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Cyberknife Dosimetric Planning Using a Dose-Limiting Shell Method for Brain Metastases

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Objective : We investigated the effect of optimization in dose-limiting shell method on the dosimetric quality of CyberKnife (CK) plans in treating brain metastases (BMs).

Methods : We selected 19 BMs previously treated using CK between 2014 and 2015. The original CK plans ($CK_{original}$) had been produced using 1 to 3 dose-limiting shells : one at the prescription isodose level (PIDL) for dose conformity and the others at low-isodose levels (10–30% of prescription dose) for dose spillage. In each case, a modified CK plan ($CK_{modified}$) was generated using 5 dose-limiting shells : one at the PIDL, another at intermediate isodose level (50% of prescription dose) for steeper dose fall-off, and the others at low-isodose levels, with an optimized shell-dilation size based on our experience. A Gamma Knife (GK) plan was also produced using the original contour set. Thus, three data sets of dosimetric parameters were generated and compared.

Results : There were no differences in the conformity indices among the $CK_{original}$, $CK_{modified}$, and GK plans (mean 1.22, 1.18, and 1.24, respectively; p=0.079) and tumor coverage (mean 99.5%, 99.5%, and 99.4%, respectively; p=0.177), whereas the $CK_{modified}$ plans produced significantly smaller normal tissue volumes receiving 50% of prescription dose than those produced by the $CK_{original}$ plans (p<0.001), with no statistical differences in those volumes compared with GK plans (p=0.345).

Conclusion : These results indicate that significantly steeper dose fall-off is able to be achieved in the CK system by optimizing the shell function while maintaining high conformity of dose to tumor.

Key Words : Radiosurgery · Brain · Neoplasm metastasis.

INTRODUCTION

Stereotactic radiosurgery (SRS) delivers a highly focused ablative radiation dose to tumors to effectively control tumors with minimized radiation toxicity to surrounding normal tissues. When treating brain metastases (BMs), for which a marginal dose as high as ≥20 Gy is usually prescribed, the dose to surrounding normal tissues or tissue volumes receiving more

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than a certain threshold dose has been implicated in the development of radiation necrosis (RN)[1,2,11,14]. A quality SRS plan requires a dose fall-off as steep as possible outside the target and an optimal dose conformity to the target[15,21,22].

To evaluate the dose fall-off property of SRS, the dose gradient index (GI), which is the ratio of the isodose volume receiving 50% of the prescription dose (PD) to the prescription isodose volume (PIV), has been proposed and used[3,6,9,13,19,20,23,24]. Studies that compared GIs among SRS modalities demonstrated the Gamma Knife (GK; Elekta, Stockholm, Sweden) to be superior to other modalities such as the CyberKnife (CK; Accuray, Sunnyvale, CA, USA) and Novalis Tx (Varian Medical Systems, Palo Alto, CA, USA)[6,9,20,24]; these findings might be translated into clinical relevance regarding radiation toxicity.

To minimize the risks of radiation-induced toxicities such as RN, the concept of hypofractionated SRS has emerged and is reportedly effective and safe, particularly for treating large BMs[4,5,7,8,10,12,17,18]. Since 2011, we adopted this approach using the CK system for large lesions with diameters of >2.5 cm. In addition to a flexible fractionation delivery of SRS, CK allows an inverse planning system along with a number of beams up to 1500 either isocentric or non-isocentric that can be adjusted depending on the clinical situation. Among factors involved in the sequential optimization process in CK planning, a dose-limiting shell function is used to create virtual shell structures around or outside the target, which limit a certain threshold dose. In pursuit of high precision in target localization (dose conformity and tumor coverage) together with steep dose fall-off outside the target, we investigated the impact of optimization in dose-limiting shell function on the dosimetric quality of CK plans in treating BMs.

MATERIALS AND METHODS

The Institutional Review Board approved this retrospective study (IRB No. 2014-0574) and informed consent was waived because of the retrospective nature of the study. For this study, we selected 19 BMs from 19 patients (median age, 58 years; 12 women and seven men) who had been treated with SRS using CK (version 9.5; Accuray) at our institution between October 2014 and May 2015. Primary cancers originated from the lung (n=7), gastrointestinal tract (n=5), and breast (n=7). Tumor volume ranged from 2.1 cm^3 to 48.0 cm^3 (median, 11.1 cm^3). To achieve steeper dose fall-off in normal brain tissue outside the target, we recently modified our previous CK planning technique to introduce a more systematic application of dose-limiting shells. In this modified technique, shells were applied at prescription isodose level (PIDL) for dose conformity, at intermediate isodose level (50% of PD) for rapid dose fall-off, and at low-isodose levels (10–30% of PD) for dose spillage. Accordingly, a modified CK plan ($CK_{modified}$) was produced in each case and compared with the original CK plan ($CK_{original}$). In addition, a GK plan was also produced using the original contour set (DICOM RadioTherapy Structure Set) of each lesion transferred to the Elekta GammaPlan system (version 9.0; Elekta, Stockholm, Sweden). Thus, triplet data sets of dosimetric parameters for each lesion were generated and analyzed.

Original CK plans

All patients were immobilized by using a thermoplastic mesh mask. The planning computed tomography (CT) images (1.25-mm slice thickness) were fused with gadolinium-enhanced three-dimensional T1 magnetization-prepared rapid acquisition gradient echo magnetic resonance images (MRI; 1.5-mm slice) in the Accuray MultiPlan system (version 4.5; Accuray) to facilitate delineation of the gross tumor volume (GTV; equal to planning target volume) and critical organ structures, including the brainstem, eyes, and optic apparatus. The sequential optimization method was used to produce all CK plans with the planning objectives of GTV coverage (CO) >99%, conformity index (CI) <1.2, and treatment time <60 minutes. A median 31 Gy (range, 22–35) was prescribed at the tumor margin of a median 75% isodose level (range, 70–81%) normalized to the maximum dose in a single session (n=5; small tumors <2.5 cm) or five daily fraction treatment (n=14; large tumors >2.5 cm). One to three fixed collimators were selected to achieve a size 30–70% of the tumor diameter depending on the tumor size and shape. One to three dose-limiting shells were used at PIDL and at low-isodose levels. A ray-tracing algorithm was used for dose calculation.

Modified CK plans and GK plans

In each case, a $CK_{modified}$ and a GK plan were produced by using the identical planning CT/MRI and contour set of the lesion. In the $CK_{modified}$ plan, five dose-limiting shells were

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used: one at PIDL, another at intermediate isodose level (50% of PD), and the other three at low-isodose levels (each at 30%, 20%, and 10% of PD). An adequate shell size at each isodose level was estimated on the basis of our previous study on favorable dose fall-off profiles of GK relative to those of CK[3]. As shown in Fig. 1, the radial distance of a shell from the margin of the target at each isodose level was calculated according to the following equation.

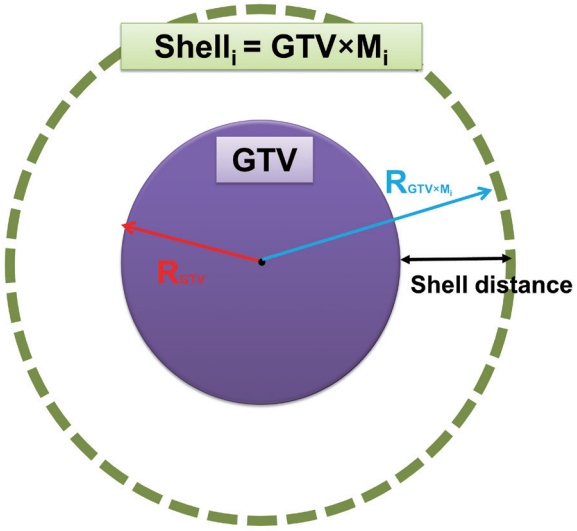

Fig. 1. A schematic representation of the relationship between the gross tumor volume (GTV) and dose-limiting shells. R_{GTV} is the equivalent spherical radius of the GTV, and $R_{GTV×Mi}$ is another equivalent spherical radius for an expanded volume of the GTV (shell$_i$) achieved by applying an empirically determined multiplication factor of M_i.

Distance of shell$_i$=$R_{GTV×Mi}$–R_{GTV}

Where R_{GTV} is the equivalent spherical radius of GTV, and $R_{GTV×M}$ is another equivalent spherical radius for an expanded volume of GTV (shell) by a multiplication factor of M that is empirically determined to achieve optimal dose conformity and dose fall-off. Table 1 presents the distances of shells from the GTV margin according to this equation. Note that an M value of 1.3 to 2 was used for shell1 at PIDL because a CI <1.2 was our planning objective. An M value of 3 was used for shell2 at 50% of PD because a steep dose gradient of GI <3 was pursued. To control low-isodose levels, M values of 8 to 13, 16 to 45, and 30 to 100 were used for shell3 at 30%, shell4 at 20%, and shell5 at 10% of PD, respectively.

GK plans were produced by adjustment of the sectors and collimators to achieve the same objectives (CO >99% and CI <1.2) as the CK planning while minimizing the dose to surrounding normal tissues. The PIDL was set to 50% of the maximum dose.

Comparison of dosimetric parameters and statistical analysis

In the triplet plans produced, the minimum, mean, and maximum doses in the target volume, CI, CO, homogeneity index (HI), GI50, GI25, $V12_{BED}$, and $V10_{BED}$ were calculated and compared. CI was defined as the ratio of the PIV to the volume of tumor receiving the PD or more. HI was defined as the ratio of the maximum dose to the PD. GI50 and GI25 were

Table 1. Dilation sizes of dose-limiting shells are listed according to the gross tumor volume

Gross tumor volume (mL)	Prescription isodose level		Intermediate isodose level		Low-isodose levels					
	Shell1* (mm)	M_1	Shell2* (mm)	M_2	Shell3* (mm)	M_3	Shell4* (mm)	M_4	Shell5* (mm)	M_5
<2	2.0	2.0	3.5	3.0	10.6	13.0	20.0	45.0	28.5	100.0
<3	2.1	1.9	4.0	3.0	12.1	13.0	21.7	40.0	30.4	85.0
<4	2.1	1.8	4.4	3.0	13.3	13.0	22.7	36.0	31.7	75.0
<5	2.1	1.7	4.7	3.0	13.7	12.0	23.4	33.0	32.0	65.0
<10	2.3	1.6	5.9	3.0	16.4	11.0	25.7	25.0	34.2	45.0
<15	2.2	1.5	6.8	3.0	17.7	10.0	26.9	21.0	37.0	40.0
<20	2.0	1.4	7.4	3.0	18.2	9.0	27.3	18.0	37.7	34.0
<30	2.0	1.4	8.5	3.0	19.3	8.0	30.3	17.0	40.6	30.0
<50	2.1	1.3	10.1	3.0	22.9	8.0	34.7	16.0	48.2	30.0

R_{GTV} is the equivalent spherical radius of the gross tumor volume ($R_{GTV} = \sqrt[3]{3×GTV/4\pi}$). $R_{GTV×Mi}$ is another equivalent spherical radius for an expanded volume of the GTV (shell$_i$) by a multiplication factor of M_i that is empirically determined as M_1=1.3 to 2.0, M_2=3, M_3=8 to 13, M_4=16 to 45, and M_5=30 to 100. *Shell$_i$ = $R_{GTV×Mi}$ – R_{GTV}

the ratios of the isodose volumes receiving 50% and 25% of PD, respectively, to PIV[5,17]. $V12_{BED}$ and $V10_{BED}$ were the tissue volumes receiving the biologically equivalent dose corresponding to 12 and 10 Gy or more in a single session (assuming a ssuming), respectively.

For detailed analysis of peripheral dose fall-off outside PIV, tissue volumes at multiple isodose levels from 90% to 10% of the PD were obtained and normalized to the PIV (relative tissue volume to PIV), and compared. Dosimetric data were analyzed using the paired t-test or the repeated measures analysis of variance (SPSS Statistics, version 22; IBM, Chicago, IL, USA). Significance levels were set as $p \leq 0.05$ for the paired t-test and $p \leq 0.05/3$ for the Bonferroni correction for multiple comparisons.

RESULTS

The treatment planning parameters and dosimetric indices for the $CK_{original}$, $CK_{modified}$, and GK plans are summarized in Table 2. Both CK plans used the same collimator (range, 1–3; median, 3) and prescription isodose level (range, 70–80%; mean, 74%). In the $CK_{original}$ and $CK_{modified}$ plans, the median numbers of shells used were 3 (range, 1–3) and 5 (range, 5–5), respectively ($p<0.001$). Since the number of beams (mean, 189 and 201; $p=0.158$) increased in $CK_{modified}$ plans as the number of shells was added, the treatment time (mean, 52 and 54; $p=0.304$) slightly increased, though there was no statistical significance.

The mean and maximum doses to GTV and HI were significantly higher in GK plans than those in both CK plans, whereas the minimum dose was significantly lower in GK (each $p<0.001$). In terms of precision in target localization, all three plans represented a high degree of dose conformity (CI=1.2±0.1) and tumor coverage (CO >99%), with no significant differences in these values among the plans, as shown in Table 2, Fig. 2A and B.

Regarding the dose to surrounding normal tissue, $CK_{modified}$ plans produced significantly lower values of GI50 and GI25 than those produced by $CK_{original}$ plans (each $p<0.001$), with no statistical differences in those values compared with GK plans ($p=0.345$ and $p=0.087$, respectively). Consistent with these, $V12_{BED}$ and $V10_{BED}$ were significantly smaller in $CK_{modified}$ plans than in $CK_{original}$ plan (each $p<0.001$), and these values

Table 2. Summary of the CyberKnife and Gamma Knife plan parameters (19 cases)

	1	2	3	Overall	Multiple comparisons†		
					1 vs. 2	1 vs. 3	2 vs. 3
	$CK_{original}$	$CK_{modified}$	GK	*p*-value*	*p*-value	*p*-value	*p*-value
Prescription isodose level (%)	73.89	73.89	50	NA	NA	NA	NA
Number of beams	189.6±43.5	201.1±56.9	NA	NA	0.158	NA	NA
Treatment time/fraction (minutes)	52.1±6.1	54.2±6.5	40.2±18	<0.001	0.304	<0.001	<0.001
D_{min} (Gy)	28.8±5.3	28.0±5.5	25.3±5.7	<0.001	<0.001	<0.001	<0.001
D_{mean} (Gy)	35.1±6.0	36.51±6.0	43.4±7.7	<0.001	<0.001	<0.001	<0.001
D_{max} (Gy)	41.1±6.7	41.3±6.6	60.9±1.1	<0.001	0.310	<0.001	<0.001
HI	1.4±0.1	1.4±0.1	2.0±0.0	<0.001	0.563	<0.001	<0.001
CI	1.22±0.1	1.18±0.1	1.24±0.1	0.079	0.064	0.407	0.061
CO	99.5±0.4	99.5±0.3	99.4±0.2	0.177	0.636	0.199	0.018
GI50	3.5±0.3	2.7±1.2	2.7±0.2	<0.001	<0.001	<0.001	0.345
GI25	9.3±1.6	7.7±1.2	7.4±1.1	<0.001	<0.001	<0.001	0.087
$V12_{BED}$‡	49.1±40.0	38.3±34.0	39.8±33.9	<0.001	<0.001	<0.001	0.030
$V10_{BED}$‡	65.2±52.8	51.7±47.1	53.6±45.7	<0.001	<0.001	<0.001	0.053

Values are presented as mean±standard deviation. *Statistical significance, $p<0.05$. †Bonferroni-corrected statistical significance, $p<0.0167$ (=0.05/3). ‡$V12_{BED}$ and $V10_{BED}$ volumes receiving the biologically equivalent dose corresponding to 12 and 10 Gy or more in a single session (assuming an lumes 10), respectively. $CK_{original}$: original CyberKnife plan, $CK_{modified}$: modified CyberKnife plan, GK : Gamma Knife plan, NA : not applicable, D_{min} : the minimum dose, D_{mean} : mean dose, D_{max} : maximum dose, HI : homogeneity index, CI : conformity index, CO : tumor coverage, GI : gradient index

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were even slightly smaller in $CK_{modified}$ plans than in GK plans, with significant or marginally significant differences (p=0.030 and p=0.053, respectively) (Table 2). Fig. 2C shows that these results are independent of tumor size. A representative case of optimized dose fall-off using the modified CK planning technique is illustrated in Fig. 3.

To evaluate the peripheral dose fall-off in more detail, relative tissue volumes to the PIV at multiple isodose levels from 90% to 10% of PD were calculated and analyzed using a linear mixed model (Table 3). At all isodose levels except at 10%, the relative tissue volumes were significantly smaller in $CK_{modified}$ plans than in the $CK_{original}$, while no statistical differences in these volumes were observed between $CK_{modified}$ plans and GK plans except at 90% isodose level.

DISCUSSION

GK is the "gold standard" intracranial SRS modality, whereas CK is a relatively new one featuring a frameless and image-guided robotic system enabling a more flexible fractionation delivery of SRS as well as extracranial applications. Recently, a new model of Gamma Knife Icon™, which also provides frameless SRS solution using cone beam CT-based image guidance, has been available[25]. As a comprehensive SRS center, our institution has been treating BMs by using either GK for single-session SRS or CK for hypofractionated SRS according to tumor size and location. The GK system, with its unique single- or multiple-isocentric dosimetric technique using 192 Cobalt-60 sources fixed and arranged around the target, is renowned for stably delivering a high-quality SRS of very steep dose

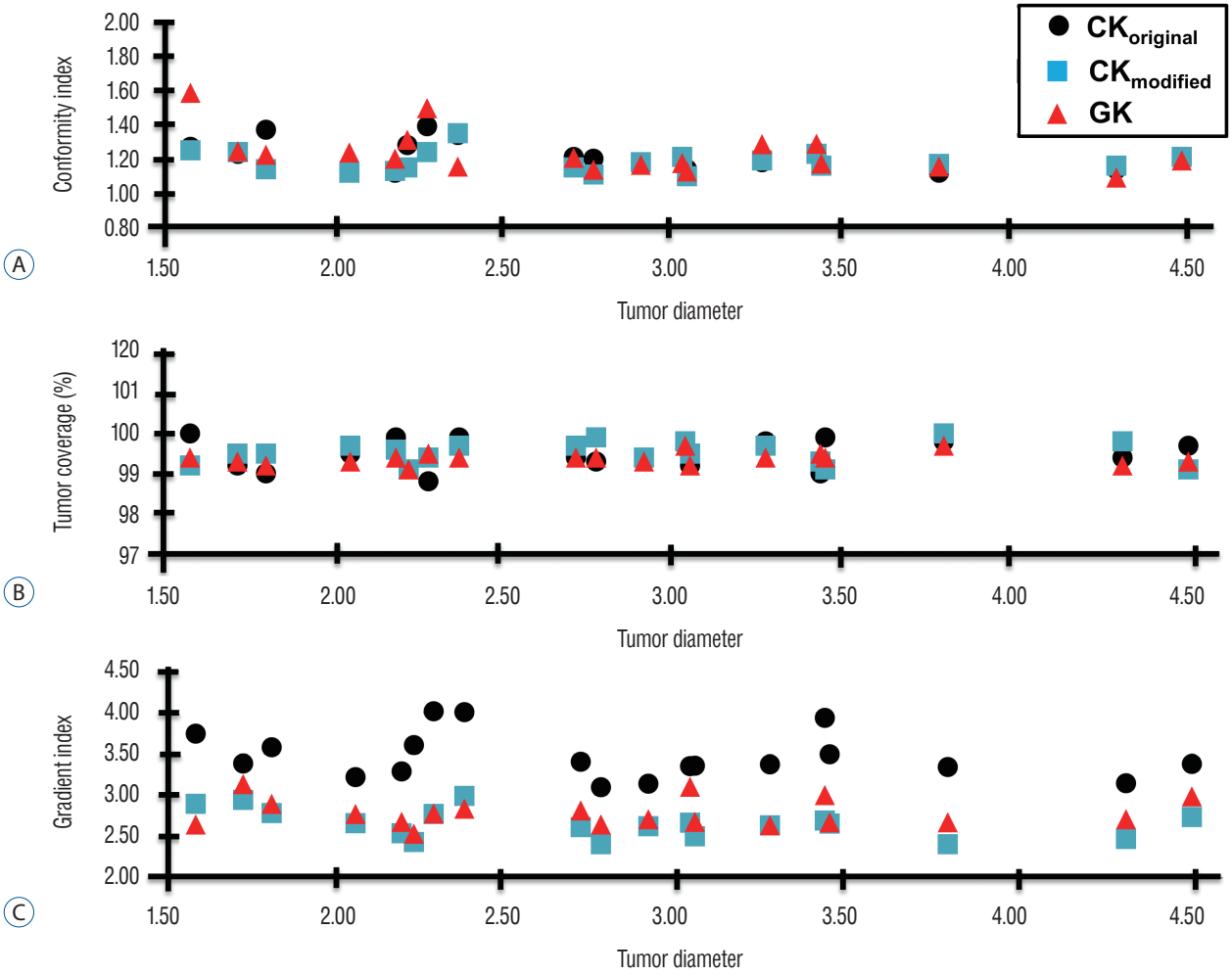

Fig. 2. Comparison of dosimetric indices plotted against tumor diameters in all 19 cases. Each black circle, blue square, and red triangle represents the value in the $CK_{original}$, $CK_{modified}$, and GK plan, in terms of the conformity index (A), tumor coverage (B), and gradient index (C). $CK_{original}$: original CyberKnife plan, $CK_{modified}$: modified CyberKnife plan, GK : Gamma Knife plan.

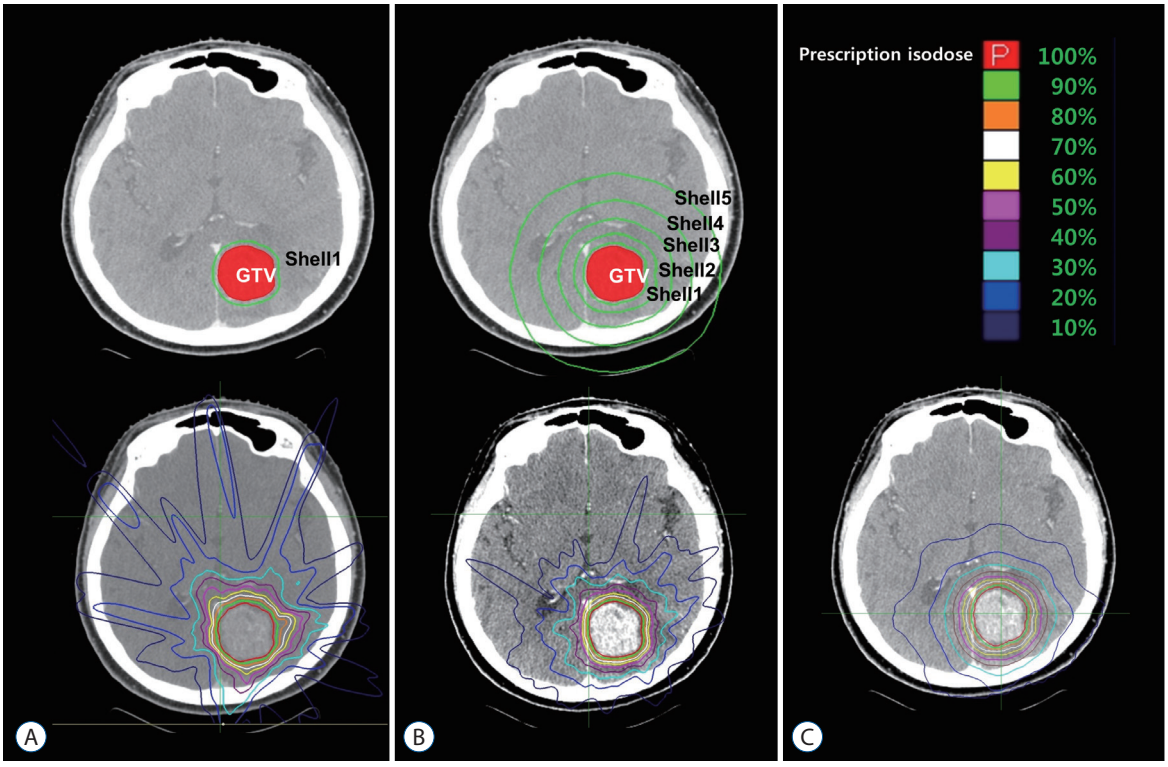

Fig. 3. A representative case of optimized dose fall-off when using the modified CK planning technique. In the original CK plan (A), a single sh ll (green line) with a distance of 3 mm from the margin of the tumor volume (shaded in red; 14.8 cm^3 in this case) was used (top). The multiple isodose lines presented in the planned dosimetric image (bottom). The isodose lines represent the percentage of the prescription dose. In the modified CK plan (B), 5 shells with distances of 2, 7, 18, 28, and 38 mm from the tumor margin were introduced and used (top). Note that the isodose lines are arranged more compactly in the planned image (bottom) than in the original plan. The value of the gradient index 3.4 in the original plan decreased to 2.5 in the modified plan in this case. In the GK plan (C), the value of the gradient index was 2.6. GTV : gross tumor volume, CK : CyberKnife.

Table 3. Comparison of peripheral dose fall-off among the CyberKnife and Gamma Knife plans

Volumes* at percent of the prescription dose	1	2	3	Overall	Multiple comparisons		
					1 vs. 2	1 vs. 3	2 vs. 3
	$CK_{original}$	$CK_{modified}$	GK	*p*-value†	*p*-value†	*p*-value†	*p*-value†
100	1	1	1	NA	NA	NA	NA
90	1.35±0.0	1.22±0.0	1.19±0.0	<0.001	<0.001	<0.001	0.008
80	1.73±0.0	1.45±0.0	1.43±0.0	<0.001	<0.001	<0.001	0.369
70	2.16±0.0	1.73±0.0	1.72±0.0	<0.001	<0.001	<0.001	0.707
60	2.71±0.0	2.10±0.0	2.15±0.0	<0.001	<0.001	<0.001	0.236
50	3.46±0.1	2.65±0.1	2.72±0.1	<0.001	<0.001	<0.001	0.345
40	4.65±0.1	3.67±0.1	3.76±0.1	<0.001	<0.001	<0.001	0.435
30	6.96±0.2	5.74±0.2	5.68±0.2	<0.001	<0.001	<0.001	0.823
20	13.44±0.6	11.27±0.6	10.51±0.6	0.002	0.012	<0.001	0.364
10	40.12±3.0	42.31±3.0	25.49±3.0	<0.001	0.115	<0.001	<0.001

Values are presented as mean±standard error. *Relative tissue volumes to the prescription isodose volume at isodose levels from 90% to 10% of the prescription dose. †Linear mixed model. $CK_{original}$: original CyberKnife plan, $CK_{modified}$: modified CyberKnife plan, GK : Gamma Knife plan, NA : not applicable

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fall-off as well as high precision in target localization. Studies comparing dosimetric quality among SRS modalities generally support the superiority of GK to other systems[3,6,9,20,24], although competing data are also available[13,23]. In treating BMs, especially in large tumors >2.5 cm, dosimetric steepness outside the target and geometric accuracy for target localization should be optimized to minimize the potential risks of RN. In this regard, we introduced a systematic application of the shell function provided by the CK system and improved our CK plan quality, which has been shown to be comparable at least to GK.

Five shells with their specific purpose were introduced outside the target : the first one at PIDL to optimize dose conformity, the second at 50% of PD to steepen dose fall-off in normal tissue, and the remaining three to control dose spillage in low-isodose area. The distance of shells from the tumor margin was inversely calculated from the preferable output values of CI and GIs at isodose lines 50%, 30%, 20%, and 10% of PD, in reference to our previous GK and CK dosimetric data in BMs[3].

In accordance with our planning objectives of CO >99% and CI <1.2, all of our original and modified CK and GK plans were able to produce comparably high conformity of dose to tumor, Several previous studies[3,6,9,13,24] have reported consistent results with ours, although others reported inconsistent data[20,23]. We actually believe that high precision in target localization depends on the physician's policy and the planning physicist's expertise rather than on the SRS machines. On the other hand, in terms of dose fall-off properties, our previous CK plans produced significantly inferior results to GK at all isodose levels. This finding may be explained, in part, by the use of numerous non-isocentric beams to construct SRS by the CK system. However, our results from the modified CK planning technique, showed a sufficient compensation for dose fall-off by optimization of the shell function. As shown in Table 2 and Fig. 2, $CK_{modified}$ plans achieved comparable values of GI50 and GI25 to GK plans while maintaining high conformity and dose coverage to tumor. Furthermore, $V12_{BED}$ and $V10_{BED}$, which were reported to be significantly associated with the development of RN[1,2,16], have been shown to be slightly smaller in $CK_{modified}$ plans than in GK plans. We speculate that an "isocentricity," that is, the degree of the use of cross-firing isocentric beams of CK plans, may have been increased by introducing multiple dose-limiting shells outside the target, thereby resulting in steeper dose fall-off in normal brain tissue. Based on these results, our technique may enhance the safety of SRS in treating BMs, especially in large tumors, which needs to be further validated.

One potential trade-off of our modified CK planning technique is an increased number of beams used with strict application of dose-limiting shells outside the target, possibly resulting in an increased treatment time. Actually, the average percent increases in the number of beams and treatment time were 5.9% and 4.1%, respectively in our $CK_{modified}$ plans, but the differences were not statistically significant, and treatment times <60 minutes are considered clinically feasible. In addition, the increased number of beams seems to affect dose control for low-isodose area less than 10% of PD (Table 3), but there was no statistical difference.

CONCLUSION

Our current study indicates that significantly steeper dose fall-off is able to be achieved using the CK system by optimization of the dose-limiting shell function while maintaining high conformity and dose coverage to tumor. The quality of CK plans produced in this way appears to be comparable at least to that of GK in terms of these parameters.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in this study.

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