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The Efficacy of Wide Resection for Musculoskeletal Metastatic Lesions of Renal Cell Carcinoma

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Abstract. *Background/Aim: This study evaluated the outcome of wide resection for metastatic renal cell carcinoma (RCC) to the bone or soft tissue. Patients and Methods: Thirty patients who underwent surgery for bone or soft tissue metastatic lesions of RCC were retrospectively evaluated. The surgical procedures were wide resection in 14 patients (group 1) and intralesional resection in 16 (group 2). Results: The 3-, 5-, 10-, and 15-year overall survival (OS) was 76%, 48%, 35%, and 23%, respectively, and OS was significantly favorable in group 1. In addition, recurrence-free survival rate was significantly higher in group 1. In the multivariate analysis, intralesional resection was an independent risk factor for poor prognosis. There was no significant difference in surgical time, though intraoperative hemorrhage was significantly larger in group 2. Conclusion: The wide resection of bone and soft tissue metastatic lesions of RCC is a favorable option for controlling local metastasis and improving prognosis.*

Renal cell carcinoma (RCC) is a tumor with high metastatic potential. Up to one third of patients with RCC will have metastases at presentation, and, of the remaining two thirds, about half will develop recurrent metastases following nephrectomy (1, 2). The most common site for metastasis from RCC is the lung (50% of patients), followed by the bone (20-50% of patients) (3). Surgical intervention is the recommended treatment for these metastases, because long-term survival after metastasectomy is well-documented (2, 4-6), while untreated patients with metastatic RCC have a poor prognosis (1). If possible, wide metastasectomy is an ideal treatment for local recurrence. However, wide resection can be difficult, depending on the surgical site or condition of the patient. In addition, because osseous metastases tend to be large, highly destructive, and hypervascular, wide resection is a therapeutic challenge for orthopedic surgeons (7). The aim of this study was to compare the long-term outcome of wide resection and intralesional resection for metastatic RCC to the bone or soft tissue and evaluate the factors associated with prognosis. These evaluations seek to clarify the efficacy of and the indications for wide resection of bone or soft tissue metastases of RCC.

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Patients and Methods

Between 1993 and 2014, 30 patients (25 men and 5 women) with a mean age of 62 (range=25-84 years) years at the time of metastasis presentation underwent surgery, excluding palliative surgery, for bone or soft tissue metastatic lesions of RCC in our institution. The surgical procedures were wide resection in 14 patients (group 1) and intralesional resection in 16 (group 2). The specific characteristics of the patients in the two groups were compared using the Mann-Whitney *U*-test or the Fisher's exact test, and are presented in Table I. Wide resection consists of wide excision of metastatic bone with osteotomy and reconstruction using a megaprosthesis or recycled bone (bone frozen by liquid nitrogen (8)). Intralesional resection consists of extensive curettage of the metastatic tumor followed by adjuvant therapy using phenol and/or ethanol, and filling the defect with bone material (artificial bone or bone cement). In nine patients, chemotherapeutic agents such as doxorubicin were mixed into the bone cement used after extensive curettage. Surgical sites included extremity bones (15 patients), the pelvis (8), thoracic bones including the rib and sternum (4), and soft tissues (3). These patients were retrospectively evaluated for overall survival (OS), recurrence-free survival (RFS), metastasis-free survival (MFS), surgical time, and intraoperative hemorrhage; comparisons between the two groups were made using Kaplan-Meier analysis, the log-rank test, and the Mann-Whitney *U*-test. In addition, factors implicated in the prognosis were retrospectively evaluated by univariate (log-rank test) and multivariate survival analysis (Cox proportional hazards analysis). Statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (9),

Table I. *Specific characteristics of the patients in the two groups.*

	Group 1	Group 2	*p*-Value
Cases (n)	14	16	
Mean age (yrs.)	62	63	*p=0.68
Gender (n)			**p=0.27
Male	12	13	
Female	2	3	
Tumor site (n)			
Upper extremities	2	3	
Trunk	7	7	
Lower extremities	5	6	
Oncological stage (n)			**p=0.15
M0	8	5	
M1	6	11	
Tissue type of RCC			**p=0.28
Clear cell type	14	16	
Non-clear cell type	0	2	
Pathological fracture (n)	2	7	**p=0.09
Performance status (n)			**p=0.08
≥80	8	4	
<80	6	12	
Motzer risk score (n)			
≤2	11	10	**p=0.1
≥3	3	6	
No. of preoperative metastatic sites (n)			*p=0.15
0 site	6	5	
1 site	4	3	
≥2 sites	4	8	
unknown	1	2	
Patients with preoperative lung metastasis (n)	4	5	**p=0.55
Patients with preoperative visceral metastasis (n)	3	3	**p=0.63

*Mann-Whitney *U*-test, **Fisher's exact test.

which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). This was a retrospective clinical case series study and was approved by the local institutional review board. All subjects were informed that data from this study would be submitted for publication and gave their consent for participation.

Results

The mean follow-up period was 52 months (range=8-257 months). The median survival time (MST) was 4.4 years, and the 3-, 5-, 10-, and 15-year OS rates were 76%, 48%, 35% and 23%, respectively (Figure 1a), and OS was significantly more favorable in group 1 compared with that of group 2 (p=0.04, Figure 1b). RFS was significantly higher in group 1 than in group 2 (p=0.001), and the 5-year RFS for the two groups were 100% and 28% respectively (Figure 1c). Only one out of sixteen patients developed a local recurrence in group 1. There was no significant difference in MFS between groups (p=0.71, Figure 1d). In univariate survival analysis, patients who had more than two other metastatic lesions before the surgery and patients underwent intralesional resection had an unfavorable prognosis (log-rank test, Table II). However, in the multivariate analysis, only intralesional resection was an independent risk factor for poor prognosis (Cox proportional hazards analysis, Table III). The Motzer/Memorial Sloan-Kettering Cancer Center criteria score (Table IV) (10), which is among the most commonly used prognostic models in metastatic RCC, had no significant impact for the OS in both the univariate (p=0.052) and the multivariate (p=0.1) analyses. The mean surgical times were 3.5 hours in group 1 and 3.0 hours in group 2, and there was no significant difference in surgical time between the groups (p=0.73). Intraoperative hemorrhage, though, was significantly greater in group 2 (421 ml *vs.* 1460 ml, p=0.003, Table V).

Discussion

Historically, metastatic renal cell carcinoma carried an unfavorable prognosis, and in patients with bone metastasis, supportive care such as palliative orthopedic procedures (closed nailing for temporary stabilization), radiotherapy and administration of bisphosphonates to reduce skeletal-related events (pain or pathological fracture) was the main course of treatment (11-12). While persistent treatment of metastatic RCC with nephrectomy and cytokine therapy have been helpful (13), the development of molecularly targeted therapy has made long-term survival possible in these patients (14). Moreover, some reports support the possibility that metastasectomy would not only improve the patient's quality of life but also prolong survival (2, 4-6). Naito *et al.* reported that, in a series involving a group of 1,463 patients with metastatic RCC, the mean survival time of the patients who underwent metastasectomy was significantly increased compared with patients who did not undergo metastasectomy (44.3 *vs.* 16.4 months) (4). Focusing on bony metastasis, Fuchs *et al.* reported that patients who had a surgical procedure had better survival rates (p=0.007) compared patients who had no surgical treatment or simple biopsy of the local lesion, with 5-year survival rates of 36% versus 8% (15). The survival in our study was even more favorable: the mean survival time and 5-year survival after metastasectomy were 52.8 months and 48%, respectively.

From these viewpoints, surgical resection can now be recommended for patients with metastatic lesions from RCC, and some guidelines indeed endorse metastasectomy in certain conditions. National Comprehensive Cancer Network (NCCN) guidelines for kidney cancer recommend that patients with a solitary resectable metastatic site be considered candidates for surgical metastasectomy (16). In

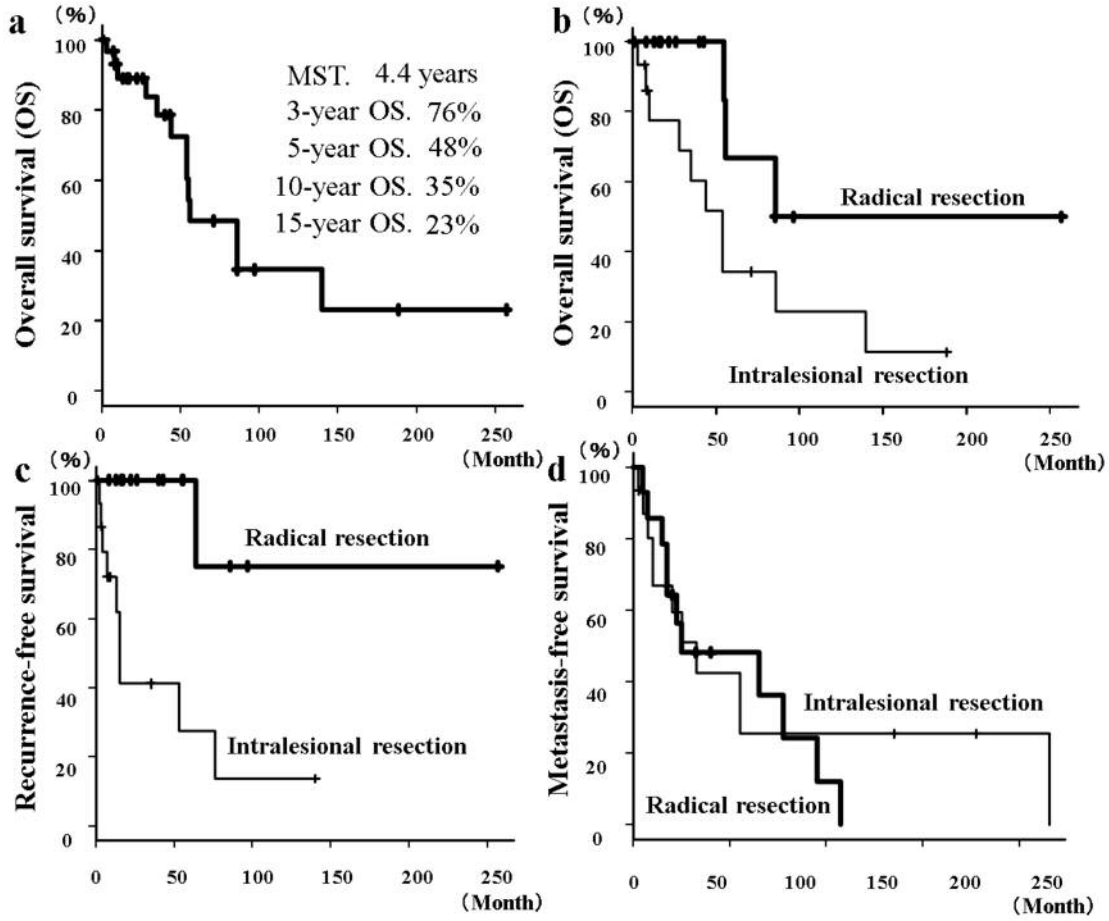

Figure 1. *(a) A Kaplan–Meier survival rate curve of the 30 patients from the time of metastasectomy. OS, Overall survival; MST, median survival time. (b) OS rate curve of the patients based on surgical method. Survival rate was significantly higher in the wide resection group than intralesional group (p=0.04). (c) Recurrence-free survival rate curve of the patients based on surgical methods. Recurrence rate was significantly lower in the wide resection group than the intralesional group (p=0.001). (d) Metastasis-free survival rate curve of the patients based on surgical methods. There was no significant difference in each group (p=0.71).*

addition, in guidelines by the Japanese urological association, surgical resection for metastasis is recommended as grade B (strong recommendation with moderate quality evidence) when the patient has a good performance status and metastatic site is resectable (17). Remarkably, the number of metastatic sites is not mentioned in the latter guidelines, though metastasectomy is limited to solitary metastasis in the former guidelines, and the indications for metastasectomy for multiple metastases remain controversial.

Many reports mentioned that the number of metastatic sites is a predictor for survival (18, 19). Lin *et al*. reported that patients presenting with an apparently solitary bone lesion had a better survival rate than patients with other patterns of metastases ($p<0.0001$), with 5-year survival rates of 35% (7). For this reason, the suggestion that metastasectomy should be limited when the metastasis site is solitary was supported by several authors and guidelines (16, 20, 21). However, among patients with metastatic disease, only a small percentage will present with a solitary metastasis. Also, some authors suggest that complete resection of all metastatic deposits within an organ was more important than the number of metastatic deposits within the organ (22, 23). Dernevik *et al*. reported that no significant survival difference existed with respect to the number of lesions excised in the patients with lung metastases (22). Kavolius *et al*. showed that best survival was achieved in patients with in a solitary metastatic site ($p<0.005$). However, long-term survival for patients with multiple metastases was possible, with 5-year survival rates of 29% as a result of metastasectomy, provided all metastatic disease could be completely removed (23). In our data, the survival was significantly lower in patients with more than two

Table II. *Univariate predictors of survival.*

Factor	n	Median survival	*p*-Value
Age (years)			
<65	20	86 (28-NA)	0.80
≥65	10	54 (35-NA)	
Gender			
Female	5	54 (8-NA)	0.89
Male	25	56 (44-140)	
C-reactive protein (mg/dL)			
>0.3	15	55 (35-NA)	0.55
≥0.3	12	56 (8-NA)	
Hemoglobin (g/dL)			
<male 13.0/female 11.5	14	140 (28-NA)	0.24
≥male 13.0/female 11.5	15	55 (10-86)	
Oncological stage			
M0	13	70.5 (44-NA)	0.43
M1	17	56 (28-140)	
Pathological grade of RCC			
Grade 1 or 2	17	86 (44-NA)	0.55
Grade 3	5	86 (8-NA)	
Karnofsky performance status			
≥80%	12	86 (28-NA)	0.18
<80%	18	54 (44-140)	
Motzer/MSKCC			
Favorable or intermediate	21	86 (44-NA)	0.05
Risk classification			
Poor	9	54 (3-NA)	
Pathological fracture			
No	21	86 (35-NA)	0.67
Yes	9	56 (3-NA)	
Preoperative metastasis			
No	8	35 (28-NA)	0.47
Yes	19	55 (44-86)	
Preoperative metastasis (≥2 sites)			
No	15	NA (35-NA)	*0.03
Yes	12	54 (8-NA)	
Post-operative recurrence			
No	20	140 (35-NA)	0.17
Yes	10	54 (8-86)	
Post-operative metastasis			
No	8	54 (54-NA)	0.61
Yes	22	56 (25-140)	
Preoperative lung metastasis			
No	18	55 (35-NA)	0.4
Yes	9	56 (3-NA)	
Preoperative visceral metastasis			
No	21	86 (35-NA)	0.19
Yes	6	44 (3-NA)	
Surgical methods			
Intralesional resection	16	54 (10-140)	*0.04
Wide resection	14	86 (55-NA)	
Target therapy			
No	18	56 (44-NA)	0.71
Yes	10	86 (28-NA)	

M0: No metastasis; M1: with metastasis; RCC: renal cell carcinoma; Motzer/ MSKCC risk classification: Motzer/Memorial Sloan-Kettering Cancer Center risk classification; Asterisks denote a statistically significant difference (*p<0.05).

Table III. *Multivariate predictors of survival.*

Factor	Hazard ratio	*p*-Value
Motzer/MSKCC classification (poor)	3.71 (0.78-17.66)	0.1
Preoperative metastases (≥2 sites)	1.71 (0.40-7.38)	0.47
Surgical procedure (wide resection)	0.24 (0.06-0.93)	0.04*

Asterisks denote a statistically significant difference (*p<0.05).

metastatic sites before metastasectomy than in patients with only one metastatic lesion. However, the mean survival of our subjects (54 months) was better than that reported by Kavolius *et al*.. In addition, there was no significant difference in survival between patients with or without a single site of metastasis before metastasectomy. From multivariate analysis, the existence of metastases (including multiple metastases) before metastasectomy was not a significant risk factor for survival, whereas surgical technique had a strong association with survival. Hence, we believe that, for patients with an acceptable general condition, metastasectomy of multiple metastases is a reasonable option that may provide relatively long survival.

When we think about surgical intervention for metastatic lesions from RCC, the appropriate extent of surgery, such as whether we treat the tumor like a primary bone tumor or not, often comes into question, though the above guidelines do not mention the type of surgical treatment. Compounding the problem, in osseous metastases from RCC, because the tumors tend to be large, highly destructive, and hypervascular, aggressive metastasectomy may lead to a loss of postoperative function and endanger the patient's health because of long surgical time or large volumes of hemorrhaging. Thus, some groups recommend marginal or intralesional resection for any metastatic disease (15, 21) while others recommend wide excision of metastatic lesions because doing so may prolong survival (23, 24). Kavolius *et al*. reported that patients who underwent curative resection (n=141) fared better than those who underwent a noncurative resection (n=70) or non-surgical initial management of metastasis (n=67), and the 5-year survival rates were 44%, 14%, and 11%, respectively (23). Fottner *et al*. reported that the histologic resection margin affected overall survival in 101 patients with RCC bone metastases, and patients with a tumor-free resection margin had a significantly better survival (p=0.028) (24). Conversely, Fuchs *et al*. reported that there was no survival advantage for patients who had a wide resection of the lesion compared with patients who had intralesional resection or intramedullary stabilization alone. However, the authors also noted that patients with complete resection and reconstruction of the metastatic lesion tended to have fewer complications, like local disease progression,

Table IV. *The Motzer/Memorial Sloan-Kettering Cancer Center criteria score.*

Influencing factors	Criteria of abnormality
Karnofsky performance status	<80
Time from diagnosis to treatment with interferon alfa, months	<12
Hemoglobin	<Lower limit of laboratory's reference range
Lactate dehydrogenase	>1.5× upper limit of laboratory's reference range
Corrected serum calcium, mg/dL	>10.0

Favorable risk: 0; Intermediate risk: 1-2 risk factors; Poor risk: ≥3 risk factors (10).

than those receiving intralesional curettage and local stabilization (15). In the present study, the survival rate and recurrence rate were significantly better in the wide resection group by univariate analysis, and intralesional resection was the major independent risk factor for poor survival by multivariate analysis. Because wide resection did not influence the metastasis rate, complete removal of the metastatic lesion was not the only determining factor accounting for increased survival in this patient group. Furthermore, since this was a retrospective study with few patients, clear treatment indications could not always be determined and may not have been applied consistently. Thus, there is the potential for selection bias in the treatment approach chosen. However, we consider it possible that the wide resection can control the local lesion well and relieve the pain from imminent fracture as well as improving patients' impaired activities of daily living, all of which might contribute to prolonged survival.

Furthermore, we regard wide resection as a safe procedure because there were no severe complications related to the surgery except in one patient with a radius metastasis who developed posterior interosseous nerve palsy after the metastasectomy. Baloch *et al*. also reported that there were seven complications, including prolonged wound healing and problems related to the endoprosthesis, none of which resulted in major morbidity among 25 patients with metastatic RCC. Furthermore, they recommended wide resection and argue that the vascularity of the tumor is not a contraindication, since the surgeon never cuts into the tumor during the procedure. Despite aggressive surgical intervention, they reported a low incidence of complications (20). In our study, though surgical time compared favorably between the two surgical techniques, intraoperative bleeding was significantly lower in wide resection. Thus, wide resection for the bone and soft tissue metastases of RCC is relatively safe and is the recommended option both for control of local disease and because of the prospect of long-term survival in some patients.

Similar to other studies, we found that patients with bone or soft tissue metastases from RCC have a good prognosis for long-term survival. Furthermore, our results suggest that wide resection of bone and soft tissue metastatic lesions of RCC are a favorable option, not only for controlling local metastasis, but also for improving prognosis. This approach can also be used for patients with multiple metastases to improve impaired activity, since patients may achieve a relatively long survival despite these metastases.

Table V. *Surgical time and surgical hemorrhage.*

	Surgical time (min)	Surgical hemorrhage (ml)
Wide resection	210±72	421±669
Intralesional resection	178±152	1,460±1,168
p-Value	0.73	0.003*

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