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FULL PAPER

Clinical outcomes of multileaf collimator-based CyberKnife for spine stereotactic body radiation therapy

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Objective: Stereotactic body radiotherapy (SBRT) for spinal metastases is becoming a prevalent therapeutic option. We aimed to evaluate the clinical feasibility and outcomes of the recently developed multileaf collimator (MLC)-based CyberKnife (CK-M) for spine SBRT.

Methods: We reviewed 119 patients of 144 cases with 229 lesions treated with CK between November 2014 and March 2016. The lesion features, dosimetric parameters and clinical outcomes were compared between fixed cone collimator based CK (CK-F) and CK-M.

Results: Of 144 cases, 78 and 66 were treated with CK-F and CK-M, respectively. CK-M achieved an adequate target volume coverage that was comparable with CK-F (median 92 vs 90%; $p = 0.03$) even in larger targets (median 64.2 vs 46.7 cm³; $p = 0.01$), respectively. CK-M showed an improvement in the gradient index ($p <$

0.001) and no difference in conformity ($p = 0.16$). With CK-M, the median beam delivery time was significantly reduced by 30% (to 34 vs 48 min; $p < 0.001$). CK-M showed 1 year local control rates that were comparable to CK-F (77 vs 78%, respectively; $p = 0.83$).

Conclusion: CK-M exhibits dosimetric data and local control that are comparable with CK-F, but with significant treatment time reduction. CK-M could be widely used in spine SBRT.

Advances in knowledge: Given the recently developed MLC in CK, we aimed to evaluate the clinical feasibility and outcomes of MLC compared with fixed cone-based CK. MLC showed equivalent plan quality and significant treatment time reduction with comparable radiological control. We report here MLC as an effective and tolerable treatment option in CK.

INTRODUCTION

As the survival rates among patients with metastatic diseases that arise from solid malignancies increase, spine metastases are becoming a common complication afflicting over 20,000 patients annually.¹ Conventional fractionated external beam radiotherapy (EBRT) of 8 Gy for a single fraction, 20 Gy for 5 fractions and 30 Gy for 10 fractions are frequently used for spine metastases.² Although conventional EBRT produces a good pain relief response with complete pain relief attained in 0–20% of patients,³ it shows poor local control (LC) in complex and bulky metastatic lesions.⁴

Spine stereotactic body radiotherapy (SBRT) can deliver a locally ablative radiation dose while maximizing pain relief and radiological LC in a convenient and effective schedule. Since the initial guidelines of the American Society of Therapeutic Radiation Oncology were published,⁵ the

patient selection criteria continues to evolve. The criteria have even been broadened to include historically contraindicated patients; such as those with three or more contiguous segments, widespread metastatic disease, pre-existing vertebral fracture and lesions with epidural disease and potential spinal instability.⁶

CyberKnife (CK) has a distinct feature of real-time tracking of target motion with intrafractional X-ray imaging and automatic positional adjustments. In 2015, certain CK series were equipped with the InCiseTM (Accuray Inc., Sunnyvale, CA) multileaf collimator (MLC). In addition to fixed-cone and IRISTM (IRIS) collimators, the current version of MLC consists of 41 leaf pairs with widths of 2.5 mm, forming a maximum field size of 120 mm by 102.5 mm.⁷ The application of MLC was postulated to higher delivery efficacy in terms of treatment time and equivalent planning in the treatment of larger and more complex tumours.⁸ Until now, there are minimal data evaluating only dosimetric

comparisons between MLC-based treatment plans^{9–11} and cone/IRIS-based plans; such studies do not describe clinical outcomes. The aim of this study was to evaluate both dosimetric feasibility and clinical outcomes of CK equipped with MLC (CK-M) in SBRT for spine metastases.

METHODS AND MATERIALS

Study population

We identified 144 consecutive patients of 179 cases with 315 lesions treated with CK SBRT between November 2014 and March 2016. Of these, the lesions of 144 cases were enrolled after excluding those that did not complete entire sessions ($n = 12$), had no follow-up radiological evaluation ($n = 19$) or were treated with IRIS-based CK ($n = 4$). We retrospectively reviewed 78 cases of fixed cone collimator-based CK (CK-F) and 66 cases of CK-M. This study was approved by the Health Institutional Review Boards of Yonsei University Hospital (IRB No. 4-2016-0994). The requirement for informed consent was waived owing to the study's retrospective nature.

Patient evaluation

Patient, tumour and dosimetric characteristics, as well as clinical outcomes, were obtained from medical records. We used the epidural spinal cord compression scales (Bilsky grade)¹² for evaluating the degree of epidural disease. We grouped the cases into two categories according to Bilsky grade: epidural space compressive disease-negative (Bilsky Grades 0–1c) and positive (Bilsky Grades 2–3). Each of the 229 spinal lesions was scored according to the spine instability neoplastic score (SINS) criteria.¹³ The SINS system classifies patients as stable, potentially unstable (indeterminate) and unstable based on the overall score.

Treatment

All patients underwent a fine-cut (1 mm) non-contrast-enhanced treatment planning CT scan in the supine treatment position. All patients were immobilized in a customized total body vacuum bag and additional thermoplastic mask for cervical spine treatment. Planning CT data and structures were transferred to the MultiPlan 5.1.2 (Accuray Inc., Sunnyvale, CA) CK planning system. Each treatment plan was generated with fixed cones mounted on the CK M6 (Accuray Inc., Sunnyvale, CA) or the InCise MLC which was installed at Yonsei Cancer Center in August 2015. All patients were treated using the Xsight spine tracking system (Accuray, Sunnyvale, CA), which uses the bony anatomy of the spine for continuous imaging, repositioning and tracking tumours without fiducial markers.

Planning CT and axial gadolinium T1 and T2 weighted MRI were fused to aid with target and spinal cord delineation. Delineation of the gross tumour volume (GTV) and clinical target volume was consistent with the recent International Spine Radiosurgery Consortium consensus guidelines.¹⁴ The gross tumour volume was defined as a gross tumour mass or osteolytic lesion identified on the planning CT, high signal intensity lesion on T₂ weighted MRI or enhanced lesion on gadolinium-enhanced T₁ weighted MRI. The planning treatment volume (PTV) was defined with no margins added to the clinical target volume. We divided the PTV into five groups according to degrees: <180°, 180°, 270°, horseshoe

and doughnut-shaped around the spinal cord. An additional 10 mm of the spinal cord (at minimum) was contoured above and below the PTV based on non-coplanar beam arrangements of CK. There was heterogeneity in the patterns of the prescribed dose (Table 1); all patients were radiation naïve at the treatment site. In the entire cohort, most patients received a total of 18 Gy in a single fraction [equivalent dose in 2 Gy per day fractions (EQD2) 42 Gy, 47 cases (32.6%)] or 32 Gy in four fractions [EQD2 48 Gy, 41 cases (28.5%)]. There were different patterns of prescription according to the collimator type; the most frequent prescription was 18 Gy in a single fraction (40 cases, 51.3% of CK-F) in CK-F and 32 Gy in four fractions (38 cases, 57.6% of CK-M) in CK-M, respectively. The dose was typically prescribed to the 80–90% isodose line for PTV.

Dosimetric parameters

Detailed dosimetric data were retrospectively collected and centrally analysed. PTV-related dosimetric parameters were evaluated for all patients, including PTV volume, percent of prescription coverage and dose to 95% of the volume. For the spinal cord, we collected data for the maximal point dose of 0.035 ml ($D_{\max}$)¹⁵ and the dose to 0.1 ml of the thecal sac, which was defined with a 1.5 mm margin with the spinal cord. To compare dosimetric parameters among the heterogeneous prescriptions, the EQD2 to the spinal cord and PTV were calculated. An α/β value of 10 Gy was used for the tumour effect and 2 Gy was used for spinal cord late effects.

The dosimetry of each plan was categorized into PTV coverage, conformity index (CI),¹⁶ new conformity index (nCI),¹⁷ homogeneity index (HI)¹⁸ and gradient index (GI).¹⁹ The detailed definition of CI is a ratio of total volume of tissue treated with prescription dose compared with the tumour volume covered by the prescription isodose reported in the CK planning system (MultiPlan 5.1.2, v. 5.1.2; Accuray Inc., Sunnyvale, CA). In addition, nCI, also reported in CK planning system, is defined as CI multiplied by ratio of total target volume to target volume receiving prescription dose or more (CI/PTV coverage).

Additionally, we compared results based on total treatment time, beam delivery time and total delivered motor units (MUs) for evaluating treatment efficacy. The beam delivery time included a beam-on time, imaging time with 1 min intervals and robot traveling time in the CK planning system. The total treatment time estimated from actual patient setup to unlock patient immobilization after treatment including patient setup time, the beam delivery time and patients' exit time.

Follow-up and relapse

All patients underwent pre-treatment evaluation and physical examination that included radiological assessment of MRI- or CT-based images of the spine. A radiation oncologist interviewed patients 1 month after treatment and every 3 months, thereafter, to assess pain and neurological symptoms. Follow-up MRI or CT was performed every 1–3 months after the end of the treatment during the first year and every 6 months thereafter. The response of spinal metastases was classified as controlled or progressed based on the criteria suggested by the SPIne response assessment

Table 1. Patient, disease and treatment characteristics

		Total	<i>n</i> = 144	Fixed	<i>n</i> = 78	MLC	<i>n</i> = 66	<i>p</i> -value
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Sex	Male	90	62.5	56	71.8	34	51.5	0.01
	Female	54	37.5	22	28.2	32	48.5	
ECOG PS	0–1	59	41.0	34	43.6	25	37.9	0.49
	≥2	85	59.0	44	56.4	41	62.1	
Tumour histology	Gastrointestinal	53	36.8	27	34.6	26	39.4	0.40
	Lung	30	20.8	21	26.9	9	13.6	
	Prostate	18	12.5	8	10.3	10	15.2	
	Renal	14	9.7	8	10.3	6	9.1	
	Melanoma	6	4.2	1	1.3	5	7.6	
	Sarcoma	5	3.5	2	2.6	3	4.5	
	Breast	4	2.8	2	2.6	2	3.0	
	Unknown primary	3	2.1	2	2.6	1	1.5	
	Other	11	7.6	7	9.0	4	6.1	
Reason to treat	Pain	102	70.8	56	71.8	46	69.7	0.58
	Pain with radiating pain	26	18.1	12	15.4	14	21.2	
	Neurological symptom	0	0.0	0	0.0	0	0.0	
	No symptom	16	11.1	10	12.8	6	9.1	
Status of metastasis	Bone	39	27.1	22	28.2	17	25.8	0.74
	Bone + visceral	105	72.9	56	71.8	49	74.2	
Status of bone metastasis	Single	32	22.2	13	16.7	19	28.8	0.08
	Multiple	112	77.8	65	83.3	47	71.2	
Bilsky grade	0–1c	104	72.2	53	67.9	51	77.3	0.21
	2–3	40	27.8	25	32.1	15	22.7	
Paraspinal space extension	No	54	37.5	25	32.1	29	43.9	0.14
	Yes	90	62.5	53	67.9	37	56.1	
SINS criteria (229 lesions)	Stable (0–6)	96	41.9	53	46.1	43	37.7	0.31
	Indeterminate (7–12)	121	52.8	55	47.8	66	57.9	
	Unstable (13–18)	12	5.2	7	6.1	5	4.4	
Compression fracture	Pre-existing fracture	47	32.6	27	34.6	20	30.3	0.58
	No fracture	97	67.4	51	65.4	46	69.7	
Treated level	Median (Range)	1 (1–5)		1 (1–5)		1 (1–4)		0.10
	Single	89	61.8	53	67.9	36	54.5	0.10
	Multiple	55	38.2	25	32.1	30	45.5	
PTV type	<180°	40	27.8	24	30.8	16	24.2	0.15
	180°	16	11.1	8	10.3	8	12.1	
	270°	55	38.2	32	41.0	23	34.8	
	Horseshoe	22	15.3	12	15.4	10	15.2	
	Doughnut	11	7.6	2	2.6	9	13.6	

(Continued)

Table 1. (Continued)

		Total	<i>n</i> = 144	Fixed	<i>n</i> = 78	MLC	<i>n</i> = 66	<i>p</i> -value
		<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	
Total dose/no. of Fxs	12–24 Gy/1 Fx	70	48.6	60	76.9	10	15.2	
	10–23 Gy/2 Fxs	5	3.5	2	2.6	3	4.5	
	24–36 Gy/3 Fxs	7	4.9	4	5.1	3	4.5	
	20–60 Gy/4 Fxs	54	37.5	12	15.4	42	63.6	
	24–48 Gy/8 Fxs	8	5.6	0	0.0	8	12.1	
Treatment session	Median (range)	2 (1–8)		1 (1–4)		4 (1–8)		<0.001
	Single	70	48.6	60	76.9	10	15.2	<0.001
	Multiple	74	51.4	18	23.1	56	84.8	

ECOG PS, Eastern Cooperative Oncology Group performance status; Fxs, fractions; PTV, planning treatment volume; SINS, spine instability neoplastic score.

in Neuro-Oncology group.²⁰ Local progression was defined as one of following: gross unequivocal increase in tumour volume or linear dimension, any new or progressive tumour within the epidural space and neurological deterioration attributable to pre-existing epidural disease with equivocal increased epidural disease dimensions.

Grading of treatment-related toxicity was performed at the time of follow-up based on the common terminology criteria for adverse events (CTCAE, v.4.03). Radiation-induced myelopathy (RM) was defined as neurological symptoms consistent with radiation damage without radiological evidence of a recurrent or progressive tumour affecting the spinal cord.²¹ At baseline, pre-existing vertebral compression fractures (VCFs) were assessed by comparison to the vertebral body (VB) height on prior imaging or, if unavailable, the average height of the immediately superior and inferior VBs. We evaluated the development of a new VCF or progression of an existing VCF at the site of treatment.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics v. 23 (SPSS Inc., Chicago, IL). Student's *t*-tests were used for normal variables and Mann–Whitney *U* test was used for ordinal but non-nominal variables between CK-F and CK-M groups. The Pearson's χ^2 tests or Fisher exact tests were employed to evaluate the differences of categorical data. All outcomes were measured from the day of SBRT to the time of the event. LC was defined as the time to local progression at the site specifically treated with CK. Overall survival (OS) was calculated as the time from treatment until death from any cause or last follow-up. The Kaplan–Meier method was used to estimate the LC and OS. Potential prognostic factors were compared using the log-rank test and factors with *p*-value less than 0.2 in univariate analyses were introduced into Cox proportional hazards model to determine the adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Logistic regression models were used to model increased VCFs as a function of collimator and other covariates. Two-tailed *p* values of ≤ 0.05 were considered statistically significant.

RESULTS

Cohort characteristics

A total of 119 patients treated with CK SBRT were included in this study: 229 lesions in 144 cases were finally analysed. Patient, disease and lesion characteristics are described in Table 1. The median age of the cohort was 62 years old (range, 18–82). On pre-SBRT neurological assessment, most cases had varying degrees of site-specific pain (*n* = 102, 71%) without any cases of neurological symptoms (*i.e.* sensory change or motor weakness). The overall disease burden in the entire cohort was relatively high; visceral organ involvement was reported in 105 cases (73%) and multiple bone metastases were reported in 112 cases (78%). Most lesions were categorized as bilsky Grade 0–1c (*n* = 104, 72%), extension to paraspinal space (*n* = 90, 63%) and either stable (*n* = 96, 42%) or indeterminate (*n* = 121, 53%) in SINS criteria. Multiple levels of spine were included in 55 cases (38%) and 270° degree of PTV type was most frequent (*n* = 55, 38%). There were no significant differences in disease and treatment characteristics between CK-F (*n* = 78, 54%) and CK-M (*n* = 66, 46%) except for the number of treatment sessions; median number of treatment sessions was one in CK-F (range, 1–4 sessions) and four in CK-M (range, 1–8 sessions), respectively (*p* < 0.001) (Table 1).

Dosimetric analysis

Dosimetric parameters of both collimator types are summarized in Table 2. For CK-M, plans were prescribed to high isodose levels. Coverage of PTV in CK-M was better than that of CK-F (median 90 vs 92%, respectively; *p* = 0.03) even with larger PTVs treated with CK-M. Despite higher prescription doses with CK-M, there were no significant differences in the doses to the spinal cord or thecal sac. The dose conformities (CI and nCI) between CK-F and CK-M suggested that they are comparable. However, CK-M showed a better homogeneous dose distribution (HI, *p* < 0.001) and dose gradient fall off (GI, *p* < 0.001).

The delivered MUs for the CK-M were reduced considerably (by 60%) compared with CK-F. This decrease in MUs resulted from a reduction in the total number of beams (median 54 vs 152 for CK-M and CK-F, respectively; *p* < 0.001) since each beam

Table 2. A comparison of dosimetric parameters between the fixed cone (Fixed) and multileaf collimators (MLC)

	Total (<i>n</i> = 144)	Fixed (<i>n</i> = 78)	MLC (<i>n</i> = 66)	<i>p</i> -value
	Median (IQR)	Median(IQR)	Median (IQR)	
PTV volume (cm ³)	52.9 (27.6;84.8)	46.7 (23.6;69.0)	64.2 (33.1;112.3)	0.01
Prescription total dose (Gy) ^a	42.0 (42.0;48.0)	42.0 (34.7;42.0)	48.0 (48.0;48.0)	<0.001
BED (Gy)	50.4 (50.4;57.6)	50.4 (41.6;50.4)	57.6 (57.6;57.6)	<0.001
PTV coverage (%)	90.4 (85.5;94.3)	90.0 (84.9;92.6)	91.8 (87.8;95.2)	0.03
Prescription isodose (%)	78.0 (75.0;80.0)	75.1 (73.0;78.0)	80.0 (77.0;82.0)	<0.001
Cord_0.035cc (Gy) ^a	52.5 (38.0;62.9)	52.7 (33.3;65.4)	51.8 (44.4;62.7)	0.55
Thecal sac_0.1cc (Gy) ^a	61.2 (44.9;72.7)	60.5 (37.1;75.0)	61.4 (52.7;72.5)	0.70
CI	1.04 (0.95;1.12)	1.02 (0.93;1.10)	1.05 (0.97;1.13)	0.16
nCI	1.27 (1.22;1.36)	1.28 (1.23;1.37)	1.27 (1.19;1.36)	0.19
HI	1.28 (1.25;1.33)	1.33 (1.28;1.37)	1.25 (1.22;1.30)	<0.001
GI	3.47 (3.06;4.04)	3.87 (3.54;4.70)	3.04 (2.86;3.36)	<0.001
Delivery time (min)	40.0 (31.0;50.0)	48.0 (38.0;53.0)	33.5 (27.0;39.0)	<0.001
Total treatment time (min)	55.0 (45.0;69.0)	65.0 (53.0;75.0)	47.0 (42.0;55.0)	<0.001
Delivered MU	14029.9 (7955.4;20864.5)	20193.7 (14141.6;23477.6)	8162.1 (6425.1;11375.2)	<0.001
Beam number	103.5 (58.0;157.5)	152.0 (123.0;180.0)	53.5 (41.0;68.0)	<0.001

BED, biologically effective dose; CI, conformity index; GI, gradient index; HI, homogeneity index; IQR, interquartile range; MU, motor unit; nCI, new conformity index; PTV, planning treatment volume.

^aThe equivalent dose in 2 Gy per day fractions was calculated for all dosimetric data using an α/β value of 10 Gy for tumour effect on PTV and a value of 2 Gy for the spinal cord late effects.

consists of multiple segments depending on the PTV shape. Total number of beams in CK-M was 35% of that in CK-F and delivery time in CK-M showed 30% decrease compared with CK-F (median delivery time 33.5 vs 48.0 min, $p < 0.001$).

In subgroup analysis based on PTV type (either $\leq 270^\circ$ or horse-shoe and doughnut-shaped) and PTV volume (cut-off value of median volume 52.9 cm³), CK-M consistently showed better dose homogeneity (HI), dose gradient fall off (GI), shorter beam delivery time, total treatment time, reduced delivered MU and number of beams [all $p < 0.05$, [Supplementary Tables 1 and 2](#) (Supplementary material available online)].

Local control (LC)

The median follow-up was 5.7 months (range, 1.1–18.8 months). Radiological progression occurred in 18 cases (12.5%). The actuarial 6 month and 1 year LC rates for the entire cohort were 88 and 78%, respectively ([Figure 1](#)). Univariate analysis results of LC are reported in [Table 3](#). For a categorical analysis of dosimetric parameters, the median values were used as the cut-off point. There was no difference in LC according to collimator type ($p = 0.83$, [Figure 2](#)), PTV volume ($p = 0.50$), PTV coverage ($p = 0.78$) and other dosimetric parameters (all $p > 0.05$). The only significant variable associated with LC was the prescribed dose with a cut-off value of 42 Gy ($p = 0.05$, HR 0.40, 95% confidence interval CIs 0.16–1.02). In the Cox proportional hazards model, two independent predictors of LC were identified: multiple levels of spine ($p = 0.04$, HR 3.59) and prescribed dose ($p = 0.01$, HR 0.24, [Table 3](#)). OS at 6 months and 1 year was 66.2 and 49.8%

after CK-F and 59.7 and 54.7% after CK-M, with no significant difference between collimator groups.

Toxicity

The overall rate of pain relief was 82% (118 of 134) at 1 month after treatment. There was no severe acute toxicity; Grade 2 generalized weakness was observed in 15 cases, Grade 2 fatigue in 14 and Grade 2 nausea in 13. There was no clinically detectable RM; however, there were 11 cases of persistent radiating pain; 4 of progressive lesions and 7 of stable lesions without clinical aggravation. 29 of 144 cases had VCFs (20%), with 14 of 97 (14%)

Figure 1. LC following treatment for the entire cohort.

Table 3. Univariate Cox regression and competing risk analyses of factors associated with local control (LC)

Variables		Univariate analysis			Multivariate analysis		
		HR	95% CIs	p-value	HR	95% CIs	p-value
Paraspinal extension	No	Ref.		0.63			
	Yes	0.80	0.31–2.02				
Bilsky grade	0–1c	Ref.		0.16	Ref.		0.37
	2–3	1.95	0.77–4.95		1.62	0.57–4.61	
Spine level	Single	Ref.		0.16	Ref.		0.04
	Multiple	1.95	0.77–4.95		3.59	1.08–11.89	
Collimator	Fixed	Ref.		0.83			
	MLC	0.89	0.30–2.64				
PTV volume	<52.9 cm ³	Ref.		0.50			
	≥52.9 cm ³	1.38	0.54–3.51				
Prescription dose ^a	<42 Gy	Ref.		0.05	Ref.		0.01
	≥42 Gy	0.40	0.16–1.02		0.24	0.08–0.75	
PTV coverage	<90.4%	Ref.		0.78			
	≥90.4%	0.88	0.34–2.22				
PTV_Dmean ^a	<52.7 Gy	Ref.		0.79			
	≥52.7 Gy	0.88	0.34–2.29				
PTV_D95 ^a	<40.2 Gy	Ref.		0.16			
	≥40.2 Gy	0.47	0.17–1.34				
Cord_D _{max} ^a	<52.5 Gy	Ref.		0.75			
	≥52.5 Gy	0.86	0.34–2.19				
Thecal sac_D _{max} ^a	<61.2 Gy	Ref.		0.41			
	≥61.2 Gy	0.67	0.26–1.73				
CI	<1.040	Ref.		0.60			
	≥1.040	0.78	0.31–1.97				
nCI	<1.275	Ref.		0.06	Ref.		0.07
	≥1.275	0.39	0.15–1.05		0.39	0.14–1.09	
HI	<1.280	Ref.		0.70			
	≥1.280	1.23	0.43–3.50				
GI	<3.470	Ref.		0.12	Ref.		0.07
	≥3.470	0.45	0.17–1.22		0.38	0.13–1.07	

CI, conformity index; D95, Dose to 95% of the volume; D_{max}, maximum dose; Dmean, Mean dose; HI, homogeneity index; HR, hazard ratio; GI, gradient index; PTV, planning treatment volume; CIs, confidence interval.

^aThe equivalent dose in 2 Gy per day fractions was calculated for all dosimetric data using an α/β value of 10 Gy for tumour effect on PTV and a value of 2 Gy for the spinal cord late effects.

de novo and 15 of 47 (32%) having progressed from an existing VCF. The median time to VCF was 4.1 months (range, 0.7–19.2 months) and 60% (18 cases) occurred within 6 months after treatment. In logistic regression, both pre-treatment VCF ($p = 0.02$, odds ratio 2.78, 95% CIs 1.21–6.41) and instability in SINS criteria ($p = 0.04$, odds ratio 2.28, 95% CIs 1.07–5.16) were associated factors of VCFs. However, dose per fraction, PTV volume,

PTV coverage and collimator option were not correlated with VCF (all $p > 0.05$).

DISCUSSION

We found that the CK-M is comparable with CK-F with respect to target coverage and conformity, even with larger target volumes. Our results also showed a reduction of approximately

Figure 2. LC after CyberKnife (CK) by collimator options: fixed collimator (Fixed) ($n = 78$), MLC ($n = 66$).

34% in delivery time compared with CK-F, with comparable LC and tolerable toxicities.

Spine SBRT has the advantage of delivering high total doses in few fractions with locally ablative intent. Several SBRT series with CK reported LC rates between 80 and 95%.^{22–27} We observed a comparable 1 year LC rate of 78%, with no difference between CK-M and CK-F. In addition, treatment of multiple spine levels was correlated with worse LC in accordance with previous study from Balagamwala et al.²⁸ Multilevel disease might inherently be more resistant to treatment and there could be a chance of missing micrometastasis paraspinal region owing to high-conformity of spine SBRT.

We examined tumour characteristics along with several dosimetric parameters of the PTV and spinal cord according to each collimator. We observed that CK-M covered larger PTV volumes without compromising either the CI values or PTV coverage with better dose homogeneity and fall off. We observed that CK-M covered larger PTV volumes without compromising either the CI values or PTV coverage with better dose homogeneity and fall off. In addition, CK-M could deliver higher prescription dose to larger PTV volumes than CK-F without compromising spinal cord dose threshold resulting in comparable LC. Consistent with our study, Jang et al.¹⁰ evaluated MLC for single or multiple brain metastases, reporting that MLC is only superior in delivery efficacy but not in conformity or dose fall off. However, their study selectively focused on brain metastases, which have significantly smaller treatment volumes and regular shapes compared with those of the spine. MLC-based treatment also exhibited dosimetric improvement when covering even larger and irregular-shaped lesions as shown in the current CK-SBRT. In accordance to the current study, Kathriarachchi et al demonstrated CK-M showed comparable conformity, target coverage, normal organ sparing, tumour control probability and normal tissue complication probability with significantly shortened treatment time in prostate radiotherapy which is relatively complicated (both larger and irregular) plan.

The main disadvantage of CK for spine SBRT is a relatively longer treatment time.²⁹ Of the limited studies regarding delivery time, one found that each CK treatment session lasts for a median 55 min, ranging from 40 to 180 min.³⁰ Most spine SBRT patients (including ours) experience pain,²² making it difficult to remain immobilized for long periods during beam delivery. Hence, we found that one of the important advantages of the MLC is its shorter delivery time.

Total treatment time depends on the total number of beams rather than the total MUs.¹⁰ Therefore, finding paths to reduce the total number of beams without compromising PTV coverage and conformity is crucial in improving treatment efficacy. Additionally, minimizing the number of preset nodes is also required to reduce the robot arm traveling time, which is longer than that of reorienting the machine.³¹ As shown in Table 2, the median MU using the CK-M was approximately 40% for the CK-F and the median beam numbers with the CK-M were lower than for the CK-F by approximately 35%, resulting in a 30% reduction in delivery time. In multiple logistic regression for delivery time (data not shown), both reduced MU (β 0.73) and reduced number of beams (β 0.53) have affected on treatment time ($p < 0.001$).

There are conflicting reports regarding the dose limitations to the spinal cord for spine SBRT. A recent multiinstitutional investigation³² estimated the probability of RM to be under 5% if the $D_{\max}$ to the thecal sac was limited to 12.4 Gy for a single fraction. In contrast to previous studies^{33,34} that suggested thresholds of approximately 10 Gy to the spinal cord to prevent RM, Yamada et al³⁵ suggested limiting the $D_{\max}$ to under 14 Gy for a single fraction. Our analysis supports their conclusions; no case of RM was observed from 31 cases (22%) treated with maximum dose of 10–15 Gy to the spinal cord for a single fraction until the last follow-up (median 7.8 months, range 1.1–18.8 months). As the MLC leaf is not focused between the fully open and midline positions, increased penumbra-leakage into the neighboring field can occur. Since the CK has no secondary jaw unlike conventional linear accelerators, CK-M might deliver leaked radiation to normal organs such as the spinal cord. However, our study showed that there was no difference in the $D_{\max}$ to spinal cord or thecal sac and no increase in the incidence of RM.

Although we are the first to report the clinical outcomes of patients treated with either CK-M or CK-F after equipping the CK systems with MLC, this single-institution, retrospective study is subject to selection and physician biases. These results are truly consecutive results of bridge the transition from a fixed cone-based CK to a MLC-based CK. Furthermore, because it includes patients with a variety of different primary tumour types, the prescription dose is wide, and there is heterogeneity of both patients and diseases. Relatively high disease burden as mentioned above also contribute to high censoring rate of local progression. All other treatment techniques, however, remained consistent throughout the period with the exception of the prescription dose and collimator selection. Another potential shortcoming of the study is that its results were based on a relatively short follow-up period

possibly owing to the high disease burden cohort; additional follow-up is, therefore, required.

In conclusion, spine SBRT for achieving ablative LC is in greater demand. We found that the recently available CK-M used an equivalent treatment plan within a significantly shorter time compared with CK-F, even with larger target volumes. There was no difference in radiological control between the two collimators and no RM was observed. CK-M could, therefore, be an effective and tolerable treatment option in the era of spine SBRT. These

preliminary results support the widespread use of CK-M for spine SBRT.

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REFERENCES

- Schmidt MH, Klimo P Jr, Vrionis FD. Metastatic spinal cord compression. *J Natl Compr Canc Netw* 2005; **3**: 711–9. doi: <https://doi.org/10.6004/jncn.2005.0041>
- Chow E, Harris K, Fan G, Tsao M, Sze WM. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007; **25**: 1423–36. doi: <https://doi.org/10.1200/JCO.2006.09.5281>
- Howell DD, James JL, Hartsell WF, Suntharalingam M, Machtay M, Suh JH, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases—equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. *Cancer* 2013; **119**: 888–96. doi: <https://doi.org/10.1002/cncr.27616>
- Mizumoto M, Harada H, Asakura H, Hashimoto T, Furutani K, Hashii H, et al. Radiotherapy for patients with metastases to the spinal column: a review of 603 patients at Shizuoka Cancer Center Hospital. *Int J Radiat Oncol Biol Phys* 2011; **79**: 208–13. doi: <https://doi.org/10.1016/j.ijrobp.2009.10.056>
- Lutz S, Berk L, Chang E, Chow E, Hahn C, Hoskin P, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011; **79**: 965–76. doi: <https://doi.org/10.1016/j.ijrobp.2010.11.026>
- Kumar R, Nater A, Hashmi A, Myrehaug S, Lee Y, Ma L. The era of stereotactic body radiotherapy for spinal metastases and the multidisciplinary management of complex cases. *Neuro-Oncology Practice* 2016; **3**: 48–58.
- Sudhar H, Kurup PG, Murali V, Velmurugan J. Dose linearity and monitor unit stability of a G4 type cyberknife robotic stereotactic radiosurgery system. *J Med Phys* 2012; **37**: 4–7. doi: <https://doi.org/10.4103/0971-6203.92714>
- Fahimian B, Soltys S, Xing L, Gibbs I, Chang S, Wang L. SU-E-T-603: evaluation of MLC-based robotic radiotherapy. *Med Phys* 2013; **40**(6Part20): 344. doi: <https://doi.org/10.1118/1.4815031>
- McGuinness CM, Gottschalk AR, Lessard E, Nakamura JL, Pinnaduwa D, Pouliot J, et al. Investigating the clinical advantages of a robotic linac equipped with a multileaf collimator in the treatment of brain and prostate cancer patients. *J Appl Clin Med Phys* 2015; **16**: 5502–. doi: <https://doi.org/10.1120/jacmp.v16i5.5502>
- Jang SY, Lalonde R, Ozhasoglu C, Burton S, Heron D, Huq MS. Dosimetric comparison between cone/Iris-based and InCise MLC-based CyberKnife plans for single and multiple brain metastases. *J Appl Clin Med Phys* 2016; **17**: 6260–. doi: <https://doi.org/10.1120/jacmp.v17i5.6260>
- Kathiriarachchi V, Shang C, Evans G, Leventouri T, Kalantzis G. Dosimetric and radiobiological comparison of CyberKnife M6™ InCise multileaf collimator over IRIS™ variable collimator in prostate stereotactic body radiation therapy. *J Med Phys* 2016; **41**: 135–43. doi: <https://doi.org/10.4103/0971-6203.181638>
- Bilsky MH, Laufer I, Fournier DR, Groff M, Schmidt MH, Varga PP, et al. Reliability analysis of the epidural spinal cord compression scale. *J Neurosurg Spine* 2010; **13**: 324–8. doi: <https://doi.org/10.3171/2010.3.SPINE09459>
- Fisher CG, DiPaola CP, Ryken TC, Bilsky MH, Shaffrey CI, Berven SH, et al. A novel classification system for spinal instability in neoplastic disease: an evidence-based approach and expert consensus from the Spine Oncology Study Group. *Spine* 2010; **35**: E1221–9. doi: <https://doi.org/10.1097/BRS.0b013e3181e16ae2>
- Cox BW, Spratt DE, Lovelock M, Bilsky MH, Lis E, Ryu S, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys* 2012; **83**: e597–e605. doi: <https://doi.org/10.1016/j.ijrobp.2012.03.009>
- Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys* 2010; **37**: 4078–101. doi: <https://doi.org/10.1118/1.3438081>
- Lomax NJ, Scheib SG. Quantifying the degree of conformity in radiosurgery treatment planning. *Int J Radiat Oncol Biol Phys* 2003; **55**: 1409–19. doi: [https://doi.org/10.1016/S0360-3016\(02\)04599-6](https://doi.org/10.1016/S0360-3016(02)04599-6)
- Paddick I. A simple scoring ratio to index the conformity of radiosurgical treatment plans. Technical note. *J Neurosurg* 2000; **93** Suppl 3(Suppl. 3): 219–22. doi: <https://doi.org/10.3171/jns.2000.93.supplement>
- Shaw E, Kline R, Gillin M, Souhami L, Hirschfeld A, Dinapoli R, et al. Radiation Therapy Oncology Group: radiosurgery quality assurance guidelines. *Int J Radiat Oncol Biol Phys* 1993; **27**: 1231–9. doi: [https://doi.org/10.1016/0360-3016\(93\)90548-A](https://doi.org/10.1016/0360-3016(93)90548-A)
- Paddick I, Lippitz B. A simple dose gradient measurement tool to complement the conformity index. *J Neurosurg* 2006; **105** Suppl(Suppl.): 194–201. doi: <https://doi.org/10.3171/sup.2006.105.7.194>
- Thibault I, Chang EL, Sheehan J, Ahluwalia MS, Guckenberger M, Sohn MJ, et al. Response assessment after stereotactic body radiotherapy for spinal metastasis: a report from the SPIne response assessment in Neuro-Oncology (SPINO) group. *Lancet Oncol* 2015; **16**: e595–603e603. doi: [https://doi.org/10.1016/S1470-2045\(15\)00166-7](https://doi.org/10.1016/S1470-2045(15)00166-7)
- Wong CS, Van Dyk J, Milosevic M, Laperriere NJ. Radiation myelopathy following single courses of radiotherapy and retreatment. *Int J Radiat Oncol Biol Phys*

- 1994; **30**: 575–81. doi: [https://doi.org/10.1016/0360-3016\(92\)90943-C](https://doi.org/10.1016/0360-3016(92)90943-C)
22. Gerszten PC, Burton SA, Ozhasoglu C, Welch WC. Radiosurgery for spinal metastases: clinical experience in 500 cases from a single institution. *Spine* 2007; **32**: 193–9. doi: <https://doi.org/10.1097/01.brs.0000251863.76595.a2>
23. Park HJ, Kim HJ, Won JH, Lee SC, Chang AR. Stereotactic body radiotherapy (SBRT) for spinal metastases: who will benefit the most from SBRT? *Technol Cancer Res Treat* 2015; **14**: 159–67. doi: <https://doi.org/10.7785/tcrt.2012.500411>
24. Gill B, Oermann E, Ju A, Suy S, Yu X, Rabin J, et al. Fiducial-free CyberKnife stereotactic body radiation therapy (SBRT) for single vertebral body metastases: acceptable local control and normal tissue tolerance with 5 fraction approach. *Front Oncol* 2012; **2**: 39. doi: <https://doi.org/10.3389/fonc.2012.00039>
25. Gerszten PC, Burton SA, Ozhasoglu C, Vogel WJ, Welch WC, Baar J, et al. Stereotactic radiosurgery for spinal metastases from renal cell carcinoma. *J Neurosurg Spine* 2005; **3**: 288–95. doi: <https://doi.org/10.3171/spi.2005.3.4.0288>
26. Tsai JT, Lin JW, Chiu WT, Chu WC. Assessment of image-guided CyberKnife radiosurgery for metastatic spine tumors. *J Neurooncol* 2009; **94**: 119–27. doi: <https://doi.org/10.1007/s11060-009-9814-7>
27. Ryu S, Yoon H, Stessin A, Gutman F, Rosiello A, Davis R. Contemporary treatment with radiosurgery for spine metastasis and spinal cord compression in 2015. *Radiat Oncol J* 2015; **33**: 1–11. doi: <https://doi.org/10.3857/roj.2015.33.1.1>
28. Balagamwala EH, Angelov L, Koyfman SA, Suh JH, Reddy CA, Djemil T, et al. Single-fraction stereotactic body radiotherapy for spinal metastases from renal cell carcinoma. *J Neurosurg Spine* 2012; **17**: 556–64. doi: <https://doi.org/10.3171/2012.8.SPINE12303>
29. Sahgal A, Larson DA, Chang EL. Stereotactic body radiosurgery for spinal metastases: a critical review. *Int J Radiat Oncol Biol Phys* 2008; **71**: 652–65. doi: <https://doi.org/10.1016/j.ijrobp.2008.02.060>
30. Muacevic A, Kufeld M, Rist C, Wowra B, Stief C, Staehler M. Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer. *Urol Oncol* 2013; **31**: 455–60. doi: <https://doi.org/10.1016/j.urolonc.2011.02.023>
31. van de Water S, Hoogeman MS, Breedveld S, Nuytens JJ, Schaart DR, Heijmen BJ. Variable circular collimator in robotic radiosurgery: a time-efficient alternative to a mini-multileaf collimator? *Int J Radiat Oncol Biol Phys* 2011; **81**: 863–70. doi: <https://doi.org/10.1016/j.ijrobp.2010.12.052>
32. Sahgal A, Weinberg V, Ma L, Chang E, Chao S, Muacevic A, et al. Probabilities of radiation myelopathy specific to stereotactic body radiation therapy to guide safe practice. *Int J Radiat Oncol Biol Phys* 2013; **85**: 341–7. doi: <https://doi.org/10.1016/j.ijrobp.2012.05.007>
33. Macbeth FR, Wheldon TE, Girling DJ, Stephens RJ, Machin D, Bleehen NM. Radiation myelopathy: estimates of risk in 1048 patients in three randomized trials of palliative radiotherapy for non-small cell lung cancer. The medical research council lung cancer working party. *Clin Oncol* 1996; **8**: 176–81.
34. Chang EL, Shiu AS, Mendel E, Mathews LA, Mahajan A, Allen PK, et al. Phase I/II study of stereotactic body radiotherapy for spinal metastasis and its pattern of failure. *J Neurosurg Spine* 2007; **7**: 151–60. doi: <https://doi.org/10.3171/SPI-07/08/151>
35. Yamada Y, Bilsky MH, Lovelock DM, Venkatraman ES, Toner S, Johnson J, et al. High-dose, single-fraction image-guided intensity-modulated radiotherapy for metastatic spinal lesions. *Int J Radiat Oncol Biol Phys* 2008; **71**: 484–90. doi: <https://doi.org/10.1016/j.ijrobp.2007.11.046>