Treatment planning

With approval from the University of Alabama at Birmingham Institutional Review Board, we identified 28 consecutive multiple target cases with 113 total targets that had been treated on our Leksell Model C (Elekta) GK with SRS. No other selection criteria were used. Each of the plans had been designed by an experienced GK physicist, and approved by an attending neurosurgeon and radiation oncologist. The GK's source was less than 2 years old over the entire range of treatments. Source activity was at least 77% of initial activity for all treatments. Treatment times and beam times were those of the actual date of treatment and not normalized to a specific source age. Descriptive statistics for the cases and individual targets are shown below in Table 1. All patients received MR imaging with contrast for planning. 4, 8, 14, and 18mm collimators were used for treatment planning. As a general rule, our institution prefers using multiple shots to emphasize conformity, rather than fewer shots to minimize treatment time. We strive for each plan to cover at least 99% of the target volume with the prescription dose, but occasionally a clinical judgment call is made in the

setting of a nearby organ at risk to accept 95% volume coverage with the prescription dose. Once acceptable coverage and conformity is achieved, optimal gradient is pursued. To optimize dose fall-off and normal tissue background dose, the prescription isodose line was between 50% and 60% for most targets. If warranted, higher and lower isodose lines (max: 86%, min: 40%) were occasionally used (e.g. for very small or particularly large targets).

To ensure congruent planning quality comparison between modalities, the prescription for all tumors was standardized to 18 Gy in a single fraction and any GK cases with heterogeneous prescriptions were re-normalized accordingly. We transferred each GK session's imaging set and all corresponding structure contours from Leksell Gamma Plan version 10.1 into Eclipse via the DICOM-RT (Digital Imaging and Communications in Medicine – radiotherapy) protocol. Because a CT volume is required for treatment planning within Eclipse, we generated an equispaced ($z = 0.25\text{cm}$) phantom CT image set, into which all structure contours were replicated. In the manner of our previously described technique⁴, we constructed 1-arc, 2-arc, and 4-arc (Figure 1) single-isocenter VMAT plans in 10MV FFF mode for simulated delivery with the TrueBeam STx (Varian) in high intensity flattening filter free (FFF) mode with HD-MLC (high definition – multi-leaf collimators). Jaw tracking was enabled. High-intensity FFF mode operates at up 2400 monitor units (MU)/s. We included additional optimization criteria to emphasize conformity and dose fall-off as well as reduced low-dose spill. Plans were optimized with the RapidArc PRO3 algorithm. We normalized each plan such that 100% of prescription dose was delivered to 99% of target volume. In contrast to Gamma Knife plans where normalization is performed for each isocenter to optimize gradient for that particular target, single-isocenter RapidArc uses a single cumulative plan normalization. Each plan received appropriate physician and physicist review to ensure clinical acceptability with regard to accepted standards for target coverage and risk of neurological complication, particularly radionecrosis. Upon initial analysis, we observed that 4-arc plans consistently generated superior plan quality to 1- and 2-arc plans and confined inter-modality comparison to the 4-arc VMAT and GK plans for increased statistical power.

Plan comparison evaluation

We quantitatively assessed both modalities' plan quality with RTOG and Paddick conformity indices; 18, 12, 9, and 4.5 Gy isodose volumes (V_{18} , V_{12} , V_9 , $V_{4.5}$); mean dose; and the area under the DVH curve between the 50 and 100% prescription isodoses (AUC_{50-100}). We limited conformity analysis to targets with volume $> 0.025\text{ cm}^3$.

$$\text{RTOG CI} = \frac{PV}{TV} \quad \text{Paddick CI} = \frac{(TV_{PV})^2}{TV \times PV} \quad AUC_{100\%-50\%} = \int V_{structure} \delta dose$$

where:

TV = target volume

PV = prescription volume

TV_{PV} = target volume within the prescribed isodose cloud

$V_{structure}$ volume of structure (absolute or relative %)

$\delta dose = 50\%$ to 100% prescription dose range

Beam-on time and treatment time were also compared. For GK, treatment time was defined to be duration between treatment room entry and frame removal as recorded in the medical record. Because the difference between delivered and re-planned GK beam-on times were negligible compared to treatment time, we used the clinical treatment times for the re-planned GK cases. The institutional average delivery time was utilized for simulated VMAT plan treatment time. Utilizing a single-isocenter approach, for a given prescription, VMAT beam-on time is independent of target number and only varies with the number of arcs.

Statistical analysis was performed with Origin 9.0 and SAS 9.3. Direct comparison was performed via paired Wilcoxon signed rank test; multivariate regression was performed via least squares regression with an identity link function.

Results

All plans met our standards for clinical acceptability, including target coverage, dose fall-off, moderate isodose spill, and critical structure exposure. Figure 2 shows the distributions of RTOG and Paddick conformity indices for both individual target and overall plan conformity. Table 2 details their respective descriptive statistics. Conformity was more favorable in multi-arc VMAT plans than GK.

Figure 3 shows the distribution of 4.5, 9, 12, and 18 Gy isodose volume levels and Figure 4 illustrates the mean brain dose distributions for both modalities. Over the entire distribution of cases, no statistically significant difference was detected in 4.5, 9, and 12 Gy isodose volume levels or mean dose.

The distribution of the V_{18} was more favorable for VMAT than GK as would be expected from the observed difference in conformity. Because the V_{12} has become a benchmark predictor for risk of radionecrosis^{8,9}, we also constructed a generalized linear model of V_{12} 's dependence on total GTV (gross tumor volume), tumor number, as well as modality to ensure that the former two were not confounding variables. The model was well-fitted to the data ($R^2 = 0.97$, $p < 0.001$) and found V_{12} to be significantly correlated with both total GTV ($p < 0.001$) and tumor number ($p = 0.013$), but not modality ($p = 0.14$). Dropping the non-significant modality correlate left an equally well-fitted model ($R^2 = 0.97$, $p < 0.001$) of V_{12} versus total GTV and tumor number that can be visualized conveniently in a contour fit plot (Figure 5).

Paddick et al. stated in their original postulation of the metric that the gradient index is inherently unsuited to comparison of dose fall-off in plans with incongruent conformity.¹⁰ However, the rapidity of the prescription dose fall-off, especially in the 9 to 18 Gy range, is an important property in radiosurgical plan evaluation. We therefore sought a more robust metric that was insensitive to individual isodose volume differences between plans. We chose to compare the area under the dose volume histogram curve (AUC-DVH) in our range of interest for each modality, a metric that has been principally employed for predicting normal tissue toxicity in genitourinary and gastrointestinal treatments^{11–13}, but not

previously for comparative SRS plan evaluation. Matlab was used to integrate each absolute dose/volume DVH curve of the body from 9 Gy to 18 Gy to obtain the AUC-DVH₉₋₁₈. A case example and the distribution for each modality are shown in Figure 6. Distributions of plan dose fall-offs was not significantly different ($p=0.44$) between GK (range: 7.97–520.0, median: 81.5 cGy-cc) and VMAT (range: 16.18–328.7, median: 80.8 cGy-cc).

Figure 7 shows the difference in beam-on time and treatment time between GK and multi-arc VMAT. For high-intensity mode FFF VMAT, at prescriptions that average less than 24 Gy/360° of arc rotation, the dose rate is determined by the gantry rotation speed and the beam-on time will not vary with target number or prescription. For the four-arc geometry we utilized here, beam-on time will always be approximately 2.5 minutes. The remainder of treatment time is constituted by positioning verification and table adjustments. Treatments range from 12 to 22 minutes.³ One table rotation is necessary for each non-coplanar arc. Gamma Knife beam-on times ranged from 17.5 to 121.2 minutes (median: 45.1, mean: 55.3 min). GK treatment times ranged from 60 minutes to 310 minutes (median: 125, mean: 148 min).

Discussion

Ma et al. found that peripheral isodose volumes are several times lower for Gamma Knife (Perfexion) than arc-based therapy multi-met SRS on both the Novalis¹⁴ and the TrueBeam STx platform¹⁵ in a four-case series. We report here, in a 28-case series of treated patients, that with sufficiently advanced planning technique, VMAT can in fact deliver plans clinically equivalent in terms of both conformity and moderate isodose spill to plans we are currently delivering with our Gamma Knife. A comparative DVH curve for a nine metastasis case is shown in Figure 8.

Comparative isodose contour maps of the nine metastasis case, a six metastasis case, and a two metastasis case are shown in Figure 9.

At increasing numbers of very small targets (e.g. >9 tumors, 0.01 – 0.1 cm³), Gamma Knife may retain a small advantage to VMAT with respect to very low isodose spill (i.e. dose < Rx_{25%}). This difference may be plan-independent and due to collimator leakage, scatter dose¹⁶, and/or the much larger area of the cranium throughout which the Gamma Knife's beam entry points are spread. Or, the advantage may be an artifact of the relatively short duration of time VMAT has been used to treat multiple metastases. In any case, the absolute differences between the two modalities seem to be very small and the authors of this study are aware of no work establishing any clinical sequelae to this very low isodose region. Even so, as our VMAT treatment strategy has evolved, we have studied a variety of methods to reduce the low-dose spill as much as possible; these include jaw-tracking and high-priority low-dose spill constraints (e.g. 2.5x optimization priority of other parameters).

In this series of patients, we noted that utilizing jaw tracking on the linac resulted in a small but consistent 2–5% reduction of the mean dose without any compromise to other dosimetric parameters. Though not necessary for a high quality plan, if available, this feature should not be neglected when treating multiple targets. Our unique Matryoshka (Russian nesting doll)

shell technique to emphasize conformity and reduce fall-off also likely contributes to our favorable low-dose spill results. However, including a heavily weighted low-dose constraint within the treatment optimization criteria is necessary for a high quality plan, and we have found it to be the single most effective contributor to reducing low-dose spill.

We have invested additional study into using a custom collimator angle selection program to further reduce low-dose spill. This technique involves iteratively summing the cumulative space between collinear targets in each leaf-pair opening of the beam's eye projection for all control points across the entire path of each arc. The collimator angle with the least total leaf-pair space is selected for each of the arcs in the designated field geometry.¹⁷ Although this technique was not used for the results presented here, we believe it may enable us to continue improving the low-dose profile of VMAT plans.

A high quality multi-met VMAT SRS plan must utilize beam geometry and optimization criteria that not only achieve the required target coverage, but also emphasize conformity, rapid fall-off, minimal moderate isodose, and minimal low isodose spill. The planner must realize that VMAT is an entirely different paradigm of SRS than Gamma Knife. In VMAT, utilizing separate isocenters and arc(s) for each target no longer makes sense when a single isocenter plan can achieve the same coverage. When additional isocenters are used, redundant monitor units are delivered, additional collimator leakage is accumulated, and peripheral dose to normal issue is needlessly increased.⁷

Achieving rapid fall-off from the prescription volume can be difficult, especially in the setting of closely situated targets. However, we have found the Matryoshka method of imposing decreasing dose ceilings on increasing diameter concentric shells about the GTV⁴ to be effective. On occasion, an additional artificial tuning structure between two targets may be necessary to mitigate moderate isodose bridging that occurs when one target is eclipsed by another for a large portion of the arc path. This phenomenon, which only occurs in GK plans with very closely situated targets, is referred to as island-blocking.¹⁸

We believe our choice of the area under the DVH region in the 9–18 Gy (or any 50–100% isodose range) is an ideal substitute to the Paddick gradient index for comparing the dose fall-off between plans with disparate conformity. It is robust with respect to inter-plan differences of singular points within the DVH (e.g. $V_{18\text{Gy}}$, $V_{9\text{Gy}}$), and instead provides the planner a quantitative perspective of the entire range of fall-off in the important moderate – high isodose region. Further study is merited to validate this parameter as a meaningful predictor of SRS treatment toxicity.

Limitations

One limitation to our study was the comparison of VMAT plans with highly refined plan geometry and optimization schema to routine clinical GK plans that had previously been delivered without any particular exhortation to the physicists to generate the absolute best plan they could. Because we desired to know if we could replicate with VMAT the high plan quality we were already achieving with GK, this was an unavoidable consequence of the study design. Slight additional improvements to GK may therefore have been possible;

however, our institution's GK planning priorities already tend to emphasize conformity and fall-off over efficiency, so it is unlikely these gains would have been meaningful.

One other limitation of our study was that the Gamma Knife Perfexion was unavailable for our comparison. Perfexion delivers improvement in both irradiatable area and ease of planning and delivery over the Model C/4C. The ability of Perfexion to more easily use hybrid shots to tailor the shape of the dose cloud to eccentrically-shaped targets or in the vicinity of organs-at-risk is another advantage¹⁹ over its predecessor. However, its beam profile has been shown to be nearly identical to the Model C/4C^{20–22}, and indeed was a design feature. Therefore, in this study of mostly spherical targets we do not expect our use of the Model C instead of Perfexion had a meaningful dosimetric impact on the results of our comparison. Technical improvements also allow treatments to be more efficiently delivered on the Perfexion than the Model C/4C. In a prospective, randomized 200 patient comparison between the Perfexion and the Model 4C, Régis et al. found median time in treatment room to be reduced from 65 to 45 minutes.²² However, that improvement is still very modest when compared to the delivery efficiency of using 10MV FFF VMAT. Almost all such treatments can be delivered in less than 20 minutes, regardless of total gross tumor volume or number of tumors.

Conclusion

We found that VMAT can achieve clinically similar plan quality to GK plans that we have been delivering at substantially increased treatment efficiency, especially with a high-intensity linac. Across all clinically delivered Gamma Knife plans we studied, multi-arc VMAT rendered improved conformity, equivalent dose fall-off, equivalent moderate and low isodose spill, and equivalent mean dose for multiple metastasis treatments. For some, the single-isocenter VMAT approach may constitute an attractive substitute to multiple isocenter methods.

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Figure 1.
Arc Configurations.

Figure 2. Distribution of RTOG and Paddick conformity indices for individual targets and overall plans.

Figure 3.
Distributions of V4.5, V9, V12, and V18 levels for Gamma Knife and Multi-Arc VMAT.

Figure 4.
Distribution of Mean Brain Doses for Gamma Knife and Multi-Arc VMAT.

Figure 5.
Contour fit plot of the predictive effects of total GTV and tumor number upon 12 Gy Isodose Volume.

Figure 6.
 Example of dose-falloff (4 met case) as assessed by AUC-DVH in 9–18Gy (Left).
 Distributions of AUC-DVH9–18 for Gamma (Right).

Figure 7.
Intermodality comparison of beam-on and treatment time.

Figure 8.
Intermodality DVH Comparison for a 7 metastasis SRS treatment.

Figure 9.
Intermodality isodose curve comparisons for a) 9, b) 6, and c) 2 metastasis SRS treatment. (Left) Gamma Knife plan; (Right) Multi-Arc VMAT replan.

Table 1

Case and Target Demographics

Cases / Total targets treated	28/112		
Tumors per case	Range: 2 – 9	Median: 3	Mean: 4.0
Case target volume (cc)	Range: 0.23 – 19.56	Median: 3.72	Mean: 4.93
Individual target volume (cc)	Range: 0.0027 – 15.01	Median: 0.14	Mean: 1.22

Table 2

Descriptive Conformity Index Statistics

		Multi-Arc VMAT			Gamma Knife		
		Range	Median	Mean	Range	Median	Mean
Overall	RTOG	1.04–1.69	1.14	1.20	1.28–7.39	1.65	1.93
Plan	Paddick	0.58–0.94	0.86	0.83	0.34–0.77	0.59	0.57
Individual	RTOG	0.99–4.31	1.29	1.51	1.21–6.10	1.94	2.30
Target	Paddick	0.23–0.99	0.75	0.72	0.16–0.81	0.49	0.49