Evaluation of predictive factors of vertebral compression fracture after conventional palliative radiotherapy for spinal metastasis from colorectal cancer

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OBJECTIVE Delayed consequences of spinal radiotherapy (RT), including vertebral compression fracture (VCF), are critical complications. However, the predisposing factors that contribute to VCF after conventional RT are unclear. The aim of this study was to assess the incidence of VCF and to determine the predictors of VCF following conventional spinal RT specific to colorectal cancer (CRC).

METHODS The authors retrospectively reviewed 237 spinal segments (147 metastatic and 90 nonmetastatic) in 53 patients with CRC who underwent RT with a median total dose of 30 Gy in 10 fractions between January 2007 and December 2014. The primary end point was the development of a VCF following RT, either de novo VCF or the progression of a baseline VCF. VCFs were assessed using the spinal instability neoplastic score (SINS) criteria.

RESULTS Among all 237 spinal segments, 22 VCFs (9.3%) were observed following RT, including 13 de novo and 9 progressive fractures, and the median time to VCF was 4 months. All VCFs developed in metastatic spines. Among 147 metastatic spinal segments, 22 fractures were observed, with a 12-month cumulative incidence of VCF of 14.8%. Results of multivariable analysis indicated sex ($p = 0.023$) and SINS class II/III ($p < 0.001$) as risk factors related to development of a VCF in metastatic spinal segments. Among the SINS criteria, a lytic tumor and the presence of a baseline VCF were identified as predictors of VCF in metastatic spinal segments.

CONCLUSIONS In osteolytic or mixed lesions that were predominant in spinal metastases of CRC, the incidence of VCF was not negligible, even in patients treated with conventional spinal RT. This was especially evident in patients with spinal metastases with a SINS score ≥ 7 . Presence of a baseline VCF after spinal RT is a predictor of VCF development and should be observed carefully.

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KEY WORDS spinal metastasis; radiotherapy; vertebral compression fracture; colorectal cancer; oncology

IN metastatic colorectal cancer (CRC), the bone, including the spine, is the third most common site for metastases following the liver and lungs.^{14,24} In addition, the incidence of bone metastases in patients with CRC is expected to increase because of the development of modern chemotherapy that leads to prolonged survival.^{2,11,16,18,26} Spinal metastasis is a significant problem in metastatic disease, because it has nonfunctional consequences due to pain and leads to decreased quality of life as the result of neurological sequelae.²⁵

Previous studies have demonstrated that radiotherapy (RT) is an efficacious treatment for spinal metastases in terms of palliation and the preservation of neurological function.^{5,6} After spinal RT, delayed consequences, including vertebral compression fracture (VCF), are critical complications in clinical practice. However, it is unknown which factors predispose patients to VCFs in association with spinal RT, especially for conventional RT,⁵ even though conventional RT is the most commonly used RT regimen for spinal metastasis in clinical practice.²⁷

ABBREVIATIONS BED = biologically equivalent dose; CRC = colorectal cancer; RT = radiotherapy; SBRT = stereotactic body radiotherapy; SINS = spinal instability neoplastic score; VCF = vertebral compression fracture.

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Although several studies have assessed VCF after palliative RT, in particular stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery,^{1,12,15,21,22} there are limited data on the development of VCF after RT using conventional fractionation for spinal metastasis of CRC. In this study, we aimed to assess the incidence of VCF and to determine the predictors of VCF following conventional spinal RT for spinal metastasis of CRC.

Methods

Study Design

We retrospectively retrieved data from 53 patients with CRC with spinal metastasis who were treated with palliative RT between January 2007 and December 2014. There were a total of 237 spinal segments, consisting of 147 metastatic and 90 nonmetastatic segments. All patients were initially diagnosed with CRC based on pathological findings. They were clinico-radiologically diagnosed as having spinal metastasis of CRC based on MRI and/or CT findings and did not receive surgical treatment for spine metastasis. In addition, all patients had a follow-up period > 3 months after spinal RT. Patients who were diagnosed as having osteoporosis and those who received hormone therapy and/or bisphosphonate therapy were excluded, because previous studies have reported that these factors might affect skeletal-related events, including pathologic fracture.^{4,13,20,23} We assessed the development of VCF after spinal RT in metastatic vertebral segments and nonmetastatic vertebral segments according to the RT volume. This study was approved by the institutional review board at Yonsei Cancer Center.

RT Treatment

All segments were treated with palliative RT using a conventional fraction size. The treatment volume of conventional RT for metastatic spine included the entire vertebral body of metastatic-involved spines, plus 1 or 2 vertebral nonmetastatic spine segments superior and inferior to the metastatic spinal segments. The RT modality, total dose, and fractions were determined with various schemes depending on the physician's judgment based on the patient's performance status, extent of spinal metastasis, and previous radiation.

Pretreatment Assessment

All irradiated spinal segments consisted of metastatic and nonmetastatic vertebrae and were examined in terms of the baseline vertebral status and clinical variables, such as age, sex, primary cancer, body mass index, spinal level, presence of pain, presence of metastasis, prior irradiation, and RT modality. Furthermore, each metastatic spinal segment was evaluated according to the baseline vertebral status and aforementioned clinical variables, and detailed radiological criteria for the spinal instability neoplastic score (SINS) were used to investigate significant factors predictive of VCF. The SINS is a scoring system of spinal instability based on 6 criteria consisting of location, intensity of pain, type of bone lesion, spinal alignment, vertebral body collapse, and posterolateral involvement, and it ranges from 0 to 18 points.⁸ The SINS divides the status

of metastatic spinal segments into 3 categories according to score: class I, stable (0–6 points); class II, potentially unstable (7–12 points); and class III, unstable (13–18 points).^{8,9} Pretreatment evaluation of patients' vertebral statuses was based on diagnostic MR and/or CT images with reference to RT and planning CT images. The type of bone lesion (blastic, lytic, or mixed) and spine alignment were classified by diagnostic and planning CT images. MR images were also used to evaluate paraspinal extension, vertebral body collapse, and posterior element involvement.

Posttreatment Assessment

A VCF was defined as the development of a new VCF or progressive VCF in a previously fractured vertebra after RT without evidence of tumor metastasis or progression. A progressive VCF was defined as > 20% reduction in vertebral body height, according to previous reports.^{3,19} We assessed the development of VCFs using follow-up MR or CT images, which were usually obtained at 1–3 month intervals after RT or based on a physician's judgment for an image examination.

Statistical Analysis

The VCF rates by all categorical variables were compared using the Fisher exact test or chi-square test. The cumulative incidence of VCF was estimated from the end date of RT to the date that the VCF developed or the date of the last imaging study if there was no fracture, taking competing events such as deaths into consideration, and the differences were evaluated by Gray's test.¹⁰ Multivariable analysis was performed by comparing the cumulative incidence of VCF using Fine and Gray regression analysis.⁷ A *p* value < 0.05 was considered statistically significant for all analyses. Statistical analyses were performed using R software version 3.2.2 (R Development Core Team).

Results

Characteristics of Patients and Irradiated Spinal Segments

The median age of the 53 patients was 61 years (range 35–77 years), and 26 (49%) patients were men. The proportion of patients with adenocarcinoma (46 of 53, 87%) was larger than that of those with signet ring cell carcinoma (1 of 53, 2%) and neuroendocrine carcinoma (6 of 53, 11%). Among all 237 irradiated spinal segments in 53 patients, the thoracic spine (102 of 237, 43.0%) was the dominant site of spinal metastasis. One hundred forty-seven (62.0%) vertebral segments had metastasis, 11 (4.6%) received prior radiation, and 17 (7.2%) had a preexisting baseline VCF.

Among all of the spinal segments, the median total dose, dose per fraction, and number of fractions of spinal RT were 30 Gy (range 8–60 Gy), 3 Gy (range 1.2–8 Gy), and 10 fractions (range 1–25 fractions), respectively. Thirty-one (13.1%) segments were irradiated with a biologically equivalent dose (BED) > 39 Gy for $\alpha/\beta = 10$ (BED _{$\alpha/\beta = 10$}). Among 147 metastatic spinal segments, 7.5% (*n* = 11) had been previously irradiated, 41.4% (*n* = 61)

TABLE 1. Baseline characteristics in all irradiated spinal and metastatic irradiated spinal segments

Variable	All Irradiated Segments		Metastatic Irradiated Segments	
	No.	%	No.	%
No. of segments	237	100	147	100
Patient age, yrs				
Median (range)	61 (35–77)		61 (35–77)	
<60	106	44.7	62	42.2
≥60	131	55.3	85	57.8
Sex				
Male	112	47.3	72	49.0
Female	125	52.7	75	51.0
Primary site				
Rectum	136	57.4	85	57.8
Colon	101	42.6	62	42.2
Pathology				
Adenocarcinoma	206	86.9	120	81.6
SRCa	5	2.1	5	3.4
Neuroendocrine carcinoma	26	11.0	22	15.0
BMI, kg/m ²				
<25	185	78.1	120	81.6
≥25	52	21.9	27	18.4
Spinal level				
Cervical	33	13.9	22	15.0
Thoracic	102	43.0	57	38.8
Lumbar	77	32.5	50	34.0
Sacral	25	10.5	18	12.2
Metastasis				
Metastatic	147	62.0		
Nonmetastatic	90	38.0		
Prior irradiation				
No	226	95.4	136	92.5
Yes	11	4.6	11	7.5
Baseline VCF				
No	220	92.8	130	88.4
Yes	17	7.2	17	11.6
Total dose, Gy				
Median (range)	30 (8–60)		30 (8–60)	
≤30	209	88.2	132	89.8
>30	28	11.8	15	10.2
Median dose of fraction, Gy (range)	3 (1.2–8)		3 (1.2–8)	
Median no. of fractions (range)	10 (1–25)		10 (1–25)	
BED _{αβ = 10} , Gy				
Median (range)	39 (14–74)		39 (14–74)	
≤39	206	86.9	131	89.1
>39	31	13.1	16	10.9

BMI = body mass index; SRCa = signet ring cell carcinoma.
All values reported as number (%) unless otherwise indicated.

FIG. 1. Cumulative incidence of VCFs in all irradiated spinal segments (Gray's test).

had a lytic lesion, and 11.6% (n = 17) had a baseline VCF. Table 1 summarizes the baseline characteristics of all irradiated spinal segments and metastatic spine segments. In addition, the detailed dose scheme of spinal RT is shown in Supplementary Table 1.

VCF Rate, Cumulative Incidence of VCF, and Predictive Variables for All Irradiated Spines

The median duration of follow-up for all patients was 10 months (range 3–99 months). Among the 237 irradiated spinal segments, 22 VCFs (9.3%) were observed following RT, including 13 de novo fractures and 9 progressive fractures, with a median time to development of 4 months (range 3–24 months). All VCFs developed in metastatic spines. Of 22 patients with a VCF, 9 underwent stabilization operation, and 13 remained asymptomatic without operation.

The VCF rate in all irradiated spines was significantly different according to metastatic involvement (metastatic vs nonmetastatic, $p < 0.001$) and presence of a baseline VCF (no vs yes, $p < 0.001$; Supplementary Table 2). The cumulative incidence of VCF at 12 months was 9.1% (Fig. 1). In the analysis of risk factors for the cumulative incidence of VCF, prior RT ($p = 0.035$), presence of a baseline VCF ($p < 0.001$), and SINS class ($p < 0.001$) were significant factors (Supplementary Table 3).

Among irradiated nonmetastatic spine segments, only 1 VCF developed in a 70-year-old woman. She developed a VCF 5 months after conventional palliative RT (25 Gy in 10 fractions). She underwent decompressive laminectomy for the VCF, and a metastatic tumor was detected on pathological examination. In this case, a VCF in an irradiated nonmetastatic spine may be induced by either progression of an adjacent involved metastatic spine segment or progression of an undetectable existing metastatic tumor. Finally, the cumulative incidence of VCF at 12

TABLE 2. VCF rate according to components of SINS in 147 metastatic spinal segments

Variable	No. of VCFs (–)	No. of VCFs (+)	VCF Rate (%) According to SINS Variable	p Value
SINS component				
Location				0.390
Rigid (S2–5)	11	0	0.0	
Semirigid (T3–10)	23	3	11.5	
Mobile spine (C3–6, L2–4)	39	6	13.3	
Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	52	13	20.0	
Pain				0.283
Pain free	7	0	0.0	
Occasional & nonmechanical	60	8	11.8	
Mechanical	58	14	19.4	
Bone lesion type				<0.001
Blastic	0	0		
Mixed	84	2	2.3	
Lytic	41	20	32.8	
Spine alignment				0.481
Normal	122	21	14.7	
Kyphosis/scoliosis	3	1	25.0	
Subluxation/translation	0	0		
Vertebral body collapse				<0.001
None of the below	87	1	1.1	
No collapse but >50% of body involved by tumor	30	13	30.2	
<50%	6	7	53.8	
≥50%	2	1	33.3	
Posterolateral involvement				0.221
Not involved	102	13	11.3	
Unilateral	13	7	35.0	
Bilateral	10	2	16.7	
SINS class				<0.001
I	83	1	1.2	
II	42	20	32.3	
III	0	1	100.0	

C = cervical; L = lumbar; S = sacral; T = thoracic.

months related to conventional RT in nonmetastatic segments was 0%.

VCF Rate, Cumulative Incidence of VCF, and Predictive Variables in Metastatic Spines

We observed 22 VCFs among 147 metastatic spinal segments (14.9%) following RT, consisting of 13 de novo fractures and 9 progressive fractures in metastatic spines. Among the 147 metastatic spinal segments, the propor-

TABLE 3. VCF rate according to various factors in 147 metastatic spinal segments

Variable	No. of VCFs (–)	No. of VCFs (+)	VCF Rate (%) According to Variables	p Value
Age, yrs				0.102
<60	49	13	21.0	
≥60	76	9	10.6	
Sex				0.106
Male	65	7	9.7	
Female	60	15	20.0	
Primary site				0.816
Rectum	73	12	14.1	
Colon	52	10	16.1	
BMI, kg/m ²				0.243
<25	104	16	13.3	
≥25	21	6	22.2	
Prior irradiation				0.215
No	117	19	14.0	
Yes	8	3	27.3	
BED _{α/β = 10} , Gy				0.017
≤39	115	16	12.2	
>39	10	6	37.5	
SINS class				<0.001
I	83	1	1.2	
II/III	42	21	33.3	

tions of SINS classes I, II, and III were 57.1% (n = 84), 42.2% (n = 62), and 0.7% (n = 1), respectively. Among the 6 SINS criteria, the type of bone lesion (p < 0.001) and vertebral body collapse status (p < 0.001) were confirmed as risk factors related to the development of VCF, whereas the location of the lesion (p = 0.390), intensity of the pain (p = 0.283), spinal alignment (p = 0.481), and posterolateral involvement (p = 0.221) were not indicated as risk factors (Table 2). In particular, when examined by location of metastatic spinal segments, the VCF rate did not statistically significantly differ between junctional and nonjunctional spinal segments (20.0% vs 10.9%; p = 0.163). Furthermore, the VCF rate in metastatic spines was affected by the RT dose (≤ 39 vs > 39 Gy of BED; p = 0.017) and SINS class (II/III vs I; p < 0.001; Table 3).

Among all metastatic spines, the 12-month cumulative incidence of VCF was 14.8% (Fig. 2A). The cumulative incidence of VCF at 12 months with a SINS class I versus II/III was 0% versus 46.8% (p < 0.001) (Table 2, Fig. 2B). Results of multivariable analysis showed that the cumulative incidence of VCF in metastatic spine segments was significantly different according to the SINS class (II/III vs I, HR 36.02, 95% CI 5.10–254.33; p < 0.001) and sex (female vs male, HR 2.73, 95% CI 1.14–6.52; p = 0.023; Table 4). Figure 3 shows a representative metastatic spinal segment with a high SINS score that developed a VCF after conventional RT.

In terms of SINS radiographic and clinical compo-

FIG. 2. Left: Cumulative incidence of VCFs in irradiated metastatic spinal segments. **Right:** Cumulative incidence stratified by the SINS class of irradiated metastatic spinal segments (Gray's test).

nents, we calculated the VCF rate in metastatic spines according to the observed risk factors, including the SINS class (I vs II/III), presence of a baseline VCF (no vs yes), and prior RT (no vs yes). The VCF rates for metastatic spines with a SINS class I and II/III were 1% and 33%, respectively. Metastatic spines with a SINS class II/III with a lytic lesion had a 40% VCF rate, whereas those with a mixed lesion had a 13% VCF rate. Moreover, the VCF rate in metastatic spines with a SINS class II/III with a lytic lesion was 47% when a baseline VCF was present, whereas the incidence was 35% when a baseline VCF was not present. In addition, metastatic spines with a SINS class II/III with a mixed lesion developed VCF at a rate of 50% when a baseline VCF was present, whereas the VCF rate was 8% when a baseline VCF was not present (Fig. 4).

During follow-up, local progression was observed in 37 of 147 metastatic spinal segments after conventional RT. The 6- and 12-month local control rates were 86.8% and 63.5%, respectively. Among the 37 segments with local progression, the median time to local progression was 8 months (range 2–15 months).

Discussion

In this study, we examined the incidence of VCF after conventional RT for spinal metastases. We presented the predictive factors of VCF precipitated by spinal metastasis of CRC after conventional palliative RT. These data highlight potential dangers associated with VCF and a spinal metastatic tumor with a high SINS score, particularly among patients with lesions with lytic features and/or a preexisting baseline VCF.

The cumulative incidence of VCF in patients with metastatic colorectal spine lesions without hormone or bisphosphonate therapy was 14.8% after palliative RT using the conventional scheme (most commonly 30 Gy in 10 fractions). In a previous systematic review, the prevalence

of VCF after conventional RT was $< 5\%$.⁵ However, we noted a relatively high rate of post-RT VCF in our patients, suggesting that spinal metastatic features of CRC may contribute to an increased incidence of VCF.^{19,21,23}

An Italian group reported that in skeletal metastases of CRC, both lytic lesions and mixed lytic/blastic lesions were more prevalent than true osteoblastic lesions.²³ They also reported that the time to skeletal-related events (defined as a pathological fracture, the need for RT or operation of the bone, and spinal cord compression) was significantly shorter for patients with lytic lesions.²³ Furthermore, a study by the MD Anderson Cancer Center reported that spinal metastasis with a lytic feature was a significant risk factor for VCF after SBRT.³

In the current study, half of the patients had spinal metastasis with a lytic feature, and the remaining patients had spinal metastasis with a mixed lytic/blastic feature; no patients had spinal metastasis with a purely blastic feature. Thus, the incidence of VCF after spinal RT in this study was higher than that in cohorts with a heterogeneous mixture of spinal metastasis of various primary tumors in other studies.^{5,21} In our previous study examining small cohorts, we also found that the rate of VCF was 9% after conventional radiation in metastatic spines with lytic or mixed lesions of CRC.¹⁷

We also examined the parameters associated with patients at risk for VCF. The effect of VCF after SBRT/stereotactic radiosurgery for spinal metastases has been well established in recent studies, and the incidence of VCF is estimated to be 11%–39%.^{1,12,15,21,22} However, the relationship between VCF rate and clinical risk factors after conventional RT has not been fully investigated, because reports of spinal RT with conventional fractionation have generally focused on acute toxicities.⁵ We selected many risk factors, such as sex, age, body mass index, spinal level, metastasis, prior RT, presence of a baseline VCF, RT dose of BED, and SINS criteria, which enabled us to predict

TABLE 4. Univariable and multivariable analysis of incidence of VCF in 147 metastatic spinal segments

Variable	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age, yrs		0.160		0.930
<60	1.00 (ref)		1.00 (ref)	
≥60	0.55 (0.24–1.27)		0.95 (0.33–2.69)	
Sex		0.064		0.023
Male	1.00 (ref)		1.00 (ref)	
Female	2.24 (0.95–5.27)		2.73 (1.14–6.52)	
Primary site		0.730		0.860
Rectum	1.00 (ref)		1.00 (ref)	
Colon	1.16 (0.51–2.63)		0.91 (0.34–2.44)	
BMI, kg/m ²		0.230		0.330
<25	1.00 (ref)		1.00 (ref)	
≥25	1.68 (0.71–3.95)		1.73 (0.57–5.21)	
Prior irradiation		0.180		0.500
No	1.00 (ref)		1.00 (ref)	
Yes	2.13 (0.70–6.44)		1.61 (0.40–6.49)	
BED _{α/β = 10} , Gy		0.150		0.140
≤39	1.00 (ref)		1.00 (ref)	
>39	2.31 (0.73–7.29)		3.08 (0.69–13.66)	
SINS class		<0.001		<0.001
I	1.00 (ref)		1.00 (ref)	
II/III	38.20 (5.48–266.00)		36.02 (5.10–254.33)	

the risk for VCF development. The findings of our study showed that, in irradiated segments, all VCFs were in metastatic spines, particularly in patients with a baseline VCF and/or prior RT. Among the metastatic spine segments, the risk of VCF was significantly increased in women with a SINS class II/III.

Among SINS radiographic and clinical components, both the type of bone lesion and baseline vertebral body collapse significantly contributed to the development of

a VCF. Most patients with metastatic spines with a SINS class I did not develop a VCF, whereas patients with spinal metastatic segments with a SINS class II/III had a high rate of VCF. It was noted that patients with SINS class II/III metastatic segments with a baseline VCF developed VCF at an incidence of up to 50%.

In addition, a preexisting baseline VCF was a strong risk factor for subsequent VCF, which has been reported in a recent, large multiinstitutional study and in a review article that evaluated VCF after spine SBRT.^{21,22} Our finding that presence of a baseline VCF was an independent predictor of fracture can be strongly associated with a spinal tumor due to CRC characterized by a lytic feature. Therefore, a spinal tumor with a baseline VCF must be monitored carefully in terms of the development of VCF after conventional palliative RT. Overall, we confirmed that SINS criteria are a powerful predictor associated with VCF in metastatic vertebral segments, even when using palliative RT with the conventional scheme as treatment.

Traditionally, conventional palliative RT includes all metastatic spine segments plus 1 or 2 levels of adjacent nonmetastatic spines superior and inferior to the metastatic spine. Although physicians are concerned about the risk of VCF in patients with irradiated nonmetastatic spines, we observed a VCF in an irradiated nonmetastatic spinal segment in only 1 patient. She was an elderly woman with tumor progression, suggesting that the inclusion of adjacent nonmetastatic spine segments in conventional palliative RT is safe without any additional risk of VCF. However, further long-term follow-up should be performed to

FIG. 3. MR image of a sagittal section before irradiation (**left**) and at development of a VCF (**right**). A metastatic spinal segment developed a de novo VCF in the T-7 vertebral segment 3 months after RT with 30 Gy in 10 fractions. Before RT, this metastatic vertebral segment had a high SINS score of 8 (semirigid location [1], mechanical pain [3], lytic lesion [2], normal spine alignment [0], no collapse but > 50% body involved by tumor [1], unilateral posterolateral element involvement [1]) without prior irradiation. Upper back pain and weakness in both legs were observed after VCF and were successfully treated by decompressive laminectomy.

FIG. 4. Rate of VCFs in metastatic spinal segments according to the following criteria, in this order: SINS class, bone lesion type, and baseline VCF (bVCF).

confirm these findings, because the exact pathophysiology of a VCF related to conventional RT is not well defined.²²

Our study has some limitations due to the retrospective data collection. First, limited clinical information was available; limited cohorts underwent spinal MRI at diagnosis and/or follow-up visit, even though MRI was more accurate in determining metastatic status or spine fracture than other imaging techniques. In addition, we could not rule out the confounding effect of the definite bone density that affected spine stability. Second, our study had a short-term follow-up period to assess delayed toxicity; thus, a longer follow-up may be needed to detect more cases of VCF.

Conclusions

In patients with metastatic colorectal spinal lesions, the incidence of VCF is not negligible due to the existence of osteolytic property, even when treating the spine with RT with conventional fractionation. In addition, in metastatic spine segments with regard to SINS components, the risk of VCF is significant in spinal segments with a lytic lesion and in those with a preexisting baseline VCF. Consideration of these factors associated with VCF is essential to appropriately assess toxicity after spinal RT.

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Disclosures

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Author Contributions

Conception and design: Koom, Lee, SK Chang. Acquisition of data: Lee, Rhee. Analysis and interpretation of data: Koom, Lee. Drafting the article: Lee, Rhee. Critically revising the article: Koom, Lee, SK Chang. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Koom. Statistical analysis: Lee, JS Chang. Administrative/technical/material support: Koom, SK Chang. Study supervision: Koom, SK Chang.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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