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Dosimetric comparison of hypofractionated stereotactic radiotherapy by three different modalities for benign skull base tumors adjacent to functioning optic pathways

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► ***Original article***

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ABSTRACT

Background*:** As the optic pathways are thought to be the structures most vulnerable to irradiation, skull base tumors involving them are especially challenging to treat. Stereotactic radiosurgery (SRS) / stereotactic radiotherapy (SRT) is an effective and safe option for the treatment of them. Characteristics of dosimetry of SRT for skull base tumors by Gamma Knife were evaluated in comparison with those by other modalities. ***Materials and Methods*:** Original Novalis (NV) multi-beam-intensity-modulated-SRT(MB-IM-SRT) plan and additional simulation plans of Gamma Knife (GK) and TomoTherapy (TT) were compared in 20 cases. For target covering, 95% dose was assigned for 95% of the planning target volume (PTV) (D[95%]=28.5 Gy / 5 fractions). Conformity index (CI), homogeneity index (HI=D95% / maximum dose of PTV)), gradient index (GI=V[47.5% dose] / V[95% dose] of body), and the doses to organs at risk (OARs) were evaluated. ***Results: CI and GI were significantly better with GK than NV or TT. HI was significantly smaller (less homogeneous) with GK. D[1 ml] and V[20 Gy] of brainstem were significantly smaller with GK than NV or TT. V[20Gy] of whole brain was also significantly smaller with GK. D[0.1 ml] and V[20 Gy] of optic pathways were smaller with GK than NV or TT, though the differences did not reach statistical significance. ***Conclusion:*** If a higher internal dose gradient is interpreted as an advantage for tumor ablation, GK SRT might be expected to be a more effective and safer treatment for skull base benign tumors adjacent to the optic pathways and brainstem when they are not large.

Keywords: *Skull base, benign tumor, radiosurgery, IMRT, optic nerve.*

INTRODUCTION

Stereotactic radiosurgery (SRS) / stereotactic radiotherapy (SRT) is an effective and safe option for the treatment of benign brain tumors [1-4], if the tumor is not large. Whether SRS/SRT can be performed safely will depend on the desired dose being administered to the tumor margin, and simultaneously an acceptable dose administered to the organs at risk (OARs) such as optic pathways and brainstem. Fractionated SRT, compared with single session SRS, has a radiobiological advantage for the protection of surrounding normal structures [4,5]. During SRT using linear accelerator (LINAC)-based SRT machines including Novalis (NV, BrainLAB, Tokyo) [6], TomoTherapy (TT, Accuray, Tokyo), and CyberKnife (CK, Accuray, Tokyo) relocatable thermoplastic head shells are used for patient fixation. On the other hand, though initially only

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an invasive stereotactic skull frame or Leksell G-frame (Elekta, Tokyo) was available during Gamma Knife (GK) SRS, Perfexion (PFX) [7], a recent version of GK, has enabled SRT using the Extend system (Elekta, Tokyo), a repositioning rigid frame using a mouth-piece system [8-10], or with a thermoplastic head shell under the latest generation Icon system (Elekta, Sweden) equipped with cone-beam computed tomography (CT) [11]. In GK we can actually freely place multiple isocenters to shape up the dose distribution and concentrate the prescription dose on the target while simultaneously reducing the dose to the OARs. As shown in most formerly published studies, GK provides better conformity and an excellent dose gradient [12], while showing less homogeneity, which may be an advantage for tumor ablation as well [13]. In this study we made simulation plans for GK in the cases treated actually by NV multi-beam (MB) intensity-modulated (IM)-SRT. In addition, simulation plans for helical TT were also made. SRT plans of three modalities for benign skull base tumors involving 'functioning' optic pathways were compared from the viewpoint of not only covering the target but also sparing the OARs. The aim of this study was to clarify the characteristics of Gamma Knife with unique radiation delivery system cobalt60 resources in skull base tumor SRT.

MATERIALS AND METHODS

This study was approved by Ethics Committee of Aichi Medical University (No. 13-142, approved on March 11th, 2014), Clinical Research Committee of Nagoya Kyoritsu Hospital (No. K062-01, on April 18th, 2014), and Nagoya City University Graduate School of Medical Sciences and Nagoya City University Hospital Institutional Review Board (No. 60-17-0007, on July 10th, 2017). Informed consent was waived. All 20 cases with skull base tumors of various volumes involving optic pathways had been clinically treated by NV IM-SRT in Nagoya Radiosurgery Center, Nagoya Kyoritsu Hospital from July, 2011 through April, 2014. NV SRT plans were made on the iPlan (BrainLAB, Tokyo) version 4.1 workstation originally and were used for actual patient treatment. The same CT image data and structure sets, including planning target volume (PTV), gross tumor volume (GTV) and OARs that were used for NV treatment, were transferred to the Leksell GammaPlan (LGP) version 10.1.1 treatment-planning workstation (Elekta, Tokyo) via a DICOM-RT [digital imaging and communications in medicine-radiation therapy] protocol from the iPlan treatment planning workstation. Multi-isocenter GK PFX plans were made. In addition, for helical TT SRT planning the same CT image data and structure sets were transferred to a Pinnacle3 workstation (Varian, Tokyo) and then TomoTherapy Planning Station version 4.1.2.2 workstation (Accuray, Tokyo). In this way, three plans, original NV SRT plan, a simulation GK PFX plan, and a simulation TT SRT plan, could be compared.

Patients

The criterion for selection was the presence of benign skull base tumors involving the optic pathways in patients with at least partial visual function in both sides of the visual fields in both eyes. In every case, the tumor was attached at least in part to the optic pathways. The diagnosis was pituitary adenoma in three patients, craniopharyngioma in eight, and skull base meningioma in nine tables 1 and 2 list the characteristics of the patients and tumors. The volumes of objects are listed in table 3.

Imaging protocol

The treatment-planning images were acquired with magnetic resonance imaging (MRI) using a 1.5-Tesla or 3.0-Tesla scanner (Signa Echo Speed Plus 1.5 T, Signa HDxt 3.0 T; GE Healthcare, Tokyo) and 4-detector CT (Light Speed Plus; GE Healthcare, Tokyo). CT images were used as the references for dose calculation in the treatment planning. CT image resolution of 512 × 512 pixels in the axial plane and slice thickness of 1.25 mm were adopted. To determine GTV (=CTV [clinical target volume]),

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contrast-enhanced CT and MRI were acquired. Conditions for non-contrast and contrast-enhanced CT were the same except for the size of the field of view. The slice thickness of MRI was specified as 1 - 2 mm, depending on the tumor size, by 3D-SPGR [3-dimensional-spoiled gradient-recalled acquisition in the steady state] sequence with gadolinium (Gd) enhancement and 3D fast spin echo.

NV treatment planning

The PTV margin was determined to be 2 mm. When the CTV was in close contact with OARs, the PTV margin was adjusted manually to avoid overlap of the PTV and OAR (PTV were modified manually). NV equipped with a micro-multileaf collimator (mMLC) with 3-mm thick leaves was used. The method of SRS/SRT with the NV system has been described previously [4, 5]. The targets were covered with a >95% isodose level. The PTV ranged from 1.1 - 93.6 ml (median, 21.4 ml). The algorithm of dose calculation in iPlan RT dose version 4.1.2 software was the pencil beam method. Dosing for all patients was planned with a single isocenter coplanar MB-IM-SRT by radiation oncologists and neurosurgeons. Parameter evaluation of the dose-volume histogram (DVH) was performed considering target coverage and the dose limitation for OARs. In the IM-SRT optimization process, tolerance doses for each OAR were converted according to a linear quadratic model, for example, less than 50 Gy in a 2 Gy per fraction (fx.) regime for optic pathways (alpha beta ratio of 2 Gy). The patients underwent IM-SRT with 6-MV photon beams clinically actually in 14 - 19 (median 18) fx. to a total dose of 40 - 47.5 (median 45) Gy (at 100% isodose = at normalization point) over 3 - 4 weeks. In this study the prescription dose was changed to 30 Gy / 5 fx. (at 100% isodose = at normalization point). No attempt was made to improve the original NV plans used in this study. Prescription dose to PTV D95 was 28.5 Gy / 5 fx. (95% dose), which was actually 28.50 - 28.95 Gy (mean, 28.71 Gy; median, 28.76 Gy). The IM-SRT treatment times were estimated for a dose rate of 320 monitor units/min, calculated in log files of patient management software for treatment.

GK PFX planning

The dose algorithm, available in LGP software is a simple tissue maximum ratio (TMR) 10 method employing the measurement-based dose calculation by replacing all anatomical structures with water-equivalent material [7]. During multi-isocenter (4mm-, 8mm-, and 16 mm-collimator) planning in each case, we intended to cover 95% of PTV with PTV margin of 2 mm with an isodose of between 45% and 55%, while simultaneously covering 99% of GTV (=CTV) with a 100% dose (30 Gy) whenever possible. The OARs were spared to the extent possible even when adjacent to the target. The treatment times with GK PFX SRT were also estimated using a dose rate of 2.722 Gy / min for ^{60}Cobalt, calculated by LGP.

TT planning

Parameters were set as follows; pitch was 0.215, field width 1.05, and modulation factor 2.6 for all cases. The dose calculation algorithm in TT Planning Station was the single polyenergetic superposition method.

Dosimetric analysis

The conformity index (CI) was defined as:
RTOG [Radiation Therapy Oncology Group] CI=PIV/PTV [14], where the volume of the prescription isodose volume (PIV) was divided by the PTV.
In addition, Paddick CI [15] was evaluated.
Paddick CI=$(TVPIV)^2/(PTV\times PIV)$, where TVPIV was the target volume covered by PIV.

The gradient index was calculated with the formula:
GI=PIVhalf/PIV [16], where PIVhalf was Prescription isodose volume, at half the prescription isodose.
Actually, GI = Volume of 47.5% isodose (half the prescribed dose) / Volume of 95% isodose (prescribed dose)

The homogeneity index (HI) was calculated with the formulas:
DHI (dose HI) = D95% (prescribed dose) / Dmax (maximum dose) and
mDHI (moderate dose HI) =D95% / D5% [17].

Dose of OARs was evaluated with the indices

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as follows:
D[0.1 ml] for optic pathways and lenses, D[1 ml] for eyes, brainstem and whole brain, and V[20 Gy] (volume receiving 20 Gy) of optic pathways, brainstem, and whole brain.

Collected dosimetry data were analyzed using R version 2.14.2 (The R Foundation for Statistical Computing). The Wilcoxon signed rank test was used to examine differences between indices of the treatment plans of the 3 modalities. Differences with $P < 0.05$ were regarded as significant.

Table 1. Case Characteristics.

Diagnosis
Pituitary adenoma (n=3)
Male / Female = 2 / 1, Age 28 – 67 (mean 46.3) years
Visual disturbance:
Incomplete bitemporal homonymous hemianopsia in Case 2
Other cranial nerve impairment:
None
Craniopharyngioma (n=8)
Male / Female = 3 / 5, Age 21 – 79 (mean 42.6) years
Visual disturbance:
Blurred vision in the right eye in Case 10
Other cranial nerve impairment:
None
Meningioma (n=9)
Male / Female = 1 / 8, Age 31 – 80 (mean 56.9) years
Visual disturbance:
Central scotoma enlargement in the left eye in Case 16
Left upper homonymous quadrianopsia in Case 18
Incomplete medial hemianopsia in Case 20
Other cranial nerve impairment:
Left abducens in Case 12
Right trigeminal in Case 14, 15, & 17
Left oculomotor in Case 20

Table 2. Characteristics of 20 tumors.

Diagnosis
Pituitary adenoma (n=3) (PTV 4.0 – 32.4 ml, mean 17.1 ml)
1 sellar,
2 sellar + extrasellar invasion
Craniopharyngioma (n=8) (PTV 1.1 – 24.6 ml, mean 10.7 ml)
3 sellar
5 suprasellar
Meningioma (n=9) (PTV 8.6 – 93.6 ml, mean 46.7 ml)
2 sellar+cavernous sinus
2 cavernous sinus
2 middle fossa
3 sphenoid ridge
Prior treatment:
1 open biopsy
19 resection (1 – 3 times)
1 EBRT (40 Gy)
Visual function:
15 normal
5 partial impairment
Involved portions of visual pathways
8 unilateral optic pathway
12 bilateral optic pathways
(11 brainstem involvement)

PTV = planning target volume
EBRT = conventional external-beam radiation therapy

Table 3. Volume of the targets and OARs.

Volume of targets	**Mean ±SD (ml)**
PTV	27.8 ± 24.4
GTV (=CTV)	17.1 ±16.4
Volume of OARs	**Mean ±SD (ml)**
Brainstem	30.5 ± 4.7
Normal brain*	1303.7 ± 115.6
Optic pathways	2.55 ± 0.56
Left eye	10.2 ± 3.1
Right eye	9.9 ± 2.3
Left lens	0.55 ± 0.32
Right lens	0.53 ± 0.30
Body (Head)	4041.4 ± 754.9

SD = standard deviation, PTV = planning target volume, GTV = gross tumor volume, CTV = clinical target volume, OAR = organ at risk, *Normal brain includes brainstem

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RESULTS

Treatment parameters of NV MB-IM-SRT, GK PFX SRT, and helical TT SRT were shown in table 4. The number of isocenters in GK plan was 12 to 39 (median, 22.5; mean 24.6). Treatment indices and statistical analysis of each index among NV, GK, and TT were shown in table 5. The mean of D95 was actually 28.71 Gy, 28.50 Gy, and 28.75 Gy in NV, GK, and TT respectively on average. CI and GI were significantly smaller (better) with GK than with NV or TT. RTOG CI was good, between 1.0 and 2.0, in all NV and GK cases. RTOG CI was greater than 2.0 (not good) in four TT cases, and between 1.0 and 2.0 in the other 16 TT cases. Paddick's CI was significantly larger (better) with GK than with NV or TT. The HI was significantly smaller (less homogeneous) with GK than with NV or TT.

D[1 ml] and V[20 Gy] of brainstem were significantly smaller with GK than with NV or TT. V[20Gy] of whole brain was also significantly smaller with GK than NV or TT. D [0.1 ml] and V[20 Gy] of optic pathways were smaller with GK than NV or TT, though the differences were not statistically significant. D[1 ml] of eye and D[0.1 ml] of lens were small, less than 10 Gy on average, with all three modalities. D[0.1 ml] of lens with NV was significantly smaller than with GK and TT.

D[0.1 ml] and V[20 Gy] of optic pathways in each case were listed in table 6. D[0.1 ml] of optic pathways was the smallest with GK in 11 cases, and V[20 Gy] was the smallest with GK in 12 cases. In eight of nine tumors with a volume of less than 15 ml in PTV, GK showed the smallest D[0.1 ml] of optic pathways, while of 11 large tumors with a volume of more than 15 ml NV showed the smallest value in 4 and TT in 4. D [0.1 ml] of optic pathways exceeded 25 Gy in 9 cases with NV, in 5 with GK, and 4 with TT. The maximum of D[0.1 ml] of optic pathways was 27.9 Gy in Case 6 with NV. It was 26.2 Gy in Case 10 with GK and 27.3 Gy in Case 18 with TT.

Illustrative case

Figure 1 showed dose planning on images of a case with skull base meningioma. In this study the dose distribution was recalculated with 100% dose of 30 Gy / 5 fx.) figure 1A). In addition, simulation plans by LGP for GK PFX (Fig 1B) and TT Planning Station for helical TT (figure 1C) were made. Figure 1B of GK shows the tumor attached to the right optic nerves and chiasm. Figure 1D shows an additional little upper section of GK, where the tumor attached to the right optic tract and was close to the brainstem. Figure 1B and 1D show that with GK the optic pathways were well spared from the high dose, while the low dose distribution was tight with GK, with a steep fall-off noted around the target. Figure 1C shows spread of the low dose to a rather broad area in TT. Figure 1A shows the low dose distribution along the beam trajectories in NV MB-IM-SRT. The optic pathways were spared a high dose distribution with each of the modalities.

Dose volume histograms (DVHs) of PTV (figure 2A), GTV (figure 2B) show high dose distribution inside the target in GK. DVHs of brainstem (figure 2C), and right optic nerve (figure 2D) show a little more dose sparing in GK, comparing with NV and TT, around a high dose distribution.

Table 4. Treatment parameters of NV IM-SRT, GK PFX SRT, and helical TT SRT.

NV MB-IM-SRT	
No. of beams (coplanar)	5 – 7 (median 5)
Beam on time / fx. (min.)	2.8 – 8.2 (mean 5.5)
GK PFX SRT	
Margin % isodose	45 – 54 (median 49)
No. of shots	12 – 39 (median 22.5)
Beam on time / fx. (min.)	15.2 – 51.4 (mean 26.4)
TT SRT	
Modulation factor	1.8 – 2.4 (mean 2.2)
Beam on time / fx. (min.)	8.8 – 18.6 (mean 12.8)

MB = multi-beam, IM = intensity-modulated, SRT = stereotactic radiotherapy, NV = Novalis, GK = Gamma Knife, PFX = Perfexion, TT = TomoTherapy, fx. = fraction

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Table 5. Radiotherapy indices of NV MB-IM-SRT, GK PFX SRT, and TT-SRT.

Parameters	NV	GK	TT
PTV D[95%] (Gy)	28.71 + 0.12	28.50	28.75 + 0.35
PTV mean dose (Gy)	29.50 + 0.50	38.25 + 1.12	31.82 + 1.39
GTV D[99%] (Gy)	27.86 + 1.26	32.14 + 1.08	27.59 + 1.03
CI (RTOG)	1.32 + 0.17	1.11 + 0.04	1.78 + 0.38
CI (Paddick)	0.70 + 0.08	0.82 + 0.03	0.53 + 0.10
DHI (D[95%]/Dmax.)	0.91 + 0.80	0.49 + 0.45	0.83 + 0.75
mDHI (D[95%]/D[5%])	0.94 + 0.01	0.58 + 0.03	0.84 + 0.04
GI (V[half PresD]/V[PresD])	4.38 + 0.66	3.48 + 1.43	4.17 + 0.62
Brainstem D[1 ml] (Gy)	18.1 + 6.1	14.6 + 6.3	20.0 + 4.4
Brainstem V[20 Gy] (ml)	1.90 + 3.02	0.72 + 1.18	1.56 + 1.78
Normal brain* V[20 Gy] (ml)	14.04 + 12.56	4.51 + 4.15	18.06 + 12.69
Body V[20 Gy] (ml)	76.4 + 64.8	51.7 + 44.6	117.3 + 113.4
OP D[0.1 ml] (Gy)	24.0 + 2.5	22.8 + 3.6	23.5 + 2.4
OP V[20 Gy] (ml)	0.56 + 0.32	0.46 + 0.26	0.52 + 0.44
Eye** D[1 ml] (Gy)	6.4 + 4.0	6.4 + 5.6	8.9 + 4.2
Lens** D[0.1 ml] (Gy)	2.0 + 1.2	4.1 + 3.7	4.4 + 3.8
Parameters	**GK-NV**	**GK-TT**	**NV-TT**
PTV mean dose (Gy)	p<0.001	p<0.001	p<0.001
GTV D[99%] (Gy)	p<0.001	p<0.001	p=0.596
CI (RTOG)	p<0.001	p<0.001	p<0.001
CI (Paddick)	p<0.001	p<0.001	p<0.001
DHI (D[95%]/Dmax.)	p<0.001	p<0.001	p<0.001
mDHI (D[95%]/D[5%])	p<0.001	p<0.001	p<0.001
GI (V[half PresD]/V[PresD])	p<0.001	p<0.001	p=0.151
Brainstem D[1 ml] (Gy)	p<0.001	p<0.001	p=0.696
Brainstem V[20 Gy] (ml)	p<0.001	p<0.001	p=0.712
Normal brain* V[20 Gy] (ml)	p<0.001	p<0.001	p<0.001
Body V[20 Gy] (ml)	p<0.001	p<0.001	p<0.001
OP D[0.1 ml] (Gy)	p=0.145	p=0.404	p=0.165
OP V[20 Gy] (ml)	p=0.097	p=0.870	p=0.025
Eye** D[1 ml] (Gy)	p=0.648	p<0.001	p<0.001
Lens** D[0.1 ml] (Gy)	p=0.001	p=0.202	p<0.001

CI = conformity index,
HI = dose homogeneity index,
mDHI = moderate DHI,
GI = gradient index,
OP = optic pathways
underline: statistically significant,
*Normal brain includes brainstem,
**Either eye or lens receiving greater radiation dose

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Table 6. D[0.1 ml] and V[20 Gy] of optic pathways.

Case	Dx	Volume (ml)		D[0.1 ml] of OP (Gy)			V[20 Gy] of OP (ml)		
		PTV	GTV	NV	GK	TT	NV	GK	TT
1	PA	14.9	8.3	24.18	25.0	24.22	0.81	0.42	0.64
2	PA	4.0	1.8	20.2	11.4	17.5	0.30	0.08	0.23
3	PA	32.4	19.5	17.5	19.5	19.3	0.11	0.17	0.12
4	CP	14.8	8.4	24.5	23.3	24.4	0.35	0.20	0.31
5	CP	1.1	0.3	22.6	17.5	23.4	0.37	0.09	0.35
6	CP	8.3	3.0	27.9	25.9	26.3	0.88	0.46	0.75
7	CP	2.3	1.0	26.1	19.2	24.7	0.58	0.24	0.57
8	CP	24.6	17.4	27.3	26.1	24.7	1.33	0.97	0.96
9	CP	23.1	14.3	26.0	24.5	25.0	1.15	0.77	0.88
10	CP	7.0	3.4	26.2	23.9	25.8	0.62	0.43	0.70
11	CP	4.1	1.9	26.0	23.3	25.2	0.78	0.42	2.15
12	MG	19.7	11.0	25.1	23.5	24.8	0.59	0.40	0.52
13	MG	60.7	38.7	21.0	23.5	25.0	0.240	0.52	0.241
14	MG	60.7	40.9	24.6	25.0	21.2	0.71	0.56	0.22
15	MG	42.2	22.6	24.6	24.2	22.2	0.800	0.804	0.37
16	MG	34.6	22.3	23.2	26.1	23.8	0.46	0.61	0.32
17	MG	55.3	33.6	25.2	26.2	22.7	0.44	0.89	0.28
18	MG	8.6	4.2	25.7	24.4	27.3	0.41	0.36	0.48
19	MG	93.6	63.3	21.6	24.4	21.8	0.21	0.58	0.19
20	MG	44.9	26.4	21.4	19.0	21.0	0.17	0.13	0.17
mean		27.8	17.1	24.0	22.8	23.5	0.56	0.46	0.52

Dx=diagnosis
PA=pituitary adenoma, CP=craniopharyngioma, MG=meningioma
PTV=planned target volume, GTV=gross tumor volume
NV=Novalis, GK= Gamma Knife, TT=TomoTherapy
underline: the smallest value among 3 modalities

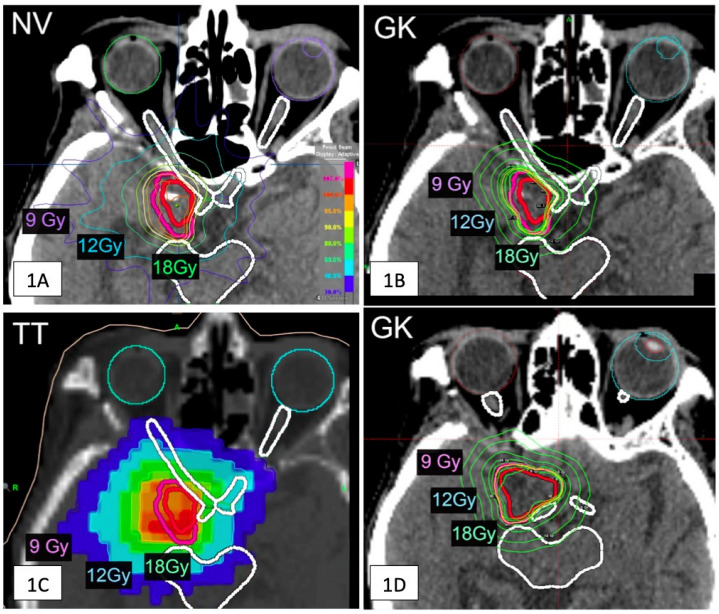


Figure 1. Case 18. Residual sphenoid ridge meningioma. Dose distribution of Novalis iPlan (**1A**), Gamma Knife GammaPlan (**1B**), and TomoTherapy Planning Station (**1C**). Each shows isodose curves of 9, 12, 18, 24, 27, 28.5, 30, and 32.1 Gy, as well as the volumes of PTV (8.6 ml, thick magenta line), GTV (4.3 ml, thick red), and OARs (optic pathways and brainstem, thick white line). **1D**: Image of a somewhat upper slice of GammaPlan.

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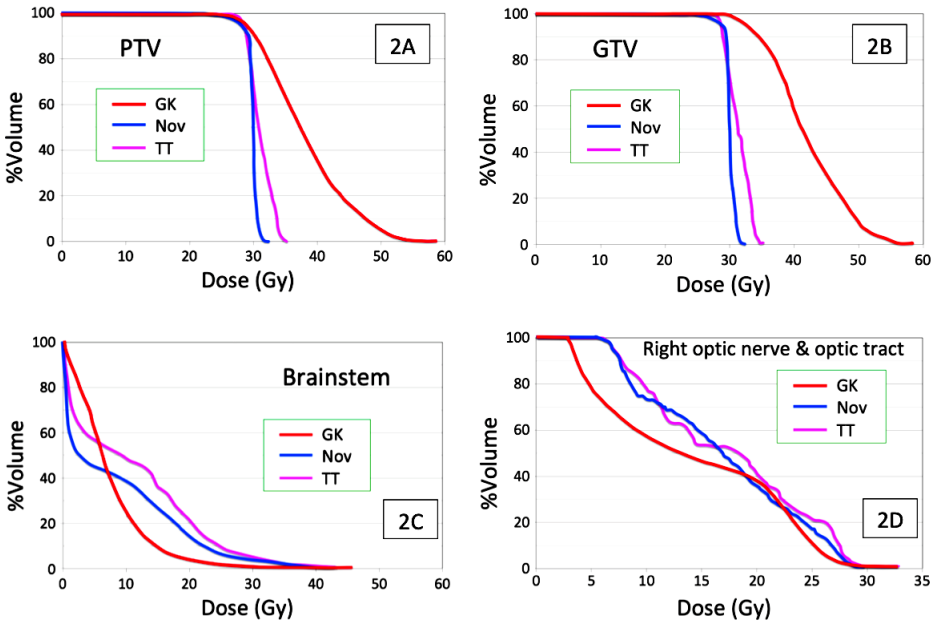


Figure 2. Dose-volume histogram (DVH) of PTV (**2A**), GTV (**2B**), brainstem (**2C**), and right optic nerve and optic tract (**2D**) by 3 modalities in Case 18.

DISCUSSION

In this study, we selected cases whose visual function of all 4 parts of the optic pathways, both optic nerves and both optic tracts, had been somewhat preserved, despite involvement by the tumors of some of them. Some earlier studies described dosimetric comparisons of SRS/SRT and IMRT among different treatment modalities [12, 18-20] but most of them assessed mainly only tumor covering, CI, HI, and GI. However, in the present study, a dosimetric comparison was conducted for benign skull base tumors involving optic pathways focusing on not only tumor covering but also OAR sparing. Particularly in the treatment of benign tumors, the long-term toxicity of radiation-induced adverse effects has to be taken into account. So, the doses administered to the OARs in cases of benign tumors have to be relatively low as compared to those of malignant ones. This is especially true of those to the optic apparatuses that are the most vulnerable to radiation, while providing an important function for daily activities. In this study, the possibility of long-term toxicity to critical organs including the optic apparatus was evaluated by V[20 Gy / 5 fx.] as well as D[0.1 ml] or D[1 ml]. We employed D[0.1ml] of optic pathways and D [1ml] of brainstem, rather than maximum doses, for OAR dose evaluation. There was local interdigitation of PTV and OARs, as a sequel to precise object contouring on thin axial-slice images, in some of the cases in this study in which the optic pathways and brainstem were attached to the tumor. For this reason the maximum dose of a very small volume was thought to be meaningless. In addition, the object sets including GTV, PTV, and OARs were made common by DICOM-RT data transfer, except for only the whole brain and body, in each dose planning for three modalities, NV, GK, and TT.

Target covering, CI, HI, and GI

PTV coverage in planning by all three modalities was unified at 28.5 Gy in 5 fx. (PTV D [95%]=95% dose of 30 Gy / 5 fx.), which was actually 28.71 Gy, 28.5 Gy, and 28.75 Gy in NV, GK, and TT respectively on average (table 5). CI and GI were superior with GK to NV and TT. HI was smaller in GK.

CI was best in GK, for both RTOG CI and Paddick CI. In addition, it was better with NV

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than TT, with a significant difference noted between them. In GK planning, additional isocenters can be easily placed to improve the conformity. CI may improve when the number of isocenters is increased. The GK PFX is equipped with an automatic collimator arrangement system without requiring manual collimator exchange, and a couch-traveling system that is approximately 10 times faster than the previous model C [12], and so the treatment time with many isocenters is considered to be within a clinically acceptable range. In our cases the number of isocenters in GK was 12 to 39 (mean 24.6, median 22.5), which was considered reasonable, and the beam on time of a fx was 15.2 to 51.4 (mean 26.4) minutes. As for the intratumoral dose, HI (DHI and mDHI) of GK was significantly much smaller (higher dose inside the target volume) than those of NV and TT. The much higher internal dose gradient could be interpreted as an advantage with regard to tumor ablation [13]. The mean doses of PTV and D[99%] of GTV were higher with GK than NV and TT. As for low dose spread in the surrounding tissue, GI of GK was significantly much smaller than those of Nov and TT. This was also shown on V [20 Gy] of normal brain and V[20 Gy] of body (tissue). Both were significantly smaller (better) in GK than in NV and TT. Between NV and TT, Normal Brain V[20 Gy] was significantly larger in TT as compared with in NV. The excellent dose fall-off noted around the target in GK is attributed to the large number of convergent beams and non-coplanar projections.

Nakazawa *et al.* [12] previously reported results consistent with those of this study with regard to CI, HI, and GI in a comparison between NV SRT and GK SRT for skull base tumors. They showed that GK provided better CI and GI than NV. Radical dose HI was larger (higher dose inside the PTV) in GK than in NV. They used more shots (12 - 50, mean 34.1) for GK SRT planning. Several other investigations have compared CI between GK and other modalities. Ma *et al.* [18] compared fan-beam IM-SRS and GK model U plans. They also reported totally consistent results. GK was better than the fan-beam IMRT [intensity-modulated radiation therapy] in sparing normal brain tissue while producing equivalent tumor dose conformity for treating medium-size intracranial lesions. The target dose homogeneity was significantly better for IMRT than for GK, which means that GK provided a higher dose inside the target. In a phantom study, Kumar *et al.* [19] reported that GK provides an advantage for all tumor sizes with respect to tumor and normal brain dose, as compared with helical TT. In contrast, Nakamura *et al.* [21] compared GK SRS and IM-SRS, employing a somewhat more complicated beam delivery (9 coplanar, 11 equally spaced non-coplanar, or 11 OAR-avoidant non-coplanar beams), for small- and medium-sized skull base tumors. They described that the IM-SRS plans achieved comparable or sometimes improved target coverage, conformity, and critical structure sparing with shorter estimated treatment times. In this study, we did not evaluate non-coplanar IMRT plan. Soisson *et al.* [22] noted that far inferior disease spread limits the ability to use non-coplanar arrangements in IMRT. In this study we did not assess CK. Kaul *et al.* [20] compared GK, CK, and NV (IMRT or DCA) in 10 patients with recurrent meningioma after surgery. They reported that the GK and CK system showed significantly higher levels of conformity than the NV system and that GK delivered the steepest dose gradient of all.

Critical organ dose

In this study, the optic pathways were involved in all 20 cases and the target was attached to the brainstem in 11 cases. D [0.1 ml] of optic nerves and D[1 ml] of brainstem were investigated. In addition, 20 Gy (in 5 fx.) volume of OARs was also employed. D[1 ml] and V[20 Gy] of brainstem, V[20 Gy] of normal brain with GK was significantly smaller as compared with NV and in TT. D[0.1 ml] and V[20 Gy] of optic nerves were smaller with GK than NV and TT, though the differences were not significant.

In tandem with the result of smaller GI in GK, our study showed that the sparing of OARs, including brainstem and normal brain, and optic pathways, was best with GK of any of the three modalities, although the difference in sparing of

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optic pathways did not reach statistical significance. Nakamura *et al.* [21] described sparing of OARs in the same study mentioned above comparing GK SRS and IM-SRS. They noted some variability in terms of modality superiority. Such variability was observed in our study as well but a tendency to superior optic pathway sparing with GK was observed. D [0.1 ml] of optic pathways was the smallest with GK in 11 of the 20 cases and V[20 Gy] was the smallest with GK in 12 cases. During treatment planning with GK, smaller shots can be placed near the edge of PTV facing the optic pathways in order to sharpen the fall-off there. Perks *et al.* [13] reported in a comparison between GK and linac SRS (fixed field and dynamic arcs) for eight acoustic neuromas that the two largest tumors (4.15 ml and 10.61 ml) demonstrated a higher brainstem dose in the GK plans, though the difference was not statistically significant. In our study the same tendency was observed. GK was superior for smaller tumors. D [0.1 ml] of lens in NV was the smallest, possibly because the beam angle of NV MB-IM-SRT was cleared away from the lens with NV.

Hypofractionated SRT

Fractionated SRT has some merits as compared with single-session SRS, especially when optic pathways, vulnerable to radiation, are adjacent to the tumors, though the optimal dose fractionation schedule should be evaluated by long-term follow-up. Patient thermoplastic shell fixation, other than rigid skull frame fixation, makes fractionated SRT easier also with GK. In GK, SRS with rigid skull frame fixation was usually performed only with MRI, with no PTV margin included in the dose planning. In IM -SRT using a thermoplastic head shell, appropriate margins of 1–2 mm are generally added [4-6]. A 2-mm margin appears reasonable in planning for intracranial lesions in NV SRT based on the evidence of our previous physical experiment [23]. In this study, we used a PTV margin of 2 mm for GK-PFX SRT, the same as that for NV SRT and TT SRT. We previously confirmed that the positional error between MRI and CT images was minimal, 0.8 mm or less in our commissioning test [24]. Several reports of clinical experience with the GK Extend system for multisession SRS have already been published [8,9,25]. Ruschin *et al.* [8] reported a repositioning error of 1.3 mm at the 95% confidence limit. With GK with Icon system the set-up error is expected to be around 1 mm. Considering these reports, a PTV margin of up to 2 mm is thought to be sufficient and reasonable. With GK, the uncertainty of positioning should be assessed precisely not only for targeting but also to avoid high doses to the OARs. With GK, as shown by low HI, a higher dose area exists inside the prescription isodose. Any part of OARs bulging into the thickness of the margin around the PTV may be exposed to a higher dose than the prescription dose. Therefore, particular attention should be paid to the dose distribution at the area of contact between PTV and OARs, especially with GK. Each modality has its own merits and demerits. In TT, dose calculation grid size is wider, about 2 mm, compared with other modalities. In addition, during treatment set-up TT does not have correction function for rotational error (pitch and yaw). In GK, it is not appropriate to employ a large fx size, such as more than 10 fx, because it is not appropriate to use a too short radiation time in each shot. In NV and TT, if the dose constraints of OARs seem unsatisfactory, much fraction size planning can be employed for OAR protection.

The present study had several limitations, with the most important one being the use of different dose calculation algorithms for each modality. Another limitation is that the original coplanar, without any non-coplanar beams, and rather homogenous distribution plans were used for NV-SRT. Adding non-coplanar beams might improve the dose distribution. However, coplanar beams are good for sparing the brainstem, which is long perpendicularly, and optic pathways, which run horizontally. In addition coplanar beams spare the cerebral hemispheres existing in the rostral side of skull base tumors. A non-homogeneous plan might be better to maintain a lower dose distribution outside the PTV. However, when higher doses in PTVs were allowed in NV-SRT planning, persistent hot areas sometimes developed inside the PTV just at the margin with the OARs.

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Further investigations including plans of volumetric modulated arc radiotherapy (VMAT) with coplanar and non-coplanar arcs and CK SRT will need to be undertaken.

In conclusion, a precise comparison of dose planning by three modalities was made including OAR sparing in this study. All three modalities provided target covering to treat benign skull base tumors involving the optic pathways. GK provides better conformity and normal tissue sparing, thereby providing advantages when treating benign tumors involving optic pathways, especially with tumors that are not large. GK SRT is expected to be an effective and safe treatment for skull base benign tumors adjacent to optic pathways and brainstem.

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