

Clinical Article

Radiosurgery Compared with External Radiation Therapy as a Primary Treatment in Spine Metastasis from Hepatocellular Carcinoma : A Multicenter, Matched-Pair Study

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Objective : The aim of this multicenter, matched-pair study was to compare the outcomes of stereotactic radiosurgery (SRS) and conventional external radiation therapy (RT) when used as a primary treatment in spine metastasis from hepatocellular carcinoma (HCC).

Methods : From 2005 to 2012, 28 patients underwent SRS as the primary treatment in spine metastasis from HCC. Based on sex, age, number of spine metastasis, Child-Pugh classification, interval from original tumor to spine metastasis, and year of treatment, 28 patients who underwent RT were paired. Outcomes of interest were pain relief, progression free survival, toxicities, and further treatment.

Results : The perioperative visual analog scale (VAS) decrease was larger in SRS group than in RT group, but the difference was not significant (3.7 vs. 2.8, $p=0.13$). When pain medication was adjusted, the number of patients with complete ($n=6$ vs. 3) or partial ($n=12$ vs. 13) relief was larger in SRS group than in RT group; however, the difference was not significant ($p=0.83$). There was no significant difference in progression free survival ($p=0.48$). In SRS group, 32.1% of patients had 1 or more toxicities whereas the percentage in RT group was 63.0%, a significant difference ($p=0.04$). Six SRS patients and 7 RT patients received further intervention at the treated segment.

Conclusion : Clinical and radiological outcome were not significantly different between the two treatments. Toxicities, however, were more prevalent in the RT group.

Key Words : Radiosurgery · Radiation therapy · Spine · Metastasis · Hepatocellular carcinoma.

INTRODUCTION

Hepatocellular carcinoma (HCC) has been well known that high incidence is in eastern Asia and that its incidence is quite low in Europe and Unites States^{11,18}. Because of the improved duration of control of the primary tumor site and improvements in imaging systems, bone metastases are noted much more frequently in HCC^{14,17}.

The role of stereotactic radiosurgery (SRS) in the treatment of spine metastasis from HCC has been rarely reported¹⁶. On the other hand, the role of conventional external radiation therapy (RT) in the treatment of spine metastasis from HCC has been the subject of controversy^{9,14}. HCC has not been considered as radiosensitive as breast, prostate, lymphoma, seminoma, and myeloma; however, there is controversy about the radiosensitivity of HCC¹⁴.

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Recently we reported that SRS provided better pain relief and better local control than that obtained from RT, when those procedures are performed as a primary treatment in spine metastasis from renal cell carcinoma (RCC)²⁶. However, RCC is notorious for resistance to RT. The results presented in this study cannot be extrapolated to spine metastasis from HCC without verification. Recent report insisted that local progression free survival was better in SRS group than that in RT group⁴. However, Child class, Karnofsky performance scale, and overall survival of SRS group were significantly better than those of RT group in this study⁴.

The aim of this multicenter, matched-pair study was to compare outcomes of SRS and RT when used as the primary treatment in spine metastasis from HCC.

MATERIALS AND METHODS

Patients

Retrospective data were collected from Ilsan Paik Hospital, Korea Cancer Center Hospital, St. Vincent's Hospital, and Seoul National University Hospital. This study was approved by the institutional review boards at the 4 participating hospitals. From 2005 to 2012, 290 metastatic spine disease patients underwent SRS at 2 hospitals. Among those patients, 40 had HCC as the primary tumor. Twelve patients were excluded because they underwent previous other treatments. The remaining 28 patients underwent SRS as a primary treatment and were included in this study's SRS group.

From the same period, a cohort of 1602 patients treated with RT as a primary treatment for spine metastasis was identified from another 2 facilities. During the study period, SRS was not available in these hospitals and, therefore, RT was performed. Among those, 113 patients had HCC as the primary tumor. Twenty-one patients were excluded because of previous surgery. The remaining 92 patients underwent RT as a primary treatment. Patient cohort was the same as that in our previous article²⁶.

The RT patients were matched with SRS patients on a 1 : 1 basis. A multidisciplinary panel consisting of spine surgeons and radiation oncologists decided on the matching criteria. The matching criteria were sex, patient age, number of spine metastasis, Child-Pugh classification, time interval from original tumor diagnosis to spine metastasis segment, and year of treatment. Based on those criteria, 28 of the 92 patients who underwent RT as a primary treatment were enrolled in the RT group.

The Eastern Cooperative Oncology Group (ECOG) scale system was used to measure performance status in this study. Ambulatory level was scored as 1 for ambulatory with no deficits, 2 for ambulatory with a limp, 3 for use of a cane or walker, 4 for wheelchair requirement, and 5 for bedridden⁷.

Mean follow-up period after treatment was 11.29±13.97 months and 11.32±8.52 months in the SRS and RT groups, respectively.

Outcome assessment

The primary outcomes of interest were pain relief and progression free survival. Secondary outcomes of interest were treatment toxicities and the need for further treatment. Although many patients had longer follow-up periods, pain relief in most patients was achieved in 4 weeks for the majority of patients in a clinical trial^{12,27}. Thus, the time point chosen for assessment of treatment effectiveness was 1 month after treatment completion. In the SRS and RT groups, pain levels were recorded before treatment and at the 1-month follow-up visit by using a visual analog scale (VAS). The VAS scores ranged from 0 (no pain) to 10 (the worst imaginable pain). Complete pain relief was defined as a complete absence of pain without the need for analgesics. Partial pain relief was defined as reduction of pain by achieving a decrease in VAS score of more than 2 with a stable or decreased use of pain medication. Stable pain was defined as the same VAS score or as a decrease in VAS score of less than 2. Pain progression was defined as any increase in VAS score or by an increased pain medication^{1,19}. Pain medication was defined as narcotics, steroids, or over the counter pain medications, used for pain relief²².

Images from axial and sagittal spine magnetic resonance imaging (MRI) and/or computed tomography (CT) were obtained. Those images were reviewed by a spine surgeon and by experienced neuroradiologists to assess local recurrence. The final written radiology report was also referenced.

Toxicities following SRS or RT were reported and graded by using the common toxicity criteria of the Radiation Therapy Oncology Group (RTOG)⁵. Vertebral compression fracture was defined as a *de novo* fracture (i.e., a new endplate fracture or collapse deformity when compared with before treatment status) or as fracture progression of an existing fracture at the treatment site⁶. Compression fracture induced by tumor progression was not considered an indicator of toxicity²¹.

SRS and RT procedure

The SRS was performed by using a Novalis shaped beam radiosurgical unit (Brain LAB, Heimstetten, Germany) or by using a CyberknifeTM (Accuray, Inc., Sunnyvale, CA, USA). The SRS procedures in each center have been previously described in detail^{3,10,24,26}. The prescribed dose or radiation was determined according to the shape of the tumor and the distance between the tumor margin and the spinal cord. In cases when the tumor margin abutted the spinal cord dura, fractionation was determined as 3 to 5. When the tumor margin was more than 3 mm away from the dura, single session radiosurgery was planned. In general, tumor volume which was covered by the prescription dose was more than 90% (mean, 96%).

In RT, no restrictions were placed on machine energy. Either parallel opposed or three fields were used. Doses were prescribed at mid-spine²⁶.

To compare the various fractionation schedules, the biological effective dose (BED) was calculated¹³. In addition, dose was cal-

culated as a 2-Gy equivalent normalized BED (nBED). The nBED was calculated by dividing BED by $[1+d/(\alpha/\beta)]$, where d is 2 Gy, and for the tumor tissue early effect, α/β is 10 ($\text{Gy}_{2/10}$) (Fig. 1).

Statistical analysis

Number of spine metastasis was compared between two groups by using Wilcoxon signed ranks test. Other continuous variables were compared by using paired t-tests. Pain relief was compared by using Bowker's test of symmetry. Other categorical variables were compared by using McNemar tests. The stratified log-rank test was used to assess differences in distributions between groups. A two-tailed p value of <0.05 was considered indicative of a significant difference. SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

RESULTS

Comparability of patients

Patient characteristics were compared between the SRS and RT groups. Both groups were not significantly different in sex (male : female, 26 : 2 in both groups), age (58.7 vs. 59.7 years, $p=0.54$), time interval from original tumor diagnosis to spine metastasis (17.7

vs. 18.4 months, $p=0.85$), Child-Pugh classification ($p=1.00$), number of spine metastasis ($p=0.72$), pretreatment ECOG status ($p=0.58$), pretreatment ambulation status ($p=1.00$), tumor volume (33.1 vs. 42.4 cc, $p=0.23$), and pretreatment VAS (6.8 vs. 5.6, $p=0.06$) (Table 1). Mean total margin dose was 35.4 ± 9.5 Gy and 31.5 ± 6.7 Gy in the SRS and RT groups, respectively ($p=0.10$). Mean number of fractions was 4.0 ± 1.5 in the SRS group and 10.2 ± 2.8 in the RT group. Mean nBED was significantly higher in the SRS group than that in the RT group (58.4 vs. 33.7 $\text{Gy}_{2/10}$, $p=0.0001$) (Table 1). Median overall survival after treatment was 8 months and 10 months in the SRS and RT groups, respectively. Overall survival after treatment was not significantly different between the two groups ($p=0.85$) (Fig. 2).

Pain relief and further intervention

Compared to pretreatment scores, post-treatment VAS scores were significantly lower in both the SRS (6.8 vs. 3.1, $p=0.0001$) and RT (5.6 vs. 2.7, $p=0.0001$) groups. When perioperative VAS score changes were compared between SRS and RT groups, the decrease in VAS scores was larger in the SRS than that in the RT group, but the difference was not significant (3.7 vs. 2.8, $p=0.13$). When pain medication was adjusted, the number of patients with complete ($n=6$ vs. 3) or partial ($n=12$ vs. 13) pain relief were differ-

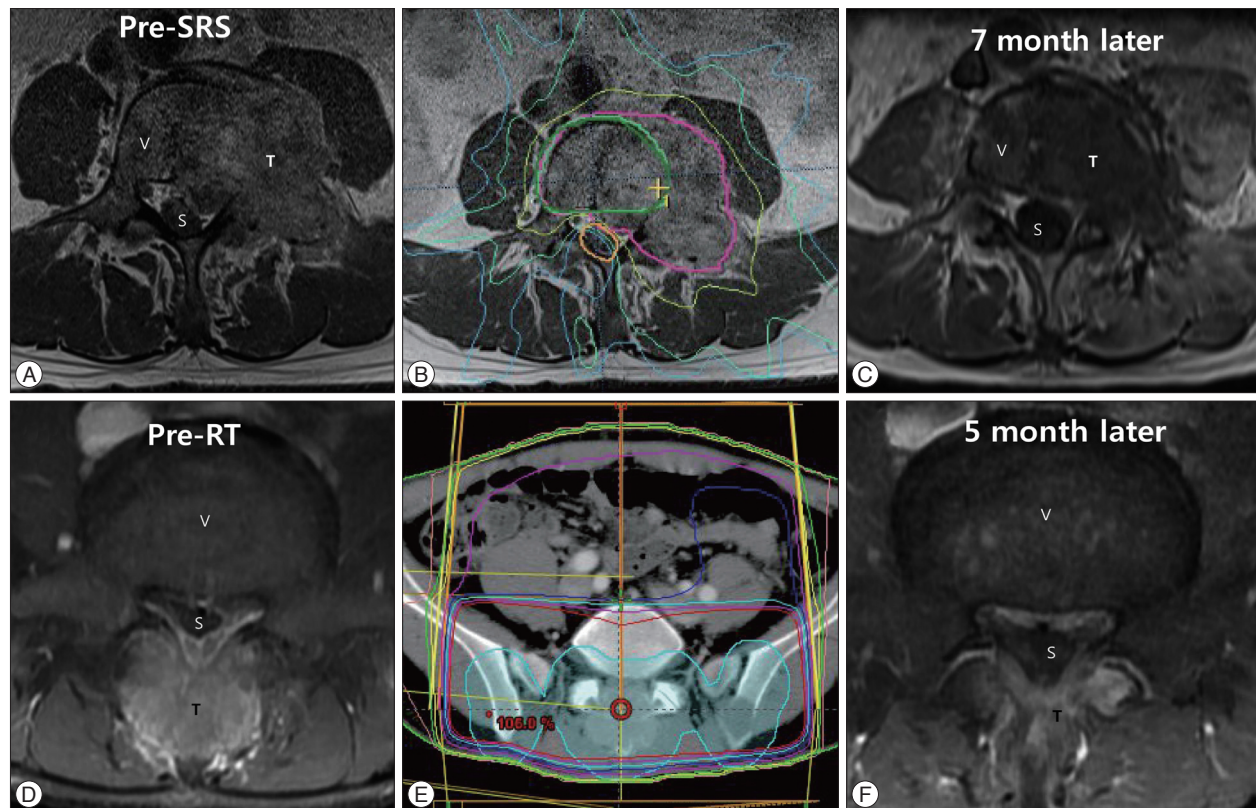


Fig. 1. Representative cases of spine metastasis from hepatocellular carcinoma (HCC) in stereotactic radiosurgery (SRS) (upper column : A, B, and C) and external radiation therapy (RT) (lower column : D, E, and F) groups. Pretreatment axial T1-weighted gadolinium-enhanced MRI reveals spine metastasis at L4 (A). This patient underwent SRS with a prescribed dose of 40 Gy in 4 fractions. Axial projection represents the 80% isodose line of the treatment. Colored outlined areas represent 120% (red), 80% (yellow), 50% (green), and 30% (blue) isodose lines of the treatment (B). MRI taken 7 months later reveals no tumor growth (C). Pretreatment axial T1-weighted gadolinium-enhanced MRI reveals spine metastasis at L5 (D). This patient underwent RT with the prescribed dose of 30 Gy in 10 fractions (E). MRI taken 5 months later reveals no tumor growth (F). V : vertebral body, S : spinal cord, T : tumor.

Table 1. Patient Characteristics of SRS and RT group

Variables	SRS (n=28)	RT (n=28)	p
Sex (M : F)	26 : 2	26 : 2	
Age, years (mean±SD)	58.7±13.8	59.7±9.9	0.54
Time interval from primary tumor to spine met, months (mean±SD)	17.7±28.1	18.4±24.2	0.85
Child-Pugh Classification (n)			1.00
A	26	25	
B	2	3	
Location of spine metastasis*			0.07*
Cervical*	7	6*	
Thoracic*	7	11*	
Lumbar*	14*	11*	
Number of spine met (n)			0.72
1	10	10	
2	8	7	
3	3	4	
≥4	7	7	
Pretreatment ECOG status			0.58
≤1	19	22	
≥2	9	6	
Pretreatment ambulation status			1.00
≤2	26	26	
≥3	2	2	
Tumor volume (cc)	33.1±29.3	42.4±25.8	0.23
Pretreatment VAS (mean±SD)	6.8±2.3	5.6±2.9	0.06
Margin radiation dose (Gy) (mean±SD)	35.4±9.5 [†]	31.5±6.7	0.1
Radiation dose, nBED (Gy _{2/10}) (mean±SD)	58.4±13.5	33.7±6.7	0.0001*

*Statistical significance, [†]SRS dose was marginal dose at 80% isodose line. SRS : stereotactic radiosurgery, RT : external radiation therapy, M : male, F : female, met : metastasis, ECOG : Eastern Cooperative Oncology Group, VAS : visual analogue scale, nBED : normalized biological equivalent dose

ent in the two groups; however, the difference was not significant ($p=0.83$) (Table 2).

Six patients in the SRS group underwent further intervention at the index segment; 3 patients underwent vertebroplasty/kyphoplasty, 2 patients underwent SRS, and 1 patient underwent RT. Mean interval after SRS was 5.2 months. Seven patients in the RT group received further intervention at the index site; 2 patients underwent surgical intervention, 3 patients underwent vertebroplasty/kyphoplasty, and 2 patients underwent SRS. Mean interval after RT was 7.1 months. The interval from first treatment to further intervention was not significantly different between the two groups ($5.2±3.9$ vs. $7.1±3.8$, $p=0.38$) (Table 2).

All surgery, SRS, and RT among further treatments were performed due to tumor progression. However, in SRS group, 2 patients underwent kyphoplasty due to compression fracture (no tumor progression) and 1 patient underwent vertebroplasty due to tumor progression. In RT group, 1 patient underwent vertebroplasty due to compression fracture (no tumor progres-

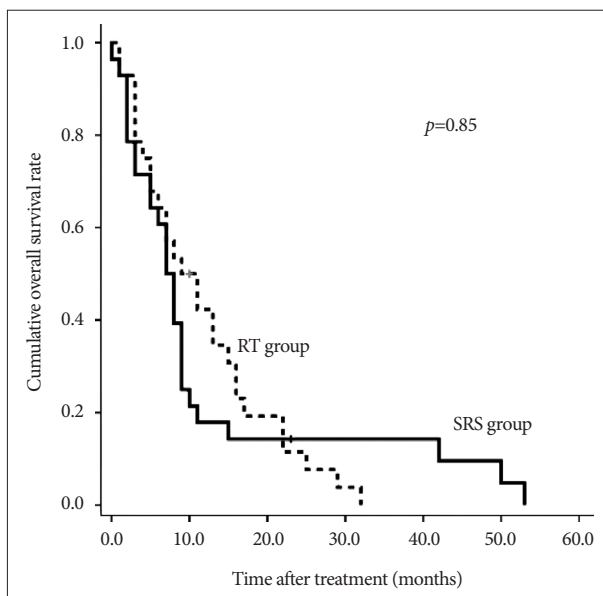


Fig. 2. Kaplan-Meier estimates of overall survival did not differ between SRS and RT groups ($p=0.85$). Median overall survival after treatment was 8 months in the SRS group and 10 months in the RT group. SRS : stereotactic radiosurgery, RT : external radiation therapy.

sion), 2 patients underwent vertebroplasty due to tumor progression (Table 2).

Local control and progression free survival

Forty seven (83.9%) patients (SRS group, n=24; RT group, n=23) underwent follow-up MRI after primary treatment. The actuarial local control rates for the spine metastases treated with SRS were 92%, 92%, 80%, 59%, and 25% at 1, 2, 3, 6, and 12 months after SRS, respectively. The actuarial local control rates for the spine metastases treated with RT were 92%, 87%, 78%, 64%, and 32% at 1, 2, 3, 6, and 12 months after RT, respectively. Median progression free survival after treatment was 10 months in the SRS group and 8 months in the RT group.

There was no significant difference in progression free survival between the two groups ($p=0.48$) (Fig. 3). Progression in other spine levels before the occurrence of index level progression was observed in 9 patients in each of the groups (Table 2).

Toxicity

In the SRS group, 32.1% (9/28) of the patients had 1 or more toxicities, whereas the percentage in the RT group was 63.0% (17/28), significantly higher percentage ($p=0.04$) (Table 2). All morbidities were RTOG grades 1 to 2. There were 2 grade 2 gastrointestinal toxicities in the SRS group. There were 5 grade 2 gastrointestinal toxicities in the RT group. There was 1 grade 2 skin toxicity in the RT group (Table 3).

The most common toxicity was gastrointestinal toxicity in both groups. Compression fracture occurred in 5 patients of the SRS group and 1 patient of the RT group. This difference was not statistically significant ($p=0.22$). Two of the compression fracture in the SRS group underwent kyphoplasty after SRS at index

level. The one compression fracture in the RT group underwent vertebroplasty after RT at index level.

DISCUSSION

Comparability of two groups

In this study, we attempted to control potential confounding

Table 2. Outcome of SRS compared with RT in Spine Metastasis from HCC

Variables	SRS (n=28)	RT (n=28)	<i>p</i>
Perioperative change of VAS (mean±SD)	3.7±2.7	2.8±2.4	0.13
Pain relief, n (%)			
Complete	6 (21.4)	3 (10.7)	0.83
Partial	12 (42.9)	13 (46.4)	
Stable	7 (25.0)	10 (35.7)	
Progression	3 (10.7)	2 (7.1)	
Progression in other spine before index level	9 (32.1)	9 (32.1)	1.00
Further treatment at index level			
Interval after first treatment, months (mean±SD)	5.2±3.9	7.1±3.8	0.38
Surgery	0	2	
Vertebroplasty, kyphoplasty	3	3	
SRS	2	2	
RT	1	0	
Toxicity, n (%)			
Total patient number	9 (32.1)*	17 (63.0)*	0.04 [†]
Nausea	4	3	
Sore throat	0	2	
Esophagitis	0	5	
Dry mouth	1	3	
Dysphagia	1	4	
Diarrhea	1	1	
Skin problem	0	1	
Compression fracture	5	1	

*Repetitions were allowed, [†]Statistical significance. SRS : stereotactic radiosurgery, RT : external radiation therapy, HCC : hepatocellular carcinoma, VAS : visual analogue scale

Table 3. Toxicity profile

	SRS group		RT group	
	Grade 1	Grade 2	Grade 1	Grade 2
Total patient number, n (%)	9 (32.1)*		17 (63.0)*	
Nausea	4	3	3	1
Sore throat	0		2	1
Dry mouth	1	1	3	1
Dysphagia	1	1	8	3
Diarrhea	1	1	1	1
Skin problem	0		1	1
Compression fracture	5	3	1	1

*Repetitions were allowed. SRS : stereotactic radiosurgery, RT : external radiation therapy, HCC : hepatocellular carcinoma

factors in case when patients who underwent RT were matched with those who underwent SRS. The matching criteria were based on those used in previous studies^{7,12} and on prognostic factors associated with metastatic spine tumor^{1,12,14}. Finally, a multidisciplinary panel decided on the criteria.

None of the patient parameters in our two groups were significantly different (Table 1). In addition, we compared overall survival after treatment between the SRS and RT groups to evaluate the patients' systemic burden^{4,28}, and overall survivals in the two groups were not different (Fig. 2).

Moreover, we only included patients who underwent SRS or RT as the primary treatment. Even though retreatment with SRS was reported to be effective^{3,10}, we only included patients with SRS and RT as their initial treatment in order to reduce the effects of potential confounding factors as much as possible.

In this study, nBED delivered was significantly higher in the

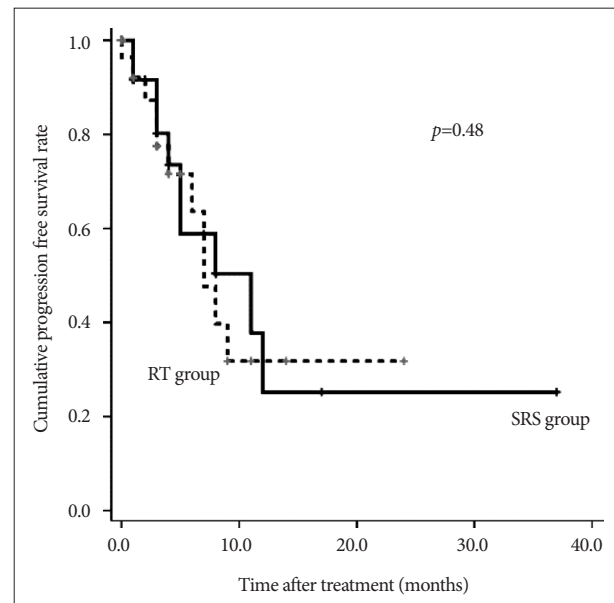


Fig. 3. Kaplan-Meier estimates of progression free survival did not differ significantly between the SRS and RT groups ($p=0.48$). Median progression free survival after treatment was 10 months in the SRS group and 8 months in the RT group. SRS : stereotactic radiosurgery, RT : external radiation therapy.

SRS group than in the RT group (Table 1). Reports on the correlation of dose with response rate have been contradictory^{11,14}. Based on our study results, we could not support that high dose SRS with a low fraction schedule is more effective on pain relief and local control than low dose RT with a high fraction schedule in the treatment of spine metastasis from HCC. However, further studies are warranted to elucidate effective dose-fraction schedule.

Outcome analysis

Many authors consider pain control, not local control, as a key treatment outcome²¹; however, other authors consider local control as the key outcome^{2,8,20}. In our study, we considered both of those endpoints. With regard to pain relief, we not only measured patients' VAS pain scores but also considered pain medication adjustment when determining pain score changes because that approach is more rigorous and more objective¹.

Among our SRS subjects, there were 18 patients (64.3%) with adjusted complete or partial pain relief; when unadjusted, 25 patients (89.3%) exhibited an improvement in pain score. These results are similar to those in a previous study (i.e., 84.6% pain relief)¹⁶.

In contrast, among the RT patients, there were 16 patients (57.2%) with adjusted complete or partial pain relief; when unadjusted, 21 patients (75%) exhibited an improvement in pain score. These results are similar or a little worse than those in previous studies (i.e., 72.7–99.5%)^{11,14,15,23}.

Regarding radiological progression free survival, our data showed similar levels of durable local control in both the SRS and RT groups. Progression in another spine level that developed before index level progression was also similar in both groups. In addition, the time interval from the first treatment to further intervention was not significantly different between the two groups. On the other hand, surgical intervention was needed in 2 patients in the RT group, but in none of the SRS group (Table 2). Overall, clinical and radiological outcome in both groups was not significantly different.

Toxicity

In our study, toxicities developed in 32.1% (9/28) of the SRS group and in 63.0% (17/28) of the RT group. This tendency is consistent with previous reports in which RT patients had more morbidities than SRS patients^{7,12}. The difference in morbidities may be the result of the relatively limited capability to exclude normal tissue from RT treatment and the need for multiple fractions in RT.

Vertebral compression fracture risk after SRS has been reported to range from 11% to 39%, higher than the fracture risk after RT (<5%)^{21,22}. In this study, compression fracture occurred in 5 patients (17.9%) in the SRS group and in 1 patient (3.6%) in the RT group. Two SRS group patients underwent kyphoplasty and 1 RT group patient underwent vertebroplasty after compression fracture. The dose per fraction in all compression fracture patients was less than 20 Gy, which is lower than the previously reported threshold for compression fracture risk (≥ 20 Gy)^{6,22}.

Osteolytic tendency in most spine metastasis from HCC may also affect compression fracture¹⁴.

Clinical implication of this study

In Korea, SRS has been covered by the national health insurance system since 2011. In Korea, if SRS is done in 3 fractions and RT is done in 10 fractions, the cost of SRS is similar to that of three-dimensional RT²⁵. The cost of SRS treatment in Korea is considered less than that in the USA where the cost of 3D RT is reported to be 71% of that of SRS¹².

In this study, pain relief and local control rate were not significantly different between the SRS and RT groups. However, with regard to toxicities, the rate in the RT group was significantly higher than that in the SRS group. When we consider the number of fraction is less in SRS than in RT, SRS must be a good alternative as a primary treatment in spine metastasis from HCC.

Limitations of this study

Several limitations of this study should be noted. First, although this is a matched-pair study, the enrolled SRS and RT patients were collected retrospectively, which can result in a selection bias. SRS and RT technique is also different in each center. Second, our sample size was low (n=28) in both groups. If more cases are included, we admit that the difference of outcomes such as pain relief could be significant. Regardless, this study reports on the largest series of cases with SRS as a primary treatment on HCC spine metastasis to date. Third, many spine metastases in this study were oligometastases (≤ 3). Therefore, the study results cannot be generalized to adjuvant treatment or widespread spine metastasis. Nevertheless, to our knowledge, this is the first multicenter study that compared the outcome of SRS with that of RT when used as a primary treatment of spine metastasis from HCC.

CONCLUSION

In this study, SRS and RT were performed as primary treatments of spine metastasis from HCC. Our analysis showed that the pain relief, progression free survival rate, and need for further treatment at the index level were not significantly different between the two treatments. Toxicities were more prevalent in the RT group.

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