Interval Between Cancer Diagnosis and Radiotherapy – An Independent Prognostic Factor of Survival in Patients Irradiated for Bone Metastases from Kidney Cancer

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Abstract. *Background/Aim: Cancer patients with metastatic disease require personalized treatment regimens. This study was performed to identify prognostic factors for overall survival (OS) following irradiation of bone metastases from kidney cancer. Patients and Methods: Data of 29 patients irradiated for bone metastases from kidney cancer were retrospectively evaluated. Ten factors were analyzed, including age, gender, performance score, interval from diagnosis of kidney cancer until radiotherapy for bone metastases, visceral metastases, other bone metastases, metastatic sites, number of irradiated sites, surgery of irradiated sites and systemic treatment prior to radiotherapy. Results: Using univariate analyses, a longer interval from diagnosis of kidney cancer radiotherapy was associated with better OS (p=0.012). Using Cox regression analysis, this factor remained significant (risk ratio=3.54, p=0.012). Conclusion: The interval from diagnosis of kidney cancer until radiotherapy is an independent prognostic factor associated with OS following irradiation of bone metastases from kidney cancer. This type of data can help personalize radiation programs.*

Cancer patients with metastatic disease require personalized treatment that meets the needs of each patient. This includes an assessment of the patient's expected remaining lifespan. For patients with a poor expected survival time, the

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treatment regimen should be short so they spend as little time as possible receiving treatment. In patients with a favorable survival prognosis, one must account for the fact that these patients may live long enough to be at risk of experiencing a local recurrence. Thus, prognostic factors that help physicians estimate a patient's survival time are important to choose the most appropriate treatment regimen.

In radiation oncology, the most frequent types of metastases include brain and bone metastases. For example, bone metastases can occur in up to 40% of patients with kidney cancer during their lives (1, 2). For these patients, various radiotherapy programs are available including single-fraction, short-course multi-fraction (over approximately 1 week) and longer-course (over 2-4 weeks) programs (2). Patients with a poor survival appear as good candidates for single-fraction or short-course radiotherapy. Those patients with favorable prognoses can benefit from longer-course programs that result in better long-term local control of irradiated bone metastases (2, 3). Therefore, it is important to be able to estimate a patient's overall survival (OS) time prior to the start of radiotherapy. This can be facilitated with the clear understanding of significant prognostic factors.

Malignant tumors vary considerably regarding their biological behavior. Therefore, it is important to identify prognostic factors in patients with bone metastases for each tumor type. This has already been performed for other situations, such as metastatic spinal cord compression (MSCC) and brain metastases (4-12). The present study was performed to identify independent prognostic factors associated with OS in patients irradiated for bone metastases from kidney cancer.

Patients and Methods

This retrospective study evaluated the data of 29 patients irradiated for bone metastases from kidney cancer without MSCC with respect to OS. The study was approved by the local ethics committee (reference: 18-254A). All patients received multifraction radiotherapy

Table I. *Distribution of the ten potential predictors of survival.*

	Number of patients (%)
Age at start of radiotherapy	
≤70 Years	15 (52)
≥71 Years	14 (48)
Gender	
Female	8 (28)
Male	21 (72)
ECOG performance score	
0-1	18 (62)
≥2	10 (34)
Unknown	1 (3)
Interval from diagnosis of kidney cancer until start of radiotherapy	
≤8 Months	16 (55)
≥9 Months	13 (45)
Visceral metastases	
No	7 (24)
Yes	22 (76)
Other bone metastases	
No	8 (28)
Yes	21 (72)
Type of metastatic site	
Spinal only	10 (34)
Extraspinal only	10 (34)
Both	9 (31)
Number of irradiated sites	
1	12 (41)
≥2	17 (59)
Surgery prior to radiotherapy	
No	16 (55)
Yes	13 (45)
Systemic treatment prior to radiotherapy	
No	10 (34)
Yes	19 (66)

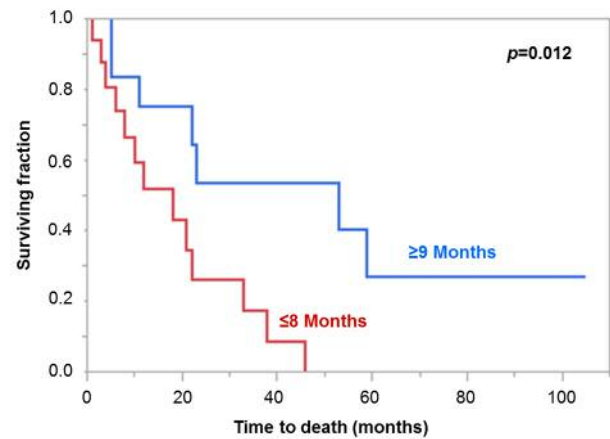ECOG: Eastern Cooperative Oncology Group.

Figure 1. *Kaplan-Meier curves for kidney cancer patients with respect the the interval between first diagnosis of cancer and start of radiotherapy. Improved survival was identified for patients with longer interval (≥9 months) compared to the shorter interval (≤8 months). The p-value was calculated using the log-rank test.*

Results

Median follow up of the entire cohort was 17 months (range=1-105 months). The OS rates at 6 months and 12 months were 78% and 63%, respectively. Using univariate analyses, only a longer interval (≥9 months) from the first diagnosis of kidney cancer to the start of radiotherapy was significantly associated with a better OS (p=0.012, Figure 1). The results of the entire univariate analyses are summarized in Table II. In the subsequent Cox regression analysis, the interval from the first diagnosis of kidney cancer to the start of radiotherapy remained significant (risk ratio=3.54, 95%Confidence Interval=1.31-11.24, p=0.012).

Discussion

Since the survival of patients with metastatic kidney cancer is poor, a great amount of data from preclinical and clinical research has been gathered (14-19). In addition to the development of new drugs, personalized treatment is another important approach. This includes selecting the most appropriate radiation program for each patient. A personalized approach ideally accounts for the patient's expected survival to avoid either over- or under-treatment. A clear understanding of prognostic factors for survival can help physicians select the optimal program for each patient. For optimizing the personalized radiation treatment, the metastatic site as well as the tumor type should be considered. This study was performed to identify significant prognostic factors for survival following irradiation of bone metastases from kidney cancer.

with 5-6×4.0 Gy (n=2), 10×3.0 Gy (n=5), 12-13×3.0 Gy (n=8), 14-15×2.5 Gy (n=11) or 20×1.8-2.0 Gy (n=3). Ten factors were analyzed for potential associations with OS, including i) age (≤70 *vs.* ≥71 years, median=70 years), ii) gender, iii) Eastern Cooperative Oncology Group (ECOG) performance score (0-1 *vs.* ≥2) (13), iv) interval from diagnosis of kidney cancer until start of radiotherapy for bone metastases (≤8 *vs.* ≥9 months, median=8 months), v) visceral metastases prior to radiotherapy (no *vs.* yes), vi) other bone metastases prior to radiotherapy (no *vs.* yes), vii) type of metastatic sites (spinal only *vs.* extraspinal only *vs.* both), viii) number of irradiated metastatic sites (1 *vs.* ≥2), ix) surgery of irradiated bone metastases prior to radiotherapy (no *vs.* yes) and x) systemic treatment prior to radiotherapy (no *vs.* yes). The distribution of these factors is given in Table I.

Statistical analyses were initially performed using the Kaplan-Meier method and the log-rank test (univariate analyses). Subsequently, those factors found significant on univariate analysis (p<0.05) were included in a multivariate analysis (Cox regression) for evaluation with respect to independence.

Table II. *Overall survival (OS) rates of the 10 investigated factors (univariate analyses).*

Factor	Overall survival		*p*-Value
	6 months (%)	12 months (%)	
Age at start of radiotherapy			
≤70 Years	78	70	
≥71 Years	79	55	0.28
Gender			
Female	88	63	
Male	75	63	0.76
ECOG performance score			
0-1	88	69	
≥2	60	48	0.28
Interval from diagnosis of kidney cancer until start of radiotherapy			
≤8 Months	74	52	
≥9 Months	83	75	**0.012**
Visceral metastases			
No	86	69	
Yes	76	61	0.66
Other bone metastases			
No	67	50	
Yes	81	66	0.64
Type of metastatic site			
Spinal only	78	56	
Extraspinal only	80	80	
Both	78	47	0.39
Number of irradiated sites			
1	82	73	
≥2	76	55	0.11
Surgery prior to radiotherapy			
No	75	61	
Yes	82	64	0.96
Systemic treatment prior to radiotherapy			
No	79	66	
Yes	78	61	0.75

ECOG: Eastern Cooperative Oncology Group, bold *p*-value=significant.

A few scoring systems for estimating the survival of patients irradiated for bone metastases already exist. One of these scores was developed in patients with spinal metastases (20). Based on the performance score, the type of primary tumor and presence of visceral metastases, three groups were created with survival times of median 3, 9 and 18.7 months. However, this score may not be useful for extraspinal bone metastases (20). More recently, other scores for patients irradiated for bone metastases were created (21, 22). One of these scoring systems was developed in patients with spinal and/or extraspinal bone metastases (21). Gender, primary tumor type, performance score, visceral metastases and two self-rating tools considering general health and quality of life were identified as significant prognostic factors. As this scoring system was very complex, a simpler system based only on performance score and primary tumor type was provided in the same report (21). Another scoring system was created from data of 1,043 patients with spinal metastases including only patients with MSCC (22). This score may not be applicable to extraspinal bone metastases. The most recent scoring tool for estimation of survival following irradiation of bone metastases was limited to symptomatic metastases of the long bones and may not be useful for patients with spinal lesions (23). Moreover, none of these studies was performed in patients with bone metastases from a specific tumor type. The present study focused on patients with kidney cancer and determined that the interval from diagnosis of kidney cancer to the start of radiotherapy for bone metastases was significantly associated with OS in both univariate and multivariate analyses. This independent prognostic factor may help physicians select a more appropriate personalized radiotherapy program for each patient. Patients with a longer interval (≥9 months), which was associated with better survival, should be considered for longer-course radiotherapy programs and patients with shorter intervals (≤8 months) for shorter programs. However, the retrospective design of this study may have led to inclusion of hidden selection biases that should be considered when applying this information. Moreover, since all patients received multi-fraction radiotherapy, the findings of this study may not be applicable to patients treated with single-fraction irradiation.

In conclusion, the interval between first diagnosis of kidney cancer and radiotherapy of bone metastases appears to be an independent prognostic factor for OS after irradiation of bone metastases from kidney cancer. This knowledge can help physicians personalize radiation programs, and this prognostic factor can potentially improve the stratification of patients in future clinical trials.

Conflicts of Interest

Authors' Contributions

D.R., R.H., S.J. and S.E.S participated in the design of the study. D.R., R.H. and S.J. provided data. D.R. and S.E.S. performed the analyses of the data and drafted the manuscript, which has been reviewed and approved by all authors.

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