Technical Innovations & Patient Support in Radiation Oncology 29 (2024) 100235

Contents lists available at ScienceDirect

Technical Innovations & Patient Support in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/technical-innovations-and-patient-support-in-radiation-oncology

Research article

Single isocenter dynamic conformal arcs-based radiosurgery for brain metastases: Dosimetric comparison with Cyberknife and clinical investigation

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ARTICLE INFO

Keywords:
Brain metastasis
Stereotactic radiosurgery (SRS)
Dosimetric study
Cyberknife
Single Isocenter Dynamic Conformal Arcs

ABSTRACT

Purpose: To compare the dosimetric quality of automatic multiple brain metastases planning (MBM) with that of Cyberknife (CK) based on the clinical tumor condition, such as the tumor number, size, and location.
Methods: 76 treatment plans for 46 patients treated with CK were recalculated with the MBM treatment planning system. Conformity index (CI), homogeneity index (HI), gradient index (GI), lesion underdosage volume factor (LUF), healthy tissue overdose volume factor (HTOF), geometric conformity index (g) and mean dose to normal organs were compared between CK and MBM for tumor number, size, shape and distance from the brainstem or chiasm.
Results: The results showed that the mean brain dose was significantly smaller in MBM than CK. CI did not differ between MBM and CK; however, HI was significantly more ideal in CK ($p = 0.000$), and GI was significantly smaller in MBM ($P = 0.000$). LUF was larger in CK ($p = 0.000$) and HTOF and g was larger in MBM ($p = 0.003$, and 0.012). For single metastases, CK had significantly better HTOF ($p = 0.000$) and g ($p = 0.002$), but there were no differences for multiple tumors. Brain dose in MBM was significantly lower and CI was higher for tumors < 30 mm ($p = 0.000$ and 0.000), whereas HTOF and g for tumors < 10 mm were significantly smaller in CK ($p = 0.041$ and $p = 0.016$). Among oval tumors, brain dose, GI and LUF were smaller in MBM, but HTOF and g were smaller in CK. There were no particular trends for tumors close to the brainstem, but HTOF tended to be smaller in CK (0.03 vs. 0.29, $p = 0.068$) for tumors inside the brainstem.
Conclusions: MBM can reduce the brain dose while achieving a dose distribution quality equivalent to that with CK.

Introduction

The brain is a common site of metastasis of malignant tumors[1]. Historically, whole brain irradiation (WBI) has been performed for patients with multiple brain metastases as a palliative treatment[2], with single-fraction (SF) / multifraction (MF) stereotactic radiosurgery (SRS) only selected for patients with a single and small metastasis and expected longer survival. However, recent improvements in radiotherapy equipment have made it possible to perform SRS for multiple metastases, and SRS is now mainstream for patients with 1–4 brain metastases [3]. Moreover, Yamamoto et al. suggested that SRS could control 5–10 brain metastases as effectively as 2–4 brain metastases with minimal invasiveness[4]. Compared to WBI, SRS can deliver higher doses to the tumor, leading to a higher tumor control rate, while maintaining a low dose to normal brain tissue, which can reduce the incidence and severity of deterioration of neurocognitive function[5]. Survival of cancer patients has been improved by recent advances in systemic therapy, and some patients with brain metastases can achieve long-term survival if brain metastases are well controlled. At the same time, there is an increasing need to reduce late cognitive effects associated with radiotherapy.

Until 2022, LINAC-based volumetric modulated arc therapy (VMAT)

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https://doi.org/10.1016/j.tipsro.2024.100235
Received 22 October 2023; Received in revised form 14 December 2023; Accepted 9 January 2024
Available online 11 January 2024

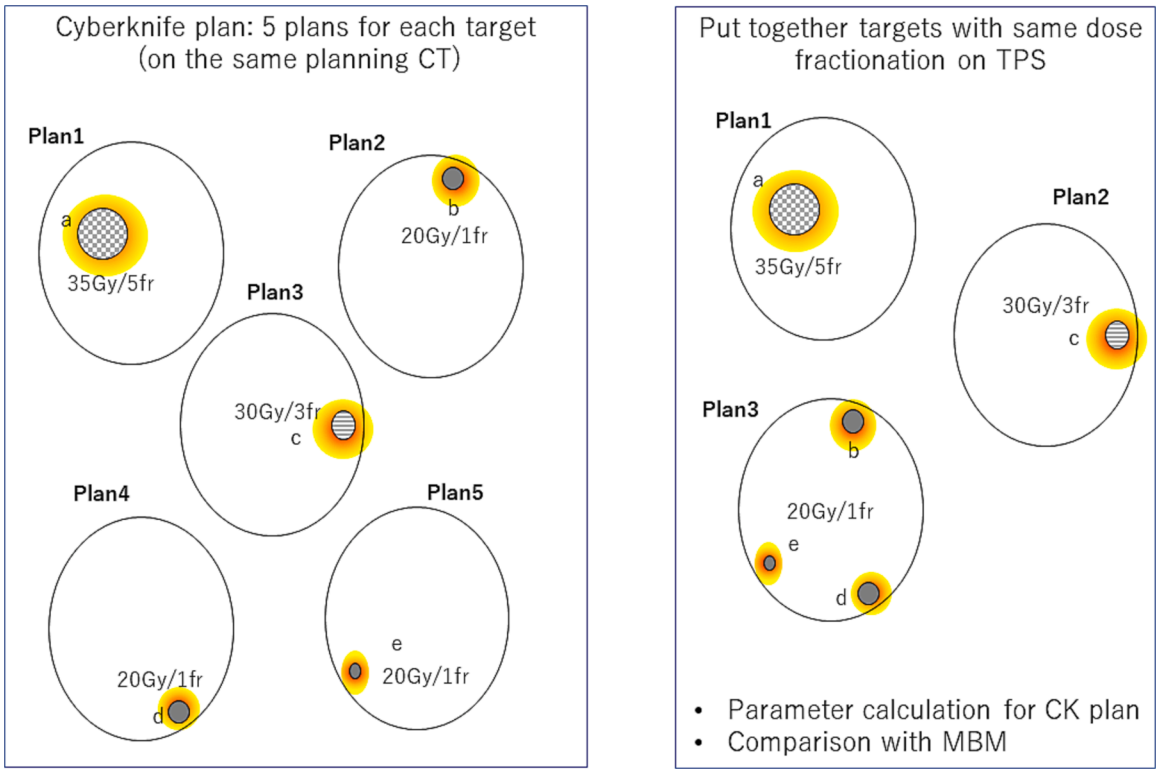

Fig. 1. Cyberknife plans in which dose distributions were summated and replanned with MBM.

Table 1
Details of treatment plans (n = 76 plans).

Item		Number of plans
Tumor number	Single	44
	Multiple	32
	2	18
	3	7
	4	3
	≥ 5 (max 16)	4
Tumor size	< 5 mm	2
median 19.95 mm	5– < 10 mm	11
range 4.2–65.6 mm	10–20 mm	25
	20–30 mm	19
	≥ 30 mm	19
Tumor shape	Circular	52
	Irregular	24
Distance from brainstem	Inside	4
	< 5 mm	15
	5–10 mm	3
	10–15 mm	4
	15–20 mm	3
	≥ 20 mm	47
Distance from optic nerve/chiasma	< 5 mm	2
	5–10 mm	3
	10–15 mm	1
	15–20 mm	0
	≥20 mm	70

Table 2
Results for all treatment plans (n = 76 plans)[a].

Item	CK	MBM	P
Brain mean dose (cGy)	111 (6–264)	107 (42–192)	0.000
Brainstem mean dose (cGy)	101 (42–320)	93 (39–313)	0.502
Chiasma mean dose (cGy)	69 (25–216)	80 (29–145)	0.676
Optic nerve dose (cGy)	45 (14–126)	55 (28–121)	0.443
CI	0.84 (0.73–0.88)	0.85 (0.76–0.90)	0.072
HI	0.32 (0.24–0.40)	0.44 (0.41–0.46)	0.000
GI	4.32 (3.42–5.35)	2.80 (2.43–3.16)	0.000
LUF	0.05 (0.04–0.06)	0.04 (0.03–0.05)	0.000
HTOF	0.11 (0.05–0.23)	0.17 (0.11–0.32)	0.003
g	0.17 (0.13–0.31)	0.22 (0.14–0.37)	0.012

[a] Data are shown as median (IQR).

was performed at our center for selected patients. Also, we referred some patients to the neighboring Cyberknife (CK) center depending on tumor characteristics, such as several metastases, larger metastases, metastases adjacent to the brainstem or chiasm, and patients who previously received cranial irradiation. CK has a robotic arm and gives an excellent dose distribution with a higher dose in the center of the tumor through use of hundreds of beams from multiple directions[6]. This is a well-established strategy for SRS for both brain and body trunk metastases [7–9]. In 2023, a new technology for SRS, called automatic multiple brain metastases (MBM) planning elements 4.0, was released in Japan (Brainlab AG, Muchen, Germany). This is designed to treat multiple targets (without no mechanical limit to tumor size and number) simultaneously with a single isocenter using the multiple noncoplanar dynamic conformal arc (DCA) technique, which allows treatment time to be shortened compared to CK. There is no mechanical limit to the number or size of tumors within a 15 cm x 15 cm irradiation field. As far as we are aware, there is little data showing that MBM can provide a dose distribution for all targets equivalent to that of CK. Therefore, the aim of this study was to compare DCA-based SRS to that in CK, and investigate the better indication according to tumor characteristics based on clinical practice.

Material and methods

Treatment planning - Cyberknife

Treatment planning for CK was based on contused CT images at 1-mm intervals fused with MRI. Patients were immobilized by an individually manufactured thermoplastic mask (MEDTEC, Toyo Medic, Tokyo, Japan). Most of the target volume (TV) was the gross tumor

Table 3
Analysis based on the number of tumors[a]

	Single (N = 44)			2 or more (N = 32)			3 or more (N = 14)			4 or more (N = 7)		
	CK	**MBM**	**P**	**CK**	**MBM**	**P**	**CK**	**MBM**	**P**	**CK**	**MBM**	**P**
Brain mean dose (cGy) Median (IQR)	111 (55–304)	109 (35–172)	**0.003**	108 (67–283)	106 (57–206)	**0.001**	123 (100–323)	114 (73–208)	0.093	111 (103–249)	114 (83–195)	0.091
Brainstem mean dose (cGy)	93 (37–306)	100 (35–313)	0.935	107 (49–374)	94 (30–313)	0.264	123 (56–361)	101 (62–396)	0.600	100 (48–320)	96 (66–227)	0.237
Chiasma mean dose (cGy)	86 (25–213)	80 (27–145)	0.977	64 (23–241)	84 (35–130)	0.544	89 (23–362)	96(49–162)	0.700	101 (34–241)	115 (72–163)	0.672
Optic nerve mean dose (cGy)	38 (10–126)	54.5 (29.3–143)	0.268	48 (25–118)	56 (22–110)	0.852	51 (31–136)	74 (38–123)	0.925	52 (32–162)	80 (42–98)	0.499
CI	0.85 (0.81–0.90)	0.87 (0.79–0.90)	0.434	0.78 (0.66–0.86)	0.80 (0.75–0.85)	**0.037**	0.76 (0.61–0.85)	0.78 (0.75–0.84)	0.096	0.77 (0.55–0.84)	0.77 (0.69–0.84)	0.499
HI	0.32 (0.19–0.37)	0.42 (0.34–0.46)	**0.000**	0.37 (0.26–0.42)	0.45 (0.43–0.47)	**0.000**	0.40 (0.36–0.44)	0.45 (0.44–0.46)	**0.012**	0.43 (0.36–0.46)	0.45 (0.44–0.46)	0.352
GI	3.40 (3.24–5.35)	2.56 (2.37–2.96)	**0.000**	4.47 (3.80–5.26)	3.07 (2.67–3.50)	**0.000**	4.57 (4.15–5.12)	3.24 (2.86–3.55)	**0.001**	4.67 (4.57–4.89)	3.31 (3.07–3.52)	**0.018**
LUF	0.05 (0.04–0.06)	0.04 (0.02–0.05)	**0.001**	0.04 (0.03–0.05)	0.04 (0.03–0.04)	0.118	0.04 (0.01–0.05)	0.03 (0.02–0.04)	0.778	0.03 (0.01–0.04)	0.04 (0.03–0.04)	0.612
HTOF	0.09 (0.04–0.14)	0.14 (0.09–0.28)	**0.000**	0.18 (0.09–0.40)	0.26 (0.15–0.33)	0.772	0.20 (0.11–0.48)	0.23 (0.18–0.30)	0.730	0.21 (0.12–0.77)	0.23 (0.21–0.43)	0.866
g	0.15 (0.10–0.23)	0.17 (0.13–0.36)	**0.002**	0.25 (0.14–0.46)	0.32 (0.21–0.38)	0.809	0.24 (0.15–0.54)	0.26 (0.21–0.37)	0.594	0.25 (0.15–0.79)	0.30 (0.24–0.48)	1.000

[a] Data are shown as median (IQR).

Table 4
Analysis based on tumor size[a]

	≧ 30 mm (N = 19)			< 30 mm (N = 57)			20–30 mm (N = 19)			10–20 mm (N = 25)			< 10 mm (N = 13)		
	CK	**MBM**	**P**	**CK**	**MBM**	**P**	**CK**	**MBM**	**P**	**CK**	**MBM**	**P**	**CK**	**MBM**	**P**
Brain mean dose (cGy) Median (IQR)	318 (196–470)	279 (192–440)	0.184	96 (54–142)	69 (34–118)	**0.000**	145 (110–195)	121 (104–167)	0.420	96 (54–107)	65 (45–90)	**0.001**	43 (23–57)	23 (15–36)	**0.001**
Brainstem mean dose (cGy)	224 (107–451)	293 (129–523)	0.139	68 (34–299)	61 (31–180)	**0.027**	110 (40–486)	124 (47–368)	0.872	90 (54–230)	61 (41–193)	**0.007**	29 (14–54)	17 (9–35)	0.059
Chiasma mean dose (cGy)	248 (45–397)	161 (90–345)	0.673	61 (22–134)	49 (25–111)	0.913	130 (33–217)	112 (52–165)	1.000	64 (28–103)	49 (28–97)	0.253	22 (11–54)	15 (7–28)	0.182
Optic nerve mean dose (cGy)	107 (46–216)	126 (88–291)	0.220	32 (12–69)	43 (17–66)	0.085	31 (9–162)	64 (48–151)	0.673	42 (17–56)	41 (21–59)	0.732	24 (8–38)	10 (4–24)	0.041
CI	0.87 (0.78–0.90)	0.87 (0.76–0.91)	0.573	0.83 (0.72–0.87)	0.82 (0.76–0.89)	**0.000**	0.85 (0.82–0.88)	0.89 (0.85–0.91)	0.053	0.81 (0.68–0.86)	0.81 (0.75–0.85)	0.231	0.75 (0.65–0.89)	0.77 (0.65–0.84)	0.650
HI	0.28 (0.19–0.32)	0.42 (0.30–0.45)	0.053	0.31 (0.23–0.35)	0.44 (0.41–0.46)	**0.000**	0.32 (0.26–0.38)	0.43 (0.41–0.46)	**0.007**	0.39 (0.28–0.46)	0.44 (0.42–0.47)	**0.025**	0.35 (0.24–0.40)	0.43 (0.41–0.47)	**0.006**
GI	3.35 (2.99–3.80)	2.53 (2.33–2.88)	**0.000**	4.75 (3.87–5.70)	2.87 (2.48–3.30)	**0.000**	3.75 (3.17–4.40)	2.41 (2.37–2.68)	**0.000**	4.88 (4.41–5.73)	2.96 (2.76–3.24)	**0.000**	6.83 (5.20–8.31)	3.5 (3.00–3.85)	**0.001**
LUF	0.05 (0.04–0.05)	0.04 (0.02–0.04)	0.227	0.05 (0.04–0.07)	0.04 (0.03–0.05)	**0.001**	0.05 (0.04–0.05)	0.03 (0.02–0.04)	**0.006**	0.05 (0.04–0.07)	0.04 (0.03–0.05)	**0.005**	0.06 (0.01–0.09)	0.05 (0.04–0.07)	0.754
HTOF	0.09 (0.04–0.20)	0.12 (0.09–0.29)	0.227	0.12 (0.08–0.24)	0.20 (0.12–0.32)	**0.005**	0.09 (0.06–0.15)	0.13 (0.11–0.15)	0.295	0.12 (0.06–0.31)	0.26 (0.18–0.33)	0.109	0.19 (0.10–0.39)	0.36 (0.21–0.50)	**0.041**
g	0.13 (0.09–0.26)	0.17 (0.12–0.39)	0.355	0.18 (0.13–0.32)	0.24 (0.16–0.37)	**0.021**	0.15 (0.11–0.18)	0.16 (0.13–0.18)	0.717	0.21 (0.15–0.37)	0.32 (0.24–0.38)	0.326	0.29 (0.14–0.43)	0.40 (0.26–0.57)	**0.016**

[a] Data are shown as median (IQR).

Table 5
Analysis based on tumor shape[a].

Item	Circular (N = 52)			Irregular (N = 24)		
	CK	MBM	P	CK	MBM	P
Brain mean dose (cGy) Median (IQR)	97 (55–145)	68 (34–121)	**0.000**	229 (141–345)	190 (128–375)	0.196
Brainstem mean dose (cGy)	65 (31–129)	56 (26–123)	0.110	326 (108–606)	366 (134–550)	0.715
Chiasma mean dose (cGy)	42 (20–105)	47 (24–97)	0.404	185 (78–282)	169 (112–286)	0.607
Optic nerve mean dose (cGy)	34 (13–71)	42 (15–73)	0.974	106 (23–210)	124 (54–282)	0.274
CI	0.84 (0.72–0.88)	0.84 (0.76–0.89)	0.303	0.85 (0.74–0.88)	0.87 (0.76–0.91)	0.092
HI	0.34 (0.22–0.41)	0.44 (0.42–0.47)	**0.000**	0.31 (0.26–0.37)	0.43 (0.30–0.45)	**0.011**
GI	4.76 (3.85–5.75)	2.87 (2.61–3.31)	**0.000**	3.43 (3.13–4.21)	2.51 (2.37–2.96)	**0.000**
LUF	0.05 (0.04–0.07)	0.04 (0.03–0.05)	**0.008**	0.05 (0.04–0.05)	0.04 (0.02–0.04)	**0.021**
HTOF	0.13 (0.06–0.27)	0.20 (0.11–0.32)	**0.009**	0.09 (0.05–0.20)	0.14 (0.10–0.34)	0.145
G	0.18 (0.13–0.35)	0.25 (0.15–0.37)	**0.017**	0.15 (0.12–0.27)	0.17 (0.13–0.37)	0.361
Mean tumor size	1.8 cm			3.5 cm		

[a] Data are shown as median (IQR).

volume (GTV) without any margins. Only for 13 targets in 5 plans, 1 mm margin was added to GTVs as planning target volume (PTV) margins. Plans were optimized with the VOLO treatment planning system (Accuray Precision Version 3.3.1.2., Accuray Inc, Sunnyvale, CA, USA) using a raytracing algorithm. The dose calculation grid was 1 mm. The treatment beams were equipped with 6 MV photon beams (800 MU/min). An iris variable aperture collimator or circular fixed collimator was used. The usual dose prescription was the TV was covered by 95 % of the prescribed dose (D_{95}), but this was modified in some patients. Plans for 145 brain metastases in 46 patients were available.

Various dose fractionation schemes were used for CK treatment depending on the tumor location, number, irradiation history, and size, including a single fraction (fr) with 15 Gy and 20 Gy, 30 Gy in 3fr, 27 Gy in 3fr, 35 Gy in 5fr, 35 Gy in 7fr, 21 Gy in 3fr, and 20 Gy in 2fr. All plans were exported in DICOM RT format and then imported in the treatment planning system (RayStation Ver 10.0, RaySearch Laboratories AB, Stockholm, Sweden). On RayStation, plans that could be irradiated simultaneously using MBM (i.e., same dose fractionation based on the same planning CT in the same patient) were summated, and the 145 plans were combined into 76 plans (Fig. 1). The details of the 76 treatment plans are shown in Table 1. The plans included 44 with single targets and 32 with multiple targets. The maximum target number was 16. The median tumor size was 20 mm (range: 4.2–65.6 mm). Nineteen plans included the target at < 5 mm from the brainstem, and 4 of these 19 plans had the target inside the brainstem.

Treatment planning – MBM

The 76 plans of the 46 patients were exported from RayStation and then imported into Elements MBM v.4.0. The treatment plans were replanned using a demonstration protocol with a single isocenter using the DCA technique. The VMAT technique is available for one target among multiple targets in this machine, but was not used in this study. The protocol was modified for irregular dose fractionation. D_{98} for the TV was used in MBM calculations, despite this differing from CK planning, because it is recommended in the protocol that we plan to use in clinical practice. The treatment beams were equipped with flattening filter free 6 MV photon beams (1200 MU/min). The number of arcs was determined automatically depending on the spatial distribution of the metastases. The arc consisted of at least one coplanar arc and 3 non-coplanar arcs with couch angles of 0, 45, 135 and 270°. The resolution of the multileaf collimator was 2.5 mm (HD 120, Varian Medical Systems, Palo Alto, CA, USA). Pencil Beam Convolution was used for inverse planning with a dose grid resolution of 2.0 mm. The treatment plans were automatically adapted to adjusted target dose homogeneity and dose constraints of the target and organs at risk based on the clinical treatment protocol.

Data analysis and dosimetric parameters

Mean dose to normal organs (brain (including targets), brainstem, chiasma, ipsilateral optic nerve) and dosimetric parameters were calculated from the dose volume histogram (DVH) of the TV, risk organs, and external tissues. When targets were located in both the right and left brain hemispheres, the ipsilateral optic nerve was defined as receiving a higher dose in the CK plan. Beam-on time of each fraction was calculated as Monitor Unit/(dose rate × fraction). Dose rate was 800 MU/min for CK and 1200 MU/min for MBM. For combined CK plans, total MU of each plan was used. The plan quality was assessed using the following parameters:

Paddick conformity index (CI)

CI describes the agreement between the dose distribution and the shape of the target[10]. The ideal value is 1.

$$CI = (TVpiv)^2/(TV \times PIV)$$

where PIV is the prescription isodose volume, and TVpiv is PIV within the target volume.

Homogeneity index (HI)

HI describes the uniformity of the dose distribution within the TV [11]. The ideal value is 0.2.

$$HI = (D_{2\%} - D_{98\%})/Prescriptiondose$$

Gradient index (GI)

GI describes the steepness of the dose gradient from PIV to the surrounding tissue. GI is the ratio of the irradiated volume enclosed by 50 % of the prescription dose divided by the prescription isodose volume[11]:

$$GI = PIV_{50}/PIV$$

where PIV_{50} is the isodose volume of the 50 % prescription dose.

Lesion underdosage volume factor (LUF)

LUF describes the ratio of the target volume that is not covered by the prescription isodose (PI)[12].

$$LUF = TV_{<PI}/TV$$

Healthy tissue overdose volume factor (HTOF)

HTOF describes the ratio of the healthy tissue volume outside the TV receiving more than the prescription isodose[12].

$$HTOF = HTV_{>PI}/TV$$

where $HTV_{>PI}$ is the healthy tissue volume covered by the prescription dose [12].

Table 6
Analysis based on distance of the tumor from the brainstem[a].

Distance from brainstem	≥ 20mm (N = 47)			< 20mm (N = 29)			< 15mm (N = 26)			< 10mm (N = 22)			< 5mm (N = 19)			Inside (N = 4)		
	CK	MBM	P	CK	MBM	P	CK	MBM	P	CK	MBM	P	CK	MBM	P	CK	MBM	P
Brain mean dose (cGy) Median (IQR)	103 (54–174)	83 (32–160)	**0.000**	157 (97–379)	140 (61–265)	**0.030**	148 (95–363)	147 (62–286)	**0.041**	203 (95–415)	171 (68–314)	0.070	249 (96–429)	178 (70–350)	0.177	69 (51–88)	39 (35–59)	0.068
Brainstem mean dose (cGy)	58 (29–110)	48 (23–96)	0.491	363 (116–499)	364 (217–583)	0.631	390 (152–520)	368 (247–645)	0.710	423 (318–574)	415 (309–663)	0.630	425 (320–621)	485 (358–701)	0.520	394 (331–772)	361 (296–617)	0.068
Chiasma mean dose (cGy)	45 (19–138)	59 (22–111)	0.751	118 (44–285)	115 (62–228)	0.699	130 (64–294)	111 (65–244)	0.443	211 (86–324)	161 (92–263)	0.476	204 (86–315)	169 (94–296)	0.948	103 (86–242)	64 (27–108)	0.144
Optic nerve mean dose (cGy)	32 (10–104)	42 (13–80)	0.541	49 (25–132)	84 (48–165)	0.101	52 (27–143)	91 (45–185)	0.139	64 (27–165.8)	109 (48–217)	0.160	54 (21–162)	84 (46–254)	0.147	45 (36–52)	50 (16–60)	0.715
PCI	0.84 (0.72–0.87)	0.84 (0.76–0.89)	0.179	0.84 (0.72–0.89)	0.84 (0.78–0.90)	0.256	0.83 (0.71–0.88)	0.85 (0.79–0.90)	0.112	0.84 (0.70–0.89)	0.85 (0.76–0.91)	0.263	0.85 (0.72–0.91)	0.86 (0.77–0.91)	0.445	0.86 (0.71–0.90)	0.83 (0.74–0.86)	0.465
HI	0.35 (0.26–0.40)	0.43 (0.41–0.45)	**0.002**	0.31 (0.18–0.42)	0.45 (0.42–0.48)	**0.002**	0.31 (0.20–0.41)	0.46 (0.42–0.48)	**0.002**	0.31 (0.20–0.42)	0.46 (0.39–0.48)	**0.016**	0.27 (0.20–0.36)	0.45 (0.30–0.48)	0.126	0.33 (0.12–0.54)	0.48 (0.47–0.48)	0.465
GI	4.34 (3.41–5.22)	2.82 (2.41–3.17)	**0.000**	4.31 (3.41–5.99)	2.79 (2.44–3.17)	**0.000**	4.32 (3.43–5.92)	2.80 (2.43–3.23)	**0.000**	2.75 (2.43–3.23)	2.75 (2.42–3.23)	**0.000**	3.75 (2.22–6.12)	2.81 (2.43–3.20)	**0.000**	6.51 (5.25–7.08)	3.26 (3.02–3.72)	0.068
LUF	0.05 (0.04–0.05)	0.04 (0.02–0.05)	**0.002**	0.05 (0.04–0.17)	0.04 (0.03–0.05)	**0.048**	0.05 (0.04–0.19)	0.04 (0.03–0.49)	0.137	0.05 (0.04–0.07)	0.04 (0.03–0.05)	0.131	0.05 (0.04–0.07)	0.04 (0.03–0.05)	0.077	0.09 (0.05–0.27)	0.06 (0.04–0.08)	0.144
HTOF	0.12 (0.08–0.27)	0.17 (0.11–0.35)	**0.043**	0.08 (0.03–0.18)	0.17 (0.11–0.29)	**0.028**	0.08 (0.03–0.18)	0.18 (0.09–0.29)	0.069	0.08 (0.03–0.16)	0.16 (0.09–0.29)	0.101	0.06 (0.03–0.15)	0.14 (0.09–0.28)	0.053	0.03 (0.01–0.07)	0.29 (0.27–0.34)	0.068
g	0.18 (0.13–0.36)	0.23 (0.14–0.41)	**0.049**	0.17 (0.10–0.28)	0.22 (0.14–0.36)	0.098	0.18 (0.11–0.31)	0.22 (0.13–0.37)	0.209	0.16 (0.11–0.31)	0.20 (0.13–0.37)	0.306	0.14 (0.09–0.30)	0.17 (0.13–0.37)	0.243	0.13 (0.10–0.29)	0.37 (0.32–0.39)	0.068

[a] Data are shown as median (IQR).

Geometric conformity index (g)

$$G = LUF + HTOF$$

Statistics

A Wilcoxon single-rank test implemented in SPSS ver. 27 (IBM Co., New York, NY, USA) was used to evaluate differences between CK and MBM. All tests were 2-tailed with $p < 0.05$ considered to be statistically significant. Differences were compared according to tumor characteristics, including tumor number, size, shape (oval/round vs. distorted), and location. Assessment of shape was subjective based on axial, coronal and sagittal CT images. A *t*-test was used to compare means.

Ethics approval

The study was approved by the institutional review board.

Results

All plans

The results for all plans are shown in Table 2. The mean brain dose was significantly smaller in MBM (111 vs. 107 cGy, p = 0.000). There was no significant difference for other at risk organs. CI did not differ significantly between MBM and CK (p = 0.072). HI was significantly closer to the ideal value of 0.2 in CK (median: 0.32 vs. 0.44, p = 0.000). GI was significantly smaller in MBM (4.32 vs. 2.80, p = 0.000). LUF was significantly smaller in MBM, but was also small in CK (0.05 vs 0.04, p = 0.000). HTOF and g were smaller in CK, but both were also small in MBM (HTOF: 0.11 vs. 0.17, p = 0.003, g: 0.17 vs. 0.22p = 0.012). MU was significantly lower for MBM plans. The mean MU value for each fraction was 10,979 (range; 2069–116899) and 3428 (range; 708–16486) for CK and MBM plans, respectively (p = 0.000), and mean beam-on time was 14 min and 3 min for CK and MBM plans, respectively.

Number of tumors

(Table 3) For a single metastasis, the trends were almost the same as those in all plans. For multiple metastases ($n \geq 2$), there were no differences in LUF, HTOF and g. CI was significantly better in MBM only in plans including ≥ 2 metastases (CK vs. MBM: 0.78 vs. 0.80, p = 0.037), but was not significant in plans including ≥ 3 metastases.

Tumor size

(Table 4) For tumors ≥ 30 mm in size, there were no significant differences between CK and MBM, other than for GI. Mean brain dose was significantly smaller in MBM for tumors smaller than 20 mm. CI was clearly better for tumors smaller than 30 mm in MBM (p = 0.000), but there was no significant difference in details by size. LUF was significantly smaller in MBM for tumors of 10–30 mm. HTOF and g tended to be lower in CK for smaller tumors and were significantly lower for tumors of < 10 mm (p = 0.041 and 0.016, respectively).

Tumor shape

(Table 5) For circular tumors, brain doses were significantly lower with a lower GI and LUF in MBM, and HTOF and g were significantly smaller in CK. For irregular-shape tumors, there were significant differences in HI, GI and LUF. This trend was similar to the results of smaller vs. larger tumors, which may be because the mean size of irregular tumors tended to be larger than that of oval tumors (18 vs. 35 mm, p = 0.088 by *t*-test).

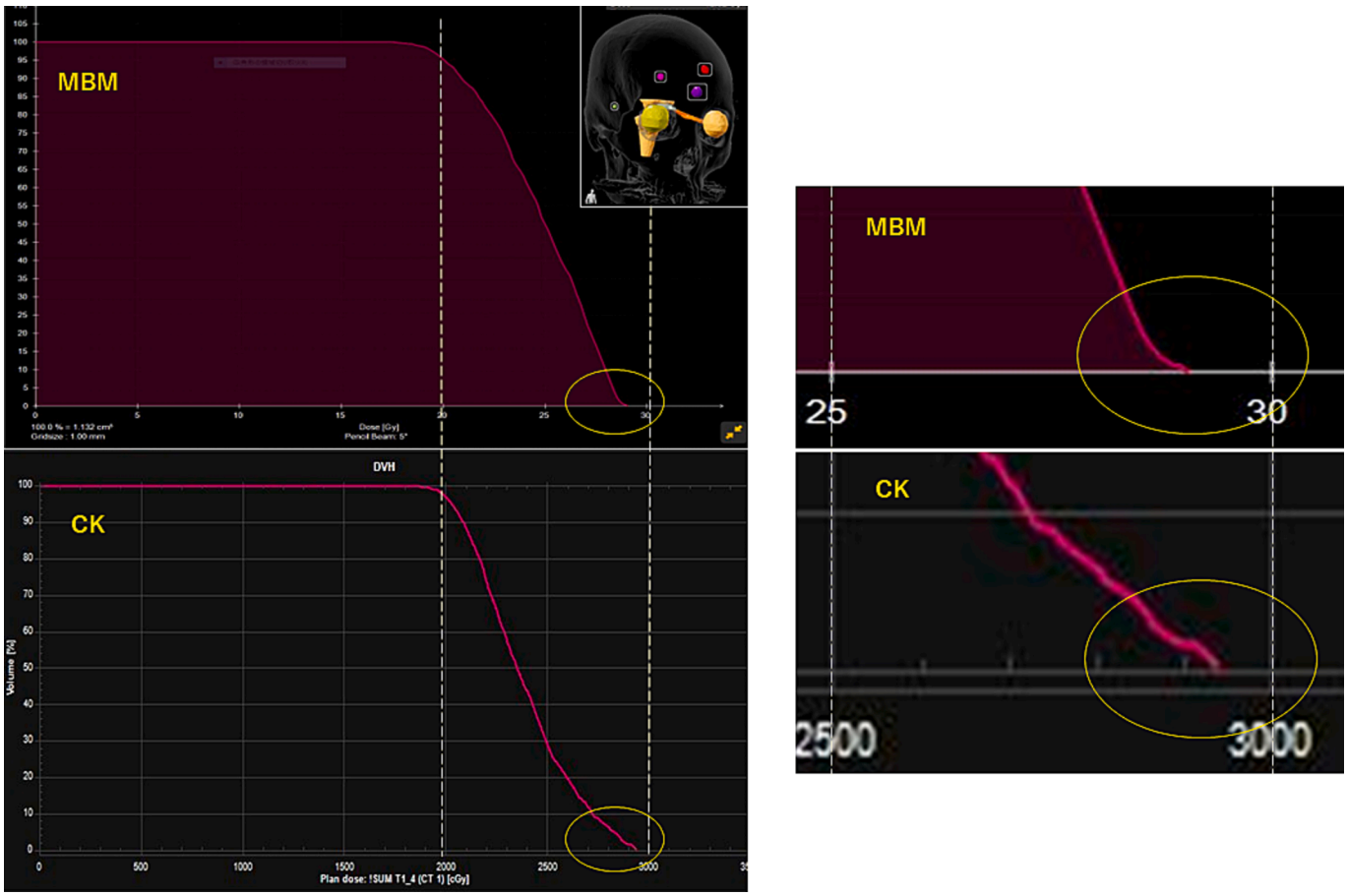

Fig. 2. Dose volume histograms (DVHs) in MBM and CK for the target volume. The DVH curve in MBM was steeper and the dose is increasing at the end of the curve.

Distance from brainstem

(Table 6) There was no significant difference in the mean brainstem dose between CK and MBM regardless of the distance from the brainstem. There was also no particular trend for tumors closer to the brainstem. However, HTOF for tumors located in the brainstem showed a tendency to be smaller in CK (0.03 vs. 0.29, $p = 0.068$).

Distance from chiasma

Only 6 plans included a tumor < 15 mm from the chiasma. There was no difference between CK and MBM among these 6 plans. except for GI. The p-values for the chiasma and optic nerve were 0.463 and 0.757, respectively.

Discussion

The prognosis of patients with multiple metastases has been considered to be poor, and WBI has historically been indicated for these patients as palliative treatment. However, recent advances in systemic treatment have made it possible for patients to have long-term survival with multiple metastases. Therefore, management of brain metastases should focus on tumor control and minimizing late cognitive toxicities to improve quality of life[9]. Then coupled with advances in radiotherapy, the indications of SRS have expanded[3,4,10–12]. Recently, LINAC-based single isocenter SRS techniques using VMAT and DCA have been developed. These techniques achieve favorable dose distribution [13–17]. Also, Rogers et al. reported favorable results of MBM that local control was 100 % and 99.8 % for patients with 5–9 brain metastases and 10–15 brain metastases[18].

Overall, our results suggest that MBM can reduce mean brain doses compared to CK. This is due to use of an algorithm of MBM that does not concentrate the beam path, and the lower dose area may overlap for multiple brain metastases in CK due to plan summation. The mean brain dose in this study was low enough for safe irradiation in MBM and CK, but MBM may have a benefit for reirradiation or combination with WBI. As for CI and GI, there were no differences in CI, and GI was lower in MBM. CI and GI are believed to be essential to evaluate plan quality: Higher CI (closer to 1.0) and lower GI are expected to achieve good tumor control and to reduce irradiation-related toxicities, respectively. Whereas, Aiyama et al. suggested GI was shown to have a minimal impact in lowering the incidence of complications for patients undergoing SRS[19]. Safety of modern SRS technique has been established. In the report of CK including 233 brain metastases in 97 patients, toxicities $\geq$ grade 3 was not observed[20]. Also, in the report from MBM for 5–15 brain metastases, there was no toxicities $\geq$ grade 3[18]. Our results suggested that MBM has steeper dose distribution, but both are considered to be equivalent in clinical practice. The concept of LUF, HTOF and g focus on the 100 % prescription dose area more than CI and GI. Our results suggested LUF was better in MBM and HTOF was lower in CK, which indicates that MBM delivered a sufficient prescribed dose to the target, but that the dose extends a little around the target. This may be due to differences in the dose prescriptions of D_{95} and D_{98} for CK and MBM, which are used in clinical practice. HI was closer to 0.2 for CK, which may be because MBM has the constraint of increasing the central dose of the tumor. Recently, the efficacy of focal dose escalation has been suggested even if homogeneity in the TV is lost[21,22]. Therefore, HI may not have much clinical significance in modern SRS. DVHs of CK (summation plan) and MBM for 4 targets are shown in Fig. 2. In this plan, the DVH curve of MBM extends into the high dose range at the end.

In our analysis by number of tumors, brain doses were significantly lower in MBM for a single metastasis; however, there was no significant difference in brain doses between MBM and CK for ≥ 3 metastases. This is probably because the distance from the isocenter to the targets and the overlapping beam paths increase the number of targets in MBM plans, although overlap of low dose areas also increased due to plan summation in CK. For other parameters, LUF was better in MBM, but HTOF and g were significantly better in single metastasis plans. For multiple tumors, there was no significant difference other than HI and GI. Given this lack of a significant difference between MBM and CK, the reduced treatment time may be an advantage of MBM for multiple metastases because all can be treated at once.

As for tumor size, brain doses were significantly lower in MBM for tumors smaller than 30 mm. However, HTOF and g were significantly smaller in CK for tumors smaller than 10 mm. For circular tumors, brain doses were lower in MBM plans and HTOF and g was smaller in CK plans. Therefore, a small tumor located adjacent to tissues at risk may be a better indication for CK. However, considering that brain doses were lower in MBM for small tumors, MBM seems to be a good indication for small metastases in cases with a history of WBI or repeated brain irradiation. There were no significant differences between CK and MBM for large tumors ($\geq$30 mm) other than GI.

SRS for brainstem metastases is an established strategy, but great care should be taken with brainstem doses. Recent studies have suggested optimal dose fractions for brainstem metastases, but they are much more modest than the usual SRS doses[23,24]. In this study, the brainstem doses for MBM were almost equal to those for CK. However, for tumors located within 5 mm of the brainstem, HTOF tended to be better in CK. Given that the high dose range in the brainstem is a clinically critical issue in SRS for the brainstem, CK seems to be a better indication than MBM for a tumor adjacent to the brainstem. The same may also be true for tumors adjacent to the optic nerve or chiasma, but no definitive statement can be made in this study due to the small sample size.

Our study has the limitation that the sample size was limited and dose constraints differed between CK and MBM, and that the CK plan was made while taking into account clinical information, but no detailed clinical information was available when making the MBM plan. Also, TV in the MBM plan was based on CK plan without PTV margins, however, in clinical practice, some PTV margin may be necessary to cover set up errors when there is certain distance between isocenter and metastases, and this may affect the mean brain dose.

Besides, some authors has discussed about contour/volume changes when transferring structures among different treatment planning systems[25,26]. However, in this study, the difference of TV between RayStation and MBM was ranged from -0.07 ml to $+$ 0.06 ml (median0.00), and the impact on the results seemed slight.

Overall, MBM can achieve a dose distribution equivalent to that of CK. Therefore, MBM or CK can be used depending on the equipment available in a facility. However, the lower mean brain dose in MBM may be an advantage for patients after repeated SRS for multiple metastases, or patients treated in combination with WBI. Also, a short treatment period by treating multiple metastases simultaneously and short treatment time may be a great benefit for patients who have difficulty lying on a bed for a long time or who must suspend systemic therapy during irradiation periods. In our study, actual treatment time was not available and beam on time was calculated from MU value and dose rate, but it is estimated that the time required for the gantry, bed, and manipulator arm to move seems similar for either the CK or MBM. However, CK has a lower trend for HTOF and g, and considering the high flexibility of treatment planning, CK may have an advantage for patients with metastases adjacent to tissues at risk such as the brainstem or chiasma.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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