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Sites of Metastasis and Survival in Metastatic Renal Cell Carcinoma: Results From the Korean Renal Cancer Study Group Database

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ABSTRACT

Background: In patients with metastatic renal cell carcinoma (mRCC), sites of metastatic involvement have been reported to be associated with a difference in survival. However, the frequency and survival according to different sites of metastases in Korean patients with mRCC remain unclear. Therefore, this study aimed to assess the frequency of metastatic site involvement and the association between sites of metastatic involvement and survival in Korean patients with mRCC.

Methods: This retrospective study used the multicenter cohort of the Korean Renal Cancer Study Group mRCC database to identify patients who started targeted therapy between December 2005 and March 2018. Data on the frequency of metastatic organ involvement at the time of mRCC diagnosis and oncologic outcomes according to different sites of metastasis were analyzed.

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Disclosure

The authors have no potential conflicts of interest to disclose.

Author Contributions

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Results: A total of 1,761 patients were eligible for analysis. Of the 1,761 patients, 1,564 (88.8%) had clear cell RCC, and 1,040 (59.1%) had synchronous metastasis. The median number of metastasis sites was 2 (interquartile range [IQR], 1–6). The median age at the initiation of systemic therapy was 60 years (IQR, 29–88), 1,380 (78.4%) were men, and 1,341 (76.1%) underwent nephrectomy. Based on the International Metastatic Renal Cell Carcinoma Database Consortium model, patients were stratified into favorable-, intermediate-, and poor-risk groups with 359 (20.4%), 1,092 (62.0%), and 310 (17.6%) patients, respectively. The lung (70.9%), lymph nodes (37.9%), bone (30.7%), liver (12.7%), adrenal gland (9.8%), and brain (8.2%) were the most common sites of metastasis, followed by the pancreas, pleura, peritoneum, spleen, thyroid, and bowel. Among the most common sites of metastasis (> 5%), the median cancer-specific survival (CSS) ranged from 13.9 (liver) to 29.1 months (lung). An association was observed between liver, bone, and pleural metastases and the shortest median CSS (< 19 months).
Conclusion: In Korean patients with mRCC, metastases to the lung, lymph nodes, bone, liver, adrenal gland, and brain were more frequent than those to other organs. Metastases to the liver, bone, and pleura were associated with poor CSS. The findings of this study may be valuable for patient counseling and guiding future study designs.

Keywords: Carcinoma, Renal Cell; Neoplasm Metastasis; Molecular Targeted Therapy; Survival; Prognosis

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of all malignancies worldwide.[1] In South Korea, RCC is the second most common urologic cancer and the 10th most common malignancy, with 6,883 newly diagnosed RCC cases in 2021.[2] Approximately one-third of the newly diagnosed RCC cases are detected at an advanced stage or with metastasis,[3] and 20–30% of localized disease cases develop local recurrence and distant metastasis after curative surgical treatment.[4]

With the introduction of new systemic therapies, such as targeted therapies and immune checkpoint inhibitors (ICIs), survival in patients with metastatic renal cell carcinoma (mRCC) has improved.[5,6] Furthermore, risk stratification models for mRCC, such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, are well recognized and correlate well with survival in mRCC, leading to therapeutic recommendations accordingly.[7,8] In addition to risk stratification models, sites of metastatic involvement have been reported to be associated with differences in survival. Several population-based analyses have reported the common metastatic sites of mRCC.[9,10] However, few studies have reported the impact of metastatic organ involvement on survival and response to systemic therapy.[11,12] In Korea, despite the increasing incidence of kidney cancer, integrated data on the prevalence of metastatic sites in mRCC and the association between metastatic sites and survival in Korean patients are lacking.

Therefore, using a multicenter dataset, this study aimed to characterize the frequency of metastatic site involvement and assess associations between sites of metastatic involvement and survival in mRCC.

METHODS

Study populations

This retrospective study used the data from 3,153 RCC patients treated with systemic therapy at 11 medical centers across South Korea from February 1994 to March 2018, collected from the Korean Renal Cancer Study Group (KRoCS) mRCC database. The KRoCS mRCC database includes information on patient demographics, pathological stages and types, laboratory results, clinical data, and types of systemic therapy. All participating centers received approval from their local research ethics board before data collection. Of the 3,153 patients with mRCC, 1,761 who began targeted therapy between December 2005 and March 2018 were included in the analysis. Data on sites of metastatic involvement, tumor and treatment details, and survival were collected from the database. The pathological stage was determined based on the 2010 version of the American Joint Committee on Cancer TNM staging system and the Heidelberg classification of renal tumors. Clinical and laboratory variables, including age, sex, and the IMDC risk group, were collected at the time of mRCC diagnosis.

Outcome measurement

The primary outcome was the prevalence of metastatic site involvement at the diagnosis of metastatic disease. Metachronous metastasis was defined as the occurrence of disease three months after curative-intent surgery for the primary tumor. Overall survival (OS) stratified by the number of metastatic organs involved, histological subtypes, and IMDC risk groups was measured. Additionally, cancer-specific survival (CSS) and progression-free survival (PFS) of first-line targeted therapy, stratified by metastatic site involvement, were measured. We hypothesized that the site of metastasis would be more strongly associated with CSS than OS. Therefore, we focused on the relationship between the site of metastatic involvement and CSS.

Statistical analysis

Continuous variables were presented as mean with standard deviation or median with interquartile range (IQR). Categorical variables were presented as frequencies and percentages. Differences in the distribution of variables among groups were evaluated using the χ^2 test, Fisher's exact test, and linear-by-linear association test for categorical variables, and Student's *t*-test for continuous variables. OS, CSS, and PFS of first-line targeted therapy were estimated using the Kaplan-Meier method and compared using the log-rank test. Additionally, restricted mean survival time was used to estimate the average survival time from the beginning of targeted therapy to 24 and 48 months.[13] Hazard ratios (HRs) for CSS by sites of metastatic involvement were calculated using multivariate Cox regression analyses and adjusted to control for imbalances in individual IMDC risk factors and the number of metastatic lesions. Adjusted HRs for CSS were reported by comparing involved with non-involved sites of metastasis, with HR > 1 denoting worse CSS. All statistical analyses were performed using SPSS version 27.0 (IBM, Armonk, NY, USA) and MedCalc version 22.0 (MedCalc Software, Ostend, Belgium). A *P* value < 0.05 was considered statistically significant.

Ethics statement

The study protocol was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the Institutional Review Board of Inje University Busan Paik Hospital (BPIRB-2024-03-027). The requirement for informed consent was waived by the Institutional Review Board due to the retrospective nature of the study.

RESULTS

Patients

A total of 1,761 patients were eligible for analysis. The median follow-up period was 21.9 (IQR, 1.7–89.0) months. The median age of the patients at the initiation of systemic therapy was 60 (IQR, 29–88) years. Of the 1,761 patients, 1,380 (78.4%) were men, and 381 (21.6%) were women. Among the patients, 88.8% (n = 1,564) had clear cell RCC, and 21.2% (n = 191) had non-clear cell RCC. A total of 1,341 (76.1%) patients underwent nephrectomy, and 721 (40.9%) patients developed metachronous metastasis. The median time from diagnosis

Table 1. Baseline characteristics

Characteristics	Total (N = 1,761)	Clear cell (n = 1,564, 88.8%)	Non-clear cell (n = 197, 21.2%)	*P* value
Age, yr	60 (29–88)	61 (33–88)	58 (26–86)	< 0.001
Sex				0.005
Male	1,380 (78.4)	1,241 (79.3)	139 (70.6)	
Female	381 (21.6)	323 (20.7)	58 (29.4)	
cT stage				0.644
T1	481 (27.3)	430 (27.5)	51 (25.9)	
T2	316 (17.9)	285 (18.2)	31 (15.7)	
T3	855 (48.6)	748 (47.8)	107 (54.3)	
T4	109 (6.2)	101 (6.5)	8 (4.1)	
cN stage				< 0.001
N0	1,094 (62.1)	1,004 (64.2)	90 (45.7)	
N1	667 (37.9)	560 (35.8)	107 (54.3)	
Sarcomatoid features				0.096
No	1,548 (87.9)	1,382 (88.4)	166 (84.3)	
Yes	213 (12.1)	182 (11.6)	31 (15.7)	
No. of metastatic organ				0.113
Single	783 (44.5)	706 (45.1)	77 (39.1)	
Two	582 (33.0)	513 (32.8)	69 (35.0)	
Three	272 (15.5)	237 (15.2)	35 (17.8)	
≥ Four	124 (7.0)	108 (6.9)	16 (8.1)	
Timing of metastasis				0.259
Synchronous metastasis	1,040 (59.1)	931 (59.5)	109 (55.3)	
Metachronous metastasis	721 (40.9)	633 (40.5)	88 (44.7)	
IMDC risk groups				0.126
Favorable	359 (20.4)	319 (20.4)	40 (20.3)	
Intermediate	1,092 (62.0)	982 (62.8)	110 (55.8)	
Poor	310 (17.6)	263 (16.8)	47 (23.9)	
Nephrectomy				0.286
No	420 (23.9)	367 (23.5)	53 (26.9)	
Yes	1,341 (76.1)	1,197 (76.5)	144 (73.1)	
Treatment for metastatic lesions				
Metastasectomy	361 (20.6)	324 (20.9)	37 (18.8)	0.496
Brain stereotactic radiosurgery	52 (3.0)	46 (3.0)	6 (3.1)	0.930
Radiotherapy	183 (10.5)	159 (10.2)	24 (12.3)	0.374
First-line systemic therapy				< 0.001
TKIs	1,612 (91.5)	1,515 (96.9)	97 (49.2)	
mTORis	149 (8.5)	49 (3.1)	100 (50.8)	
First-line TKIs				0.728
Sunitinib	1,000 (62.0)	942 (62.2)	58 (59.8)	
Pazopanib	377 (23.5)	363 (24.0)	14 (14.4)	
Sorafenib	215 (13.3)	193 (12.7)	22 (22.7)	
Others	20 (1.2)	17 (1.1)	3 (3.1)	
First-line mTORi				< 0.001
Everolimus	31 (20.8)	21 (42.9)	10 (10.0)	
Temsirolimus	118 (79.2)	28 (57.1)	90 (90.0)	

Values are presented as number (%) or median (interquartile range).
IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, TKI = tyrosine kinase inhitor, mTORi = mammalian target of rapamycin inhibitor.

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of RCC to metachronous metastasis was 34.8 (IQR, 3.1–158.7) months. Based on the IMDC model, 359 (20.4%) patients were classified as favorable risk, 1,092 (62.0%) as intermediate risk, and 310 (17.6%) as poor risk. Furthermore, 1,612 (91.5%) patients were treated with tyrosine kinase inhibitors (TKIs), and 149 (8.5%) were treated with mammalian target of rapamycin inhibitors as first-line targeted therapy. Regarding metastatic lesion treatment, 361 (20.6%) patients underwent metastasectomy, 52 (3.0%) with brain metastases were treated with stereotactic radiosurgery, and 183 (10.5%) were treated with radiotherapy. Patients with non-clear cell RCC were less likely to be male (70.6%), more likely to have lymph node metastasis (54.3%), and more likely to receive first-line mammalian target of rapamycin inhibitors (50.8%) than those with clear cell RCC (all, $P < 0.05$). **Table 1** shows the baseline characteristics of the patients.

Sites of metastasis

The median number of metastatic organs was 2 (IQR, 1–6 sites). Of the 1,761 patients, 783 (44.5%) had single-organ metastasis (**Table 1**). **Fig. 1** shows the distribution of RCC metastases. Analysis of multiple metastases revealed that the lung (70.9%), lymph nodes (37.9%), bone (30.7%), liver (12.7%), adrenal gland (9.8%), and brain (8.2%) were the six most common sites of metastasis across the entire cohort. Additionally, the pancreas, peritoneum, spleen, thyroid, and bowel were less frequent sites of metastasis (< 5%). Analysis of single-organ metastases in the absence of any other sites of disease revealed that the lung (57.3%), bone (16.6%), and lymph nodes (13.5%) were the three most frequent sites of metastasis (> 5%).

Survival

The median OS, PFS of first-line targeted therapy, and CSS of patients with mRCC treated by targeted therapy were 27.0 (95% confidence interval [CI], 24.8–28.9), 6.7 (95% CI, 5.9–7.3), and 28.2 (95% CI, 26.3–30.8) months, respectively. A significant difference in OS was observed among the IMDC risk groups ($P < 0.001$) (**Fig. 2A**). Patients with single-site metastasis had significantly longer median OS than those with metastases to multiple organs

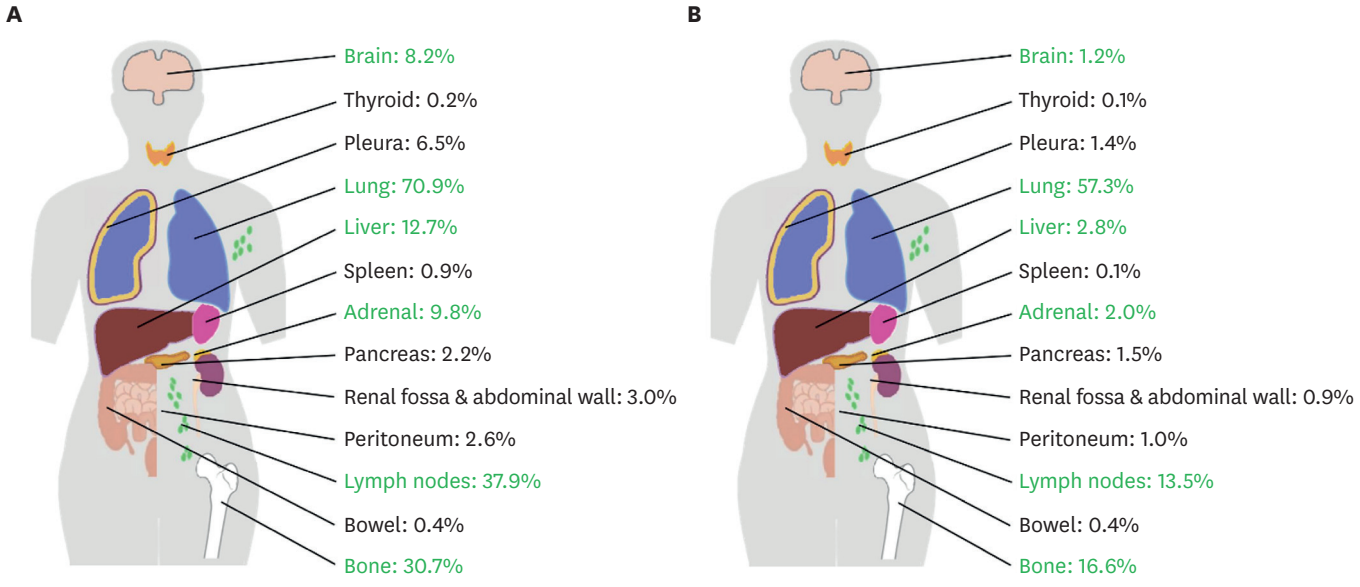

Fig. 1. Distribution of renal cell carcinoma metastases by location. (**A**) Whole cohort (multiple metastases included). (**B**) Single-organ metastasis in the absence of any other disease sites.

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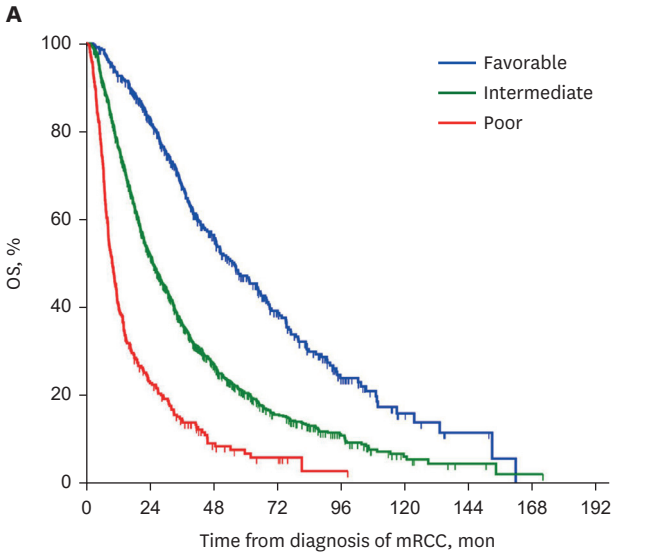
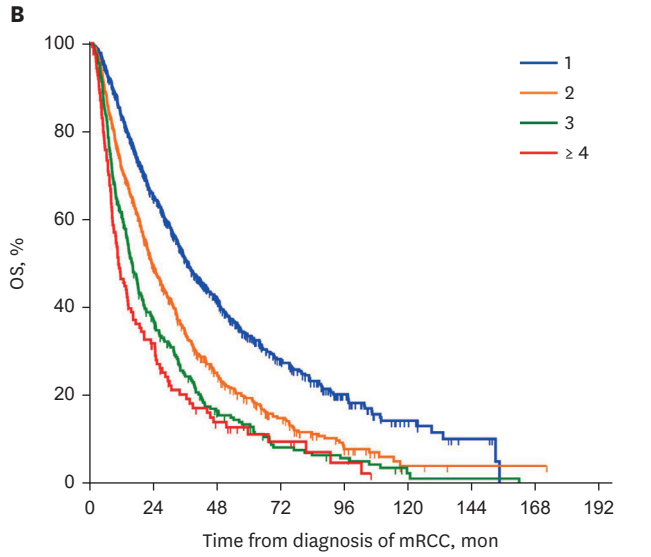
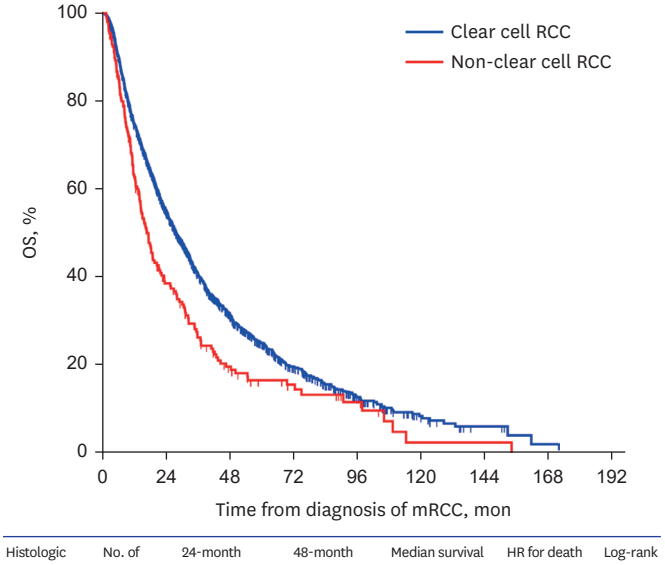


IMDC risk group	No. of patients	24-month RMST (95% CI)	48-month RMST (95% CI)	Median survival (95% CI)	HR for death (95% CI)	Log-rank *P* value
Favorable	359	22.3 (21.8–22.8)	38.7 (37.3–40.1)	55.6 (48.5–64.6)	Reference	
Intermediate	1,092	18.6 (18.2–19.0)	27.6 (26.7–28.6)	25.1 (23.2–27.9)	1.97 (1.74–2.22)	*P* < 0.001
Poor	310	12.4 (11.5–13.3)	16.1 (14.5–17.8)	9.9 (8.4–11.3)	4.41 (3.58–5.44)	



No. of metastatic sites	No. of patients	24-month RMST (95% CI)	48-month RMST (95% CI)	Median survival (95% CI)	HR for death (95% CI)	Log-rank *P* value
1	783	20.2 (19.7–20.6)	32.7 (31.6–33.9)	37.3 (33.9–41.8)	Reference	
2	582	17.9 (17.3–18.6)	26.5 (25.2–27.9)	23.6 (21.7–27.0)	1.55 (1.37–1.75)	*P* < 0.001
3	272	15.6 (14.7–16.6)	21.8 (19.8–23.7)	16.3 (14.1–18.6)	2.08 (1.74–2.47)	
≥ 4	124	13.7 (12.2–15.1)	18.6 (15.8–21.4)	11.0 (8.90–14.6)	2.55 (1.95–3.34)	



Histologic subtype	No. of patients	24-month RMST (95% CI)	48-month RMST (95% CI)	Median survival (95% CI)	HR for death (95% CI)	Log-rank *P* value
Clear cell	1,564	18.5 (18.2–18.9)	28.6 (27.7–29.4)	55.6 (48.5–64.6)	Reference	*P* < 0.001
Non-clear cell	197	16.1 (15.0–17.2)	22.8 (20.5–25.2)	25.1 (23.2–27.9)	1.46 (1.21–1.77)	

Fig. 2. OS for patients with mRCC. (**A**) OS according to the IMDC risk groups. (**B**) OS according to the number of metastatic organs. (**C**) OS according to histological subtypes.
OS = overall survival, mRCC = metastatic renal cell carcinoma, IMDC = International Metastatic Renal Cell Carcinoma Database Consortium, RMST = restricted mean survival time, CI = confidence interval, RCC = renal cell carcinoma.

(*P* < 0.001) (**Fig. 2B**). Additionally, patients with clear cell RCC had significantly longer median OS than patients with non-clear cell histology (*P* < 0.001) (**Fig. 2C**). CSS varied substantially according to the site of metastatic involvement. **Fig. 3** shows the CSS results

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Involved metastatic site	No. of patients (%)	24-month RMST (95% CI)	48-month RMST (95% CI)	Median survival (95% CI), mon	Adjusted HR (95% CI)	Median survival, mon	*P* value
Thyroid	4 (0.2)	15.4 (7.0–23.9)	22.0 (7.0–36.9)	8.5 (5.3–40.1)	1.65 (0.61–4.44)		0.313
Liver	233 (12.7)	14.6 (13.6–15.7)	20.2 (18.1–22.4)	13.9 (11.4–16.4)	1.46 (1.22–1.75)		< 0.001
Bone	540 (30.7)	16.3 (15.6–17.0)	23.3 (21.8–24.7)	18.1 (15.9–20.1)	1.24 (1.09–1.41)		0.001
Pleura	115 (6.5)	16.1 (14.6–17.6)	23.7 (20.4–26.9)	17.8 (13.8–26.3)	1.13 (0.90–1.41)		0.285
Peritoneum	46 (2.6)	16.0 (13.4–18.6)	24.5 (19.1–30.0)	19.2 (9.6–36.5)	0.95 (0.67–1.34)		0.770
Renal fossa and abdominal wall	53 (3.0)	17.6 (15.6–19.5)	22.8 (19.0–26.6)	20.6 (14.6–25.2)	1.23 (0.90–1.66)		0.180
Lymph nodes	667 (37.9)	16.9 (16.3–17.5)	25.1 (23.8–26.4)	20.7 (18.1–23.4)	1.08 (0.95–1.23)		0.202
Brain	152 (8.2)	16.9 (15.6–18.2)	25.1 (22.2–27.8)	21.8 (16.5–28.5)	0.84 (0.68–1.03)		0.102
Adrenal	172 (9.8)	17.7 (16.5–18.9)	27.4 (24.7–30.0)	25.1 (19.6–34.0)	0.75 (0.61–0.92)		0.007
Lung	1,249 (70.9)	18.6 (18.2–19.1)	29.0 (28.1–30.0)	29.1 (26.5–31.7)	0.84 (0.74–0.95)		0.007
Bowel	7 (0.4)	17.6 (11.0–24.2)	28.4 (14.7–42.2)	32.9 (2.5–48.1)	0.58 (0.24–1.43)		0.243
Spleen	8 (0.5)	19.5 (15.2–23.8)	30.3 (18.2–42.5)	36.2 (10.4–36.4)	0.38 (0.14–1.02)		0.056
Pancreas	39 (2.2)	21.3 (19.4–23.2)	36.5 (31.5–41.6)	67.7 (28.2–123.3)	0.31 (0.19–0.49)		< 0.001

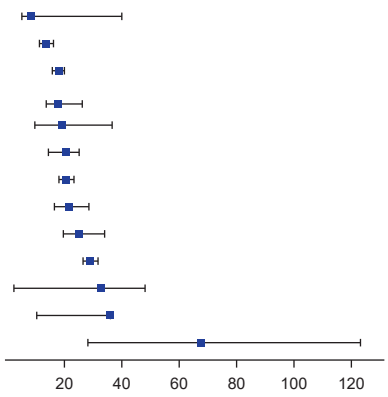

Fig. 3. CSS based on the site of metastatic involvement in metastatic renal cell carcinoma. Survival time is presented in ascending order of median survival. Patients with multiple sites of metastatic involvement were included in the analyses of all groups according to their metastases. CSS was calculated from the time of diagnosis of metastatic disease to death from cancer or censored at the time of the last follow-up. The adjusted HR was reported by comparing involved with non-involved sites of metastasis, adjusted by International Metastatic Renal Cell Carcinoma Database Consortium risk groups and the number of metastatic organs. An adjusted HR > 1 indicates worse CSS.
CSS = cancer-specific survival, HR = hazard ratio, RMST = restricted mean survival time, CI = confidence interval.

based on the site of metastatic involvement in mRCC. Among the frequent sites of metastasis (> 5%), the median CSS ranged from 13.9 months for metastasis to the liver to 29.1 months for metastasis to the lung. Metastases to the liver, bone, and pleura were associated with the shortest median CSS (< 19 months). Among the common single metastatic sites, liver metastasis was associated with the shortest median CSS (21.2 months [95% CI, 16.3–43.8]), and bone metastasis was associated with the shortest median PFS of first-line targeted therapy (4.9 months [95% CI, 3.4–8.2]) (**Fig. 4**).

DISCUSSION

In 2021, RCC accounted for 6,883 cases, making up 2.5% of the 277,523 newly diagnosed cancer cases in Korea.[2] The age-standardized incidence rate for kidney cancer in Korea was 7.5 per 1,000,000 population in 2021, while the worldwide age-standardized incidence rate in 2020 was 4.6 per 1,000,000.[2,14] Over the last five years (2017–2021), the stage distribution at diagnosis for RCC in Korea was as follows: 73.5% were at the localized stage, 11.1% at the regional stage, and 10.8% at the distant metastatic stage. The corresponding five-year survival rates were 97.9%, 81.4%, and 10.8%, respectively. Given that approximately 10% of kidney cancers in Korea are mRCC, the KRoCS mRCC database used in our study serves as an excellent data source, capturing approximately 19% of newly diagnosed mRCC cases in Korea annually. Consequently, our study results indirectly reflect the composition of mRCC in Korea, which is superior compared to other single-center retrospective data-based studies.

Different cancers have different sites of frequent metastasis or recurrence, and survival has been reported to vary according to the timing of metastasis, number of metastatic sites involved, and metastatic tumor burden.[15] Furthermore, differences in survival according to various metastatic sites have also been reported.[16] Similar findings have been observed in kidney cancer. A population-based study using the Surveillance, Epidemiology, and End Results database showed that the lung, lymph nodes, bone, liver, and brain are common sites of metastasis in mRCC and reported that survival varies depending on the metastatic sites.[10]

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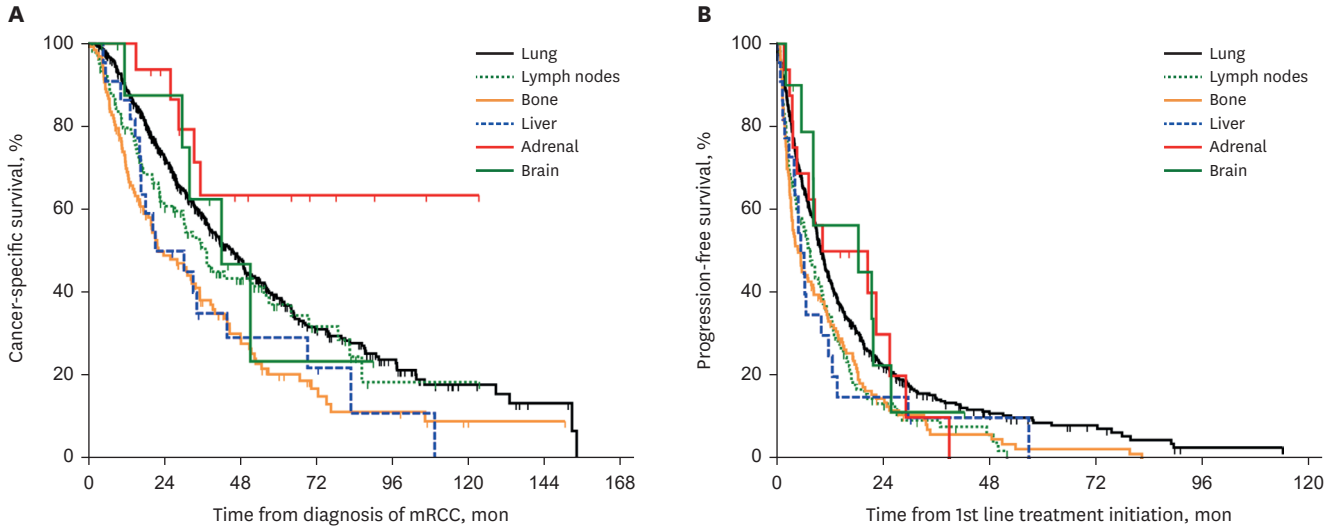

Metastatic sites	No. of patients	24-month RMST (95% CI)	48-month RMST (95% CI)	Median survival (95% CI)	Hazard ratio (95% CI)	Log-rank *P* value
Lung	449	21.3 (20.8–21.8)	35.4 (34.0–36.9)	45.6 (38.0–49.6)	Reference	
Lymph nodes	106	19.3 (18.0–20.7)	31.6 (28.3–35.0)	37.5 (27.4–57.1)	1.19 (0.90–1.59)	
Bone	130	17.6 (16.3–19.0)	27.2 (24.1–30.2)	22.2 (17.6–35.2)	1.75 (1.33–2.32)	
Liver	22	19.2 (16.6–21.7)	28.6 (22.1–35.1)	21.2 (16.3–43.8)	1.64 (0.93–2.91)	*P* < 0.001
Adrenal	16	23.4 (22.4–24.4)	40.8 (35.5–46.1)	Not reached	0.40 (0.23–0.69)	
Brain	10	22.4 (19.5–25.2)	38.2 (29.7–46.7)	42.1 (11.5–51.2)	0.95 (0.42–2.16)	

Metastatic sites	No. of patients	24-month RMST (95% CI)	39-month RMST (95% CI)	Median survival (95% CI)	Hazard ratio (95% CI)	Log-rank *P* value
Lung	449	11.9 (11.2–12.7)	14.5 (13.3–15.7)	10.1 (9.1–11.2)	Reference	
Lymph nodes	106	9.5 (8.0–11.1)	11.0 (8.8–13.2)	7.6 (4.5–10.1)	1.39 (1.09–1.78)	
Bone	130	9.2 (7.7–10.6)	10.6 (8.6–12.5)	4.9 (3.4–8.2)	1.47 (1.17–1.84)	
Liver	22	8.4 (5.2–11.6)	10.1 (5.2–15.0)	5.5 (2.8–10.1)	1.51 (0.90–2.54)	*P* < 0.001
Adrenal	16	14.2 (9.7–18.6)	16.3 (10.1–22.5)	10.4 (3.7–25.5)	0.91 (0.55–1.51)	
Brain	10	15.0 (9.8–20.3)	16.9 (9.7–24.1)	18.4 (2.1–25.8)	0.84 (0.46–1.56)	

Fig. 4. Survival for single-organ metastasis in the absence of any other sites of disease. (**A**) Cancer-specific survival. (**B**) Progression-free survival of first-line targeted therapy.
RMST = restricted mean survival time, CI = confidence interval, mRCC = metastatic renal cell carcinoma.

These results are consistent with our investigation of Korean patients. This study showed that metastases to the lung, lymph nodes, bone, liver, adrenal gland, and brain were more frequent than those to other organs, and over 55% of patients had multiple metastatic organ involvement.

The strength of this study lies in its detailed examination of metastatic patterns at up to 13 sites and its analysis of CSS after adjusting for the IMDC risk model and the number of metastatic organs involved. This approach aimed to assess the prognosis according to different metastatic sites as objectively as possible. In addition to differences in survival according to metastatic sites, this study comprehensively demonstrated differences in survival based on IMDC risk and the number of metastatic organs involved, indicating that the large cohort used in this analysis is a representative database of mRCC. A major difference between this study and previous population-based studies is that all patients included in the analysis were actively treated with targeted systemic therapy. Thus, this study clearly reflects differences in treatment response due to variations in metastatic sites. Pancreatic and splenic metastases were associated with favorable prognoses, whereas liver, bone, and pleural metastases were associated with poor prognoses.

Patients with bone metastases had worse prognoses than those with metastases to other sites. Additionally, bone metastases had the shortest median PFS among single-site metastases. This poor prognosis in these patients may be due to the interactions between cancer cells and the tumor microenvironment, especially the bone microenvironment, which can lead to bone destruction and rapid tumor growth.[17] Recent studies have shown the potential benefit of cabozantinib, a multikinase inhibitor targeting VEGFR, MET, and AXL, in patients with

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bone metastases. The METEOR trial, a phase III clinical trial comparing cabozantinib with everolimus in the second-line setting, demonstrated a PFS benefit in patients with bone metastases.[18] Additionally, recent data from a subgroup analysis of the Checkmate-9ER trial evaluating the efficacy of nivolumab combined with cabozantinib confirmed the OS and PFS benefits of the combination in bone metastases.[19] In addition to systemic therapy, local therapies, including radiotherapy and surgery, are effective in preventing skeletal-related adverse events and systemic treatment-resistant bone metastasis.[20]

In this study, liver metastases showed poor outcomes in terms of CSS and PFS of first-line targeted therapy. These findings are similar to those of previous studies, which reported a poor prognosis in terms of PFS and OS.[21-23] However, the reason for or mechanism of worse survival in patients with liver metastasis remains unclear. It is hypothesized that the unique organ microenvironment of the liver may select for a more aggressive clinical phenotype with poor response to targeted therapy.[23-25] Furthermore, liver metastases often occur in association with metastases to other organs. In this study, the incidence of liver metastasis was 12.7% in the analysis of multiple-organ metastasis, whereas it was only 2.8% in the analysis of single-organ metastasis. Thus, liver metastasis is a consequence of the multiple hematogenous spread of RCC and may be a survival-limiting step due to the resulting tumor burden.

Among 13 metastatic organs included in the analysis, the pancreas and spleen were rarely affected by metastasis in mRCC, and the CSS of these types of metastases was better than that of other metastatic organs. Currently, different practice patterns regarding the management of pancreatic lesions have been developed.[26,27] Previous studies have reported prolonged OS in patients with oligometastatic pancreatic lesions managed by both metastasectomy and systemic therapy.[27,28] However, systemic therapy with minimally invasive interventions, such as stereotactic body radiotherapy, may be a reasonable approach for patients with metastatic pancreatic disease because surgical resection of metastatic pancreatic lesions is associated with high morbidity. Additionally, systemic therapy has a survival benefit similar to that of surgery. Splenic metastasis is uncommon due to the anatomical distinction of the splenic architecture and the physiological and immunological action of the spleen.[29-31] In this study, only 0.5% of patients experienced metastatic disease to the spleen. Splenic metastasis of RCC is extremely rare, and only a few cases have been reported.[32] It is difficult to determine the treatment options and prognosis of splenic metastasis of RCC due to the lack of data. However, this study showed better CSS of splenic metastasis. Additionally, surgical resection and systemic therapy have been reported to be appropriate treatment options.[32,33]

Thyroid metastasis was observed in only 0.2% of the patients, reflecting an extremely rare incidence. However, RCC remains the most common cancer that metastasizes to the thyroid.[34] Complete surgical resection and systemic treatment for metastatic thyroid lesions have been reported to provide prolonged survival benefits.[35,36] However, this study showed that thyroid metastases had the worst prognosis because most patients had multiple metastases involving the thyroid rather than solitary metastases.

In this study, brain metastasis was observed in approximately 8.2% of all patients, but only 1.2% had solitary metastases. This is a typical feature of the hematogenous spread of RCC, and proactive and routine brain imaging is necessary in patients with hematogenous metastatic spread, such as lung and liver, or in those with multiple metastases. In contrast to other studies, the relatively favorable prognosis for CSS in this study was due to the fact that more than a third of brain metastases received brain metastasis-directed therapy, such

as stereotactic radiotherapy.[37] Brain metastasis-directed therapy and use of drugs effective against brain metastases are important for improving survival.[38] However, pivotal clinical trials of targeted therapies have generally excluded patients with brain metastases because of their poor performance status. Fortunately, a recent multicenter retrospective study reported significant intracranial activity of cabozantinib and an intracranial response rate of 47–55% with or without concomitant brain-directed local therapy.[39]

Current guidelines for mRCC recommend metastasectomy or metastasis-directed therapy in selected patients because surgical extirpation of the primary disease and metastatic sites has been reported to result in durable disease-free survival in carefully selected patients.[40,41] Although no specific protocol has been identified, oligometastatic lesions are generally accepted as candidates for metastasis-directed therapy with or without systemic therapy.[40] Since improved survival has been reported with metastasis-directed therapy in well-selected patients, further studies on metastatic lesions with poor response or survival, such as those in the brain and liver, are needed.

Our study has implications for personalizing treatment and monitoring. First, our results can help refine risk stratification models for more accurate patient outcome predictions and treatment tailoring based on the site of metastasis. In fact, the current IMDC risk group model lacks certain prognostic markers such as tumor burden, metastasis site, and variant histology. Therefore, further studies building upon our results may contribute to the development of a more refined prognostic model. Second, our results emphasize the need to develop protocols for proactive imaging studies related to metastasis assessment and follow-up, and to investigate the efficacy of metastasis-directed therapy. For instance, our study demonstrated a relatively favorable prognosis for brain metastases compared to previous reports. However, routine imaging for the evaluation of brain metastases is not yet recommended. Nonetheless, our findings suggest that metastasis-directed therapies, such as Gamma Knife for brain metastases, may relieve symptoms and enhance patient survival. Therefore, establishing the appropriate timing for evaluation is crucial. Third, the variance in prognosis according to the site of metastasis indirectly highlights the importance of selecting appropriate systemic therapy agents. Most patients in our study received TKI monotherapy as first-line systemic therapy, but recent guidelines suggest that ICI + ICI or ICI + TKI combination regimens have shown improved responses. Furthermore, differences in the treatment response of metastatic lesions were observed according to variations in the combination regimen.[42-44] Therefore, it is necessary to establish personalized assessments for improved treatment according to the site of the metastatic lesion, select appropriate therapeutic agents, and develop markers to help predict treatment outcomes.

This study represents a retrospective analysis of a database, which inherently has several potential limitations. First, when investigating survival rates in metastatic disease, multiple factors influence patient outcomes. Therefore, the analysis may not be entirely free from confounding effects, including baseline comorbidities. In this study, we investigated differences in survival based on metastatic sites. To minimize the impact of the number of metastatic organs and the IMDC risk group, which significantly affects survival, we employed HRs adjusted for these variables to determine CSS. This approach minimized bias arising from retrospective analysis, distinguishing it from a typical intervention study. Second, a relatively high proportion of patients with mRCC presented with a primary tumor stage of T1 or lower. Since the study was conducted on patients with mRCC who were treated in the department of urology across multiple centers, the patient cohort included a significant

proportion of metachronous metastases that occurred during the follow-up period after surgical treatment. This composition differs from that of a typical clinical trial, which often includes a significant proportion of synchronous metastases. Consequently, there may be some inherent bias in the database. Third, this study did not include patients with mRCC managed by alternative strategies, such as active surveillance and best supportive care alone, or those who never started systemic therapy due to the nature of the database. The focus was primarily on mRCC patients who initiated systemic therapy for metastatic disease. Finally, despite recent advances in ICIs for treating mRCC, this study did not include the outcomes of ICIs. However, because targeted therapy still plays an important role in the first-line treatment of IMDC favorable-risk disease and disease that does not respond to first-line ICIs, further clinical evidence regarding systemic therapy with targeted therapy is needed.

In conclusion, lung, lymph node, bone, liver, adrenal gland, and brain metastases were more frequent than other organ metastases in Korean patients. In patients receiving active systemic treatment, metastases to the liver, bone, and pleura were associated with poor CSS, whereas metastases to the pancreas were rare but associated with the longest median CSS. These findings are useful for patient counseling and developing individualized treatment strategies for patients with mRCC. However, further studies on metastasis-directed therapy and new systemic therapies are needed to improve survival outcomes according to different types of metastatic involvement.

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