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Molecular-targeted Therapy and Surgery May Prolong Survival of Renal Cell Carcinoma Patients with Bone Metastasis: A Multi-institutional Retrospective Study in Japan

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Abstract. *Aim: To determine prognostic factors for overall survival (OS) in renal cell carcinoma (RCC) patients with bone metastasis in the targeted-therapy era. Patients and Methods: We conducted a retrospective multi-institutional review of the medical records of 149 RCC patients with bone metastasis. Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Univariate and multivariate Cox proportional hazard regression analyses were performed to identify independent factors associated with OS. Results: The median OS was 13.4 months. In multivariate analysis, molecular-targeted therapy, nephrectomy and surgery for bone metastasis were independent prognostic factors. Bone-modifying agents (BMAs) were not associated with OS. The median OS of patients receiving molecular-targeted therapy after diagnosis of bone metastasis was significantly better than that of those who did not receive targeted therapy. Conclusion: Molecular-targeted therapy, nephrectomy and surgery for bone metastasis should be considered for RCC patients with metastasis in the bones.*

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Bone is the second most common metastatic site of renal cell carcinoma (RCC) in approximately 30% of metastatic RCC (mRCC) patients (1). Previous studies concerning bone metastasis from RCC reported that the median overall survival (OS) was 9-12 months (2, 3) in the cytokine era and 16-20 months (4-6) in patients who received sunitinib therapy. Some studies showed that bisphosphonates combined with sunitinib might improve OS compared to sunitinib alone (4, 5). These results indicate that molecular-targeted therapy with or without a bone-modifying agent (BMA) may provide a better oncological outcome for mRCC patients with bone metastasis than previous systemic therapy, such as that using interferon-alfa. Meanwhile, a large retrospective study showed that bone metastasis was a prognostic factor for survival in patients who were treated with sunitinib (6), whereas low Karnofsky performance status (KPS), a high lactate dehydrogenase level, low serum haemoglobin level, high corrected serum calcium level and time from the initial RCC diagnosis to the start of systemic

therapy of <1 year were independent prognostic factors, though bone metastasis was not, in mRCC patients who were treated with interferon-alfa as the initial systemic therapy (7). Furthermore, the presence of bone metastasis was associated with shorter survival in a phase 3 trial of everolimus compared to a placebo in mRCC patients on a vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) who progressed (8), although low KPS, a low haemoglobin level and high corrected serum calcium, but not bone metastasis, were associated with shorter survival in multivariate analysis of previously treated mRCC patients in the cytokine era (9). Thus, whether mRCC patients with bone metastasis in the targeted-therapy era have better oncological outcomes than those in the cytokine era is still unclear. In the present study, we attempted to determine prognostic factors for OS in RCC patients with bone metastasis using data from both the cytokine era and the targeted-therapy era. We also examined the effects of various therapies, including molecular-targeted therapy, cytokine therapy, nephrectomy, surgery for bone metastasis and radiation therapy, for improving survival in RCC patients with bone metastasis.

Patients and Methods

Study population. This study was approved by the institutional review board of each institute. We retrospectively collected clinical data of 149 RCC patients with bone metastasis at 12 Japanese institutions between January 2003 and January 2012. Data were collected consecutively to avoid selection bias. Patients were excluded from analysis if they had malignancies other than RCC that might cause bone metastasis.

The starting point for analysis was defined as the date of diagnosis of bone metastasis from RCC. During the study period, all therapeutic decisions, including the choice of the respective systemic therapies, radiation therapy or surgery, were left to the discretion of each attending physician based on individual disease characteristics and the patient's request. Patients generally underwent lung and abdominal computed tomography every 3 months. The decision as to whether a bone scan should be done was made by each physician and not based on strict criteria.

Statistical analysis. The primary outcome of interest was the OS time measured in months from the diagnosis of bone metastasis to the date of death or last follow-up. Survival was estimated using the Kaplan-Meier method and compared with the log-rank test. Variables considered in survival analysis were gender, age, histology, nephrectomy, Memorial Sloan-Kettering Cancer Center (MSKCC) risk, multiplicity of bone metastasis, extraosseous metastasis, lung metastasis, liver metastasis, brain metastasis, surgery, radiation therapy (RT), systemic therapy, cytokine therapy, targeted therapy and BMA (zoledronic acid or denosumab). Univariate and multivariate Cox proportional hazards regression analyses were performed to identify independent factors associated with OS. All tests were 2-sided with statistical significance considered to be $p<0.05$. Statistical analysis was done using JMP® 10.0 (SAS Institute Inc., Cary, NC, USA).

Table I. *Patients' characteristics (n=149).*

Characteristic	No. Patients	%
Gender		
Male	107	72
Female	42	28
Age at diagnosis of bone metastasis		
Median (range)	67 (17-92)	
Histology		
Clear cell	106	71
Non-clear cell	13	9
Unknown	20	20
Nephrectomy		
Yes	112	75
No	37	25
MSKCC risk		
Favourable	15	10
Intermediate	81	54
Poor	53	36
Multiplicity of bone metastasis		
Solitary	58	39
Multiple	91	61
Extraosseous metastasis		
Yes	107	72
No	42	28
Systemic therapy		
Cytokine	31	21
Targeted therapy	69	46
Cytokine + targeted therapy	11	7
None	38	26
Bone-modifying agents		
Yes	62	42
No	87	58

MSKCC, Memorial Sloan-Kettering Cancer Centre.

Results

Patients' characteristics (Table I). The median age of the study patients was 67 years. Approximately 70% of patients had clear cell histology. One hundred twelve patients (80%) had bone metastasis at the initial diagnosis of RCC. At the time of diagnosis of bone metastasis, 81 patients (54%) had intermediate MSKCC risk and the rest were split between 15 with favourable status (10%) and 53 with poor (36%) status. Ninety-one patients (61%) had multiple bone metastases. One hundred seven patients (72%), including 84 patients (56%) with lung metastasis, had extraosseous metastasis. A total of 80 patients (53%) received molecular-targeted therapy. BMA was administered to 62 patients (42%) in whom zoledronic acid and denosumab were used for 52 (35%) and 10 (7%), respectively.

Treatment. A total of 111 patients (74%) received systemic therapy, including interferon-alfa in 39, low-dose interleukin-2 in 10, sorafenib in 31, sunitinib in 47, axitinib in 10,

Table II. *Systemic therapy in each line.*

Drug	1st-line (N=111)	2nd-line (N=37)	3rd-line (N=17)	4th-line (N=5)
IFN-alfa	39	0	0	0
IL-2 (low dose)	3	7	0	0
Sorafenib	21	8	2	0
Sunitinib	34	7	6	0
Axitinib	1	4	4	2
Everolimus	7	7	4	2
Temsirolimus	6	4	1	1

IFN, Interferon; IL-2, interleukin-2.

Table III. *Surgery for 20 patients with bone metastasis.*

Surgical procedure	Bone	Bone metastasis	
		Solitary	Multiple
Resection	Humerus	5	2
	Rib	3	0
	Vertebra	0	1
Osteosynthesis after curettage	Femur	4	1
	Tibia	1	0
	Humerus	1	0
Posterior spinal fusion	Vertebra	1	1

everolimus in 20 and temsirolimus in 12. Of the 111 patients, 74 (67%) were treated with only one regimen, followed by 20 (18%) receiving up to second-line, 12 (11%) receiving up to third-line and 5 (5%) receiving up to fourth-line therapy. The distribution of the selected drug in each line is shown in Table II.

RT for bone metastasis was performed in 101 patients (68%). Sixty-three of the patients (62%) underwent definitive field RT defined as irradiation targeting all bone metastases. The other 38 patients (38%) received palliative field RT that did not cover all sites of bone metastasis.

A total of 20 patients (13%) underwent surgical treatment. The most common procedure was resection of the metastatic lesion in 11 (55%), followed by osteosynthesis after curettage in 7 (35%) and posterior spinal fusion in 2 patients (10%) (Table III).

Survival analysis. The median OS was 13.4 months (95% confidence interval (CI)=9.7-15.9 months). In multivariate analysis, molecular-targeted therapy (hazard ratio (HR)=0.44, 95% CI=0.29-0.68, p=0.0002), MSKCC risk (HR=2.40, 95% CI=1.21-5.23, p=0.0111 in intermediate *vs*. favourable;

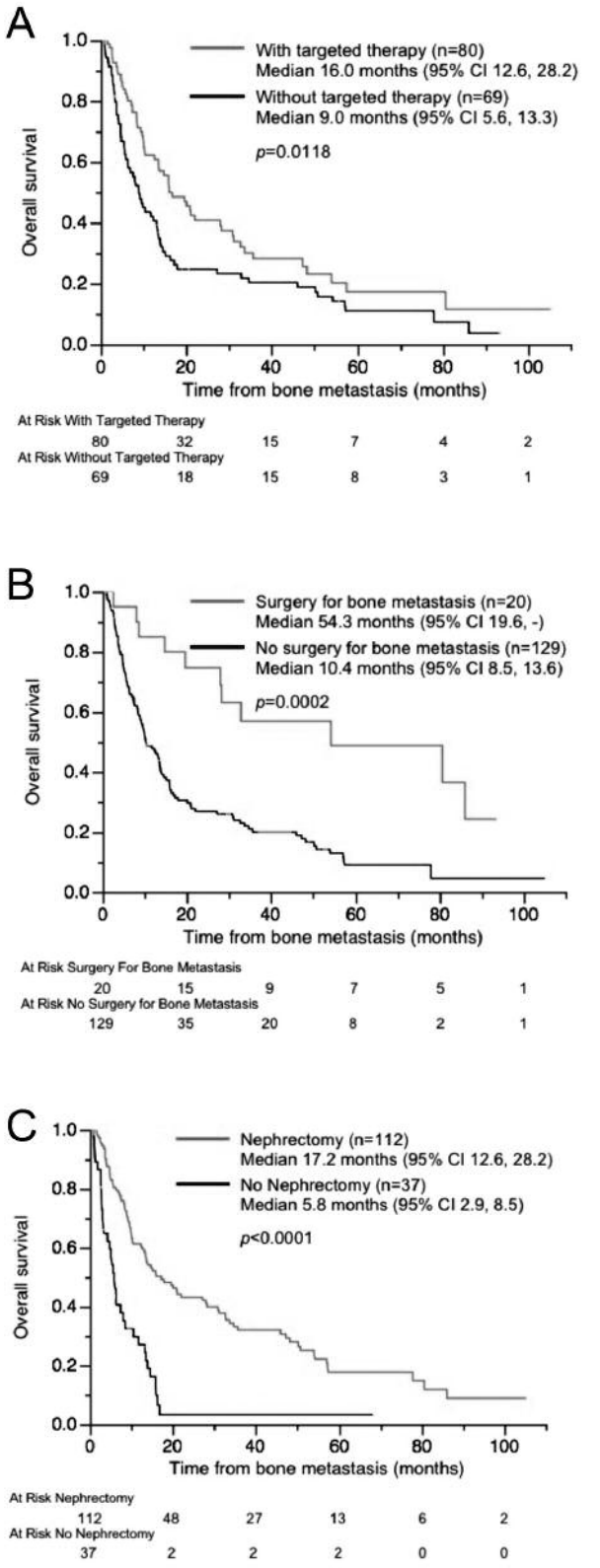

Figure 1. *Kaplan-Meier curve of OS in patients with bone metastasis by the presence/absence of targeted therapy (A), surgery for bone metastasis (B) and nephrectomy (C).*

Table IV. *Prognostic factors for overall survival in RCC patients with bone metastasis.*

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Gender (M *vs.* F)	0.87 (0.59-1.31)	0.5043		
Age (continuous)	1.02 (1.00-1.03)	0.0468	1.00 (0.99-1.02)	0.6607
Histology				
Clear cell	Reference			
Non-clear cell	1.67 (0.83-3.03)	0.1417		
Sarcomatoid differentiation	1.16 (0.41-2.60)	0.7526		
Nephrectomy	0.33 (0.22-0.51)	<0.0001	0.61 (0.39-0.97)	0.0366
MSKCC risk group				
Favourable	Reference			
Intermediate	1.96 (1.04-4.08)	0.0352	2.40 (1.21-5.23)	0.0111
Poor	3.85 (2.02-8.13)	<0.0001	4.37 (2.09-9.92)	<0.0001
Multiplicity of bone metastasis	1.96 (1.34-2.92)	0.0005	1.43 (0.91-2.28)	0.1223
Extraosseous metastasis	1.87 (1.24-2.91)	0.0023	1.71 (0.89-3.25)	0.1070
Lung metastasis	1.61 (1.12-2.33)	0.0104	1.23 (0.72-2.20)	0.4594
Liver metastasis	1.52 (0.88-2.47)	0.1304		
Brain metastasis	1.50 (0.58-3.14)	0.3617		
Surgery for bone metastasis	0.31 (0.16-0.57)	<0.0001	0.42 (0.20-0.81)	0.0085
RT for bone metastasis	0.75 (0.51-1.11)	0.1494		
No RT	Reference			
Palliative field RT	1.09 (0.68-1.73)	0.7269		
Definitive field RT	0.61 (0.39-0.94)	0.0244	0.64 (0.40-1.02)	0.0614
Systemic therapy	0.71 (0.48-1.06)	0.0952		
Cytokine therapy	0.99 (0.67-1.45)	0.9764		
Molecular-targeted therapy	0.63 (0.44-0.91)	0.0126	0.44 (0.29-0.68)	0.0002
BMA	1.28 (0.88-1.84)	0.1937		

HR, Hazard ratio; CI, confidence interval; MSKCC, Memorial Sloan-Kettering Cancer Centre; RT, radiation therapy; BMA, bone-modifying agent.

HR=4.37, 95% CI=2.09-9.92, $p<0.0001$ in poor *vs.* favourable), nephrectomy (HR=0.61, 95% CI=0.39-0.97, $p=0.0366$) and surgery for bone metastasis (HR=0.42, 95% CI=0.20-0.81, $p=0.0085$) were independent prognostic factors (Table IV). BMAs (zoledronic acid and denosumab) were not associated with OS. The median OS of patients receiving molecular-targeted therapy after diagnosis of bone metastasis was significantly better than that of those who did not receive targeted therapy (16.0 *vs.* 9.0 months, $p=0.0118$) (Figure 1A). When patients who underwent surgery for bone metastasis were compared to those without such treatment, the difference in OS between them was statistically significant ($p=0.0002$, Figure 1B). The difference in OS between patients with nephrectomy and those without nephrectomy was also statistically significant ($p<0.0001$, Figure 1C).

Discussion

The present study showed that the median OS of patients who received molecular-targeted therapy after diagnosis of bone metastasis (16 months) was significantly better than that of those who did not receive targeted therapy (9 months). These survivals are compatible with those in previous retrospective studies in each era (2-6). We also demonstrated that molecular-targeted therapy was an independent prognostic factor for OS in RCC patients with bone metastasis. In large randomized trials that showed the superior oncological outcome of the study arm (targeted agents) for mRCC over the control arm (cytokine or placebo), approximately one-third of patients had bone metastasis (10-13). These data also support our results suggesting advances of targeted agents in treatment for RCC patients with bone metastasis, although subgroup analyses of patients with bone metastasis were not published in those trials.

The roles of nephrectomy and surgery for bone metastasis in improving the survival of RCC patients with bone involvement were demonstrated in the present study, although more patients who received surgery for bone metastasis had favourable backgrounds, including nephrectomy ($p=0.0274$) and favourable or intermediate MSKCC risk ($p=0.0061$) than patients without bone surgery. In addition to the positive

results in two randomized trials (14, 15), the combined analysis (16) indicated that cytoreductive nephrectomy (CN) appeared to improve OS in patients with mRCC treated with interferon therapy independent of patients' performance status, the site of metastasis and the presence of measurable disease. Although two randomized studies concerning CN combined with targeting agents are ongoing at the moment (ClinicalTrials.gov Identifiers: NCT00930033 and NCT01099423), large retrospective series (17-20) have suggested that CN remains associated with improved survival in the targeted era except for patients with multiple negative prognostic factors (18, 19). A Japanese multi-institutional study showed that CN may provide survival benefit not only for mRCC patients who receive cytokine therapy but also for those receiving targeted therapy or those without systemic therapy (20). Furthermore, numerous studies have reported the prognostic impact of metastasectomy for mRCC patients. Recently, a systematic review of local therapy for metastases from RCC, such as metastatectomy and radiotherapy, identified 2,180 studies, but found only 16 non-randomized comparative studies reporting on 2,350 patients eligible for final inclusion (21). The results suggested that mRCC patients treated with complete metastasectomy had better survival and symptom control (including pain relief in bone metastases) than those treated with either incomplete or no metastasectomy (21), although all included studies were retrospective, non-randomized, comparative studies, thus resulting in a high risk of bias associated with non-randomization, attrition and selective reporting (22). There was considerable variation in the type and distribution of systemic therapies (cytokines and targeted agents) and in reporting the results. Fuchs *et al*. (23) retrospectively analyzed the survival of 60 patients with solitary bone metastasis from RCC and showed that patients with surgical treatment survived longer than those who had no surgical treatment. Their results also indicated that wide surgical excision of a solitary bone metastasis was not mandatory to improve survival but that stabilization might provide benefits for prevention of local disease progression and complications (23). Although not all patients underwent definitive surgical treatments for bone metastasis in our series (Table III), these treatments were significantly associated with favourable OS in multivariate analysis. Thus, surgical treatments should be considered when they are tolerable for patients.

BMAs were not associated with OS in the present study, though several studies suggested that BMAs together with VEGFR-TKIs improve survival in RCC patients having bone metastasis (4, 5). There are various possible reasons for the lack of any association between the use of BMAs and OS in this study. First, patients who received a BMA had a tendency to have extraosseous and multiple bone metastases compared to those without a BMA (data not shown). This bias may have affected the survival outcome. Second, 12 (19%) of the 62 patients treated with a BMA did not receive molecular-targeted therapy (no systemic therapy in 8, cytokine therapy in 4). The proportion of patients receiving BMAs is different from previous studies that reported the efficacy of BMAs on survival in patients who were treated with sunitinib (4, 5). Third, there is no evidence of a survival benefit of BMA use for patients with bone metastasis in randomized phase 3 trials (24). Thus, BMAs appear to yield a benefit in terms of reduction in skeletal-related events but not for survival prolongation (24, 25).

This study has certain limitations since it was a multi-institutional retrospective study representing an unselected heterogeneous cohort of RCC patients with bone metastasis. It is possible that the physicians' experience might have affected the differences in results and institutional bias may exist. Differences in terms of OS between patients with and without targeted therapy might be associated with medical progress in general and other factors that were not evaluated in this study. The limited cohort size means that data must be interpreted with due caution and require validation in larger, prospective series.

In conclusion, this study suggests that molecular-targeted therapy, nephrectomy and surgery for bone metastasis can prolong survival of RCC patients with bone metastasis. Multidisciplinary approaches with these treatments are recommended.

Conflicts of Interest

HK received lecture fees from Pfizer. The other Authors declare that there are no financial or personal conflicts of interest associated with this study.

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References

1 Bianchi M, Sun M, Jeldres C, Shariat SF, Trinh QD, Briganti A, Tian Z, Schmitges J, Graefen M, Perrotte P, Menon M, Montorsi F and Karakiewicz PI: Distribution of metastatic sites in renal cell carcinoma: a population-based analysis. Ann Oncol *23*: 973-980, 2012.

2 Kume H, Kakutani S, Yamada Y, Shinohara M, Tominaga T, Suzuki M, Fujimura T, Fukuhara H, Enomoto Y, Nishimatsu H and Homma Y: Prognostic factors for renal cell carcinoma with bone metastasis: who are the long-term survivors? J Urol *185*: 1611-1614, 2011.

3 Toyoda Y, Shinohara N, Harabayashi T, Abe T, Akino T, Sazawa A and Nonomura K: Survival and prognostic classification of patients with metastatic renal cell carcinoma of bone. Eur Urol *52*: 163-168, 2007.

4 Beuselinck B, Wolter P, Karadimou A, Elaidi R, Dumez H, Rogiers A, Van Cann T, Willems L, Body JJ, Berkers J, Van Poppel H, Lerut E, Debruyne P, Paridaens R and Schoffski P: Concomitant oral tyrosine kinase inhibitors and bisphosphonates in advanced renal cell carcinoma with bone metastases. Br J Cancer *107*: 1665-1671, 2012.

5 Keizman D, Ish-Shalom M, Pili R, Hammers H, Eisenberger MA, Sinibaldi V, Boursi B, Maimon N, Gottfried M, Hayat H, Peer A, Kovel S, Sella A, Berger R and Carducci MA: Bisphosphonates combined with sunitinib may improve the response rate, progression free survival and overall survival of patients with bone metastases from renal cell carcinoma. Eur J Cancer *48*: 1031-1037, 2012.

6 Motzer RJ, Escudier B, Bukowski R, Rini BI, Hutson TE, Barrios CH, Lin X, Fly K, Matczak E and Gore ME: Prognostic factors for survival in 1059 patients treated with sunitinib for metastatic renal cell carcinoma. Br J Cancer *108*: 2470-2477, 2013.

7 Motzer RJ, Bacik J, Murphy BA, Russo P and Mazumdar M: Interferon-alfa as a comparative treatment for clinical trials of new therapies against advanced renal cell carcinoma. J Clin Oncol *20*: 289-296, 2002.

8 Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Kay A, Ravaud A and RECORD-1 Study Group: Phase 3 trial of everolimus for metastatic renal cell carcinoma: Final results and analysis of prognostic factors. Cancer *116*: 4256-4265, 2010.

9 Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S and Mazumdar M: Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol *22*: 454-463, 2004.

10 Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, Oudard S, Negrier S, Szczylik C, Kim ST, Chen I, Bycott PW, Baum CM and Figlin RA: Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med *356*: 115-124, 2007.

11 Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, Grunwald V, Thompson JA, Figlin RA, Hollaender N, Urbanowitz G., Berg WJ, Kay A, Lebwohl D, Ravaud A and RECORD-1 Study Group: Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet *372*: 449-456, 2008.

12 Rini BI, Halabi S, Rosenberg JE, Stadler WM, Vaena DA, Ou SS, Archer L, Atkins JN, Picus J, Czaykowski P, Dutcher J and Small EJ: Bevacizumab plus interferon alfa compared with interferon alfa monotherapy in patients with metastatic renal cell carcinoma: CALGB 90206. J Clinl Oncol *26*: 5422-5428, 2008.

13 Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, Zarba JJ, Chen M, McCann L, Pandite L, Roychowdhury DF and Hawkins RE: Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. J Clin Oncol *28*: 1061-1068, 2010.

14 Mickisch GH, Garin A, van Poppel H, de Prijck L, Sylvester R, European Organisation for, Research and Treatment of Cancer Genitourinary Group: Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: A randomised trial. Lancet *358*: 966-970, 2001.

15 Flanigan RC, Salmon SE, Blumenstein BA, Bearman SI, Roy V, McGrath PC, Caton JR Jr, Munshi N and Crawford ED: Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med *345*: 1655-1659, 2001.

16 Flanigan RC, Mickisch G, Sylvester R, Tangen C, Van Poppel H and Crawford ED: Cytoreductive nephrectomy in patients with metastatic renal cancer: A combined analysis. J Urol *171*: 1071-1076, 2004.

17 Conti SL, Thomas IC, Hagedorn JC, Chung BI, Chertow GM, Wagner TH, Brooks JD, Srinivas S and Leppert JT: Utilization of cytoreductive nephrectomy and patient survival in the targeted therapy era. Int J Cancer *134*: 2245-2252, 2014.

18 Culp SH, Karam JA and Wood CG: Population-based analysis of factors associated with survival in patients undergoing cytoreductive nephrectomy in the targeted therapy era. Urol Oncol *32*: 561-568, 2014.

19 Heng DY, Wells JC, Rini BI, Beuselinck B, Lee JL, Knox JJ, Bjarnason GA, Pal SK, Kollmannsberger CK, Yuasa T, Srinivas S, Donskov F, Bamias A, Wood LA, Ernst DS, Agarwal N, Vaishampayan UN, Rha SY, Kim JJ and Choueiri TK: Cytoreductive nephrectomy in patients with synchronous metastases from renal cell carcinoma: Results from the International Metastatic Renal Cell Carcinoma Database Consortium. Eur Urol *66*: 704-710, 2014.

20 Tatsugami K, Shinohara N, Kondo T, Yamasaki T, Eto M, Tsushima T, Terachi T, Naito S and Japanese Society of Renal Cancer: Role of cytoreductive nephrectomy for Japanese patients with primary renal cell carcinoma in the cytokine and targeted therapy era. Int J Urol *22*: 736-740, 2015.

21 Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, Staehler M, Powles T, Ljungberg B and Bex A: Local treatments for metastases of renal cell carcinoma: A systematic review. Lancet. Oncol *15*: e549-561, 2014.

22 Ljungberg B, Bensalah K, Canfield S, Dabestani S, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Mulders P, Powles T, Staehler M, Volpe A and Bex A: EAU guidelines on renal cell carcinoma: 2014 update. Eur Urol *67*: 913-924, 2015.

23 Fuchs B, Trousdale RT and Rock MG: Solitary bony metastasis from renal cell carcinoma: Significance of surgical treatment. Clin Orthop Relat Res *431*: 187-192, 2005.

24 Saylor PJ, Armstrong AJ, Fizazi K, Freedland S, Saad F, Smith MR, Tombal B and Pienta K: New and emerging therapies for bone metastases in genitourinary cancers. Eur Urol *63*: 309-320, 2013.

25 Lipton A, Colombo-Berra A, Bukowski RM, Rosen L, Zheng M and Urbanowitz G: Skeletal complications in patients with bone metastases from renal cell carcinoma and therapeutic benefits of zoledronic acid. Clin Cancer Res *10*: 6397S-6403S, 2004.

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