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Outcomes of Patients With Late-Relapse Metastatic Renal Cell Carcinoma Treated With Targeted Therapies: A Single Institution Experience

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Background: Late relapse with presentation of metastatic disease >5 years after nephrectomy with curative intent is a known behavior of renal cell carcinoma (RCC), but data on outcomes, especially regarding targeted therapies, are limited. In this study, we analyze clinicopathologic features and response to targeted therapy in patients with late-relapse metastatic RCC (mRCC).

Methods: We retrospectively reviewed clinical data on consecutive patients treated with targeted therapy for mRCC diagnosed >5 years after nephrectomy with curative intent.

Results: A total of 24 patients (100% clear cell histology, median age 72 years, 83% males, all with prior nephrectomies) met inclusion criteria; 71% had favorable risk, and 25% had intermediate risk by International Metastatic Renal Cell Carcinoma Database Consortium criteria. The estimated median overall survival for all patients was 60.5 months, and the 3-year overall survival rate was 71.78% (95% confidence interval, 47.98%-84.77%). All patients were treated with targeted therapy; first-line treatments included pazopanib (46%), sorafenib (25%), sunitinib (17%), and cytokine (13%), with no significant difference in time to treatment failure between therapies. Median time on first-line therapy was 19.7 months; 67% of patients received second-line treatment. Metastases were detected at considerable rates in sites considered historically uncommon, such as the pancreas, adrenal glands, and soft tissue.

Conclusion: Patients with late-relapse mRCC treated with targeted therapy had prolonged survival that compared favorably to historical controls, and metastases in uncommon sites were noted.

Keywords: *Cancer–renal cell, metastasis, nephrectomy*

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INTRODUCTION

Renal cell carcinoma (RCC) is an increasingly common malignancy in the United States and accounts for approximately 90% of kidney cancer cases.[1] The increased detection of small, localized lesions has led to more opportunities to resect RCC with curative intent.[2] However, approximately 30% of patients who have undergone a nephrectomy with curative intent develop metastatic disease recurrence.[3] In patients who relapse after having no evidence of disseminated disease at the time of resection, most metastases occur within 2 years of resection, although late recurrence >5 years after resection is a known biologic behavior of RCC.[3,4] In fact, a large cohort study published in 2014 found that 26% of patients receiving targeted therapy after curative-intent nephrectomy relapsed >5 years after resection of the primary tumor.[5]

Studies have characterized patients with late relapse, occurring after a disease-free interval >5 years, in terms of patient and tumor prognostic features to adjust surveillance protocols and increase the length of surveillance in patients with an increased propensity to relapse after 5 years.[6,7] A 5-year disease-free interval is most commonly used to define the late-relapse population and has been shown to be the most useful interval length in clinical practice.[7] The prognosis and response to targeted therapies of patients with late relapse are less studied. The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic model reliably predicts the survival and treatment response of patients with metastatic RCC (mRCC), allowing for improved patient counseling and application of clinical trials.[8] Patients with late relapse are associated with favorable patient and tumor characteristics, but their specific outcomes are less understood.

We retrospectively analyzed patients with late relapse after nephrectomy with curative intent at our institution to

characterize the survival and response to targeted therapy within this unique subset of patients with mRCC.

METHODS

Study Population

We retrospectively reviewed clinical data on consecutive patients treated with targeted therapy for mRCC diagnosed >5 years after nephrectomy with curative intent. All patients were treated at our institution between November 1, 2006, and November 1, 2013. Inclusion criteria were tumors previously treated with radical or partial nephrectomy to render the patient with no evidence of disease, no evidence of metastases at the time of surgery, and relapse to any stage of mRCC after a disease-free survival >5 years.

Patients were treated with pazopanib, sunitinib, sorafenib, and cytokines as first-line therapy. Treatment was interrupted or doses were adjusted as needed in response to adverse events and according to standard guidelines. First-line therapy was continued until evidence of disease progression, unacceptable adverse events, or death. Second-line therapies included temsirolimus, everolimus, and axitinib. Prognostic features of the cohort prior to the initiation of targeted therapy were described according to the IMDC model (also referred to as the Heng criteria). The Heng criteria are an externally validated prognostic model for patients with mRCC who receive targeted therapy.[9] The model stratifies patients into favorable, intermediate, and poor survival groups. The risk factors are >1 year from diagnosis to systemic therapy, Karnofsky Performance Scale status score <80 (a score >80 indicates that the patient has only minor symptoms from his/her illness), low hemoglobin, elevated calcium, elevated neutrophil count, and elevated platelet count.

Outcomes and Statistical Analysis

Overall survival, the primary outcome, was defined as the time from initiation of first-line treatment to death from any cause. Secondary outcomes were time to treatment failure and treatment response. Time to treatment failure was defined as the time between initiation of a targeted therapy treatment to drug cessation, death, or censoring. Treatment response was scored via the Response Evaluation Criteria in Solid Tumors v.1.1.[10] Adverse events were graded using the Common Terminology Criteria for Adverse Events v.4.[11] The Kaplan-Meier method was used for survival analysis. We used analysis of variance to identify significant differences between groups.

RESULTS

Clinical and Pathologic Characteristics

Of the 520 patients with all stages of RCC who were analyzed, 28 patients were found to have stage I-III RCC, underwent nephrectomy and relapsed late, and developed mRCC recurrence >5 years from the date of nephrectomy. Four patients were excluded because they did not have complete data available for analysis. The study cohort consisted of 24 patients. Median follow-up was 38.3 months (range, 6.7-129.3 months). Table 1 shows patient characteristics. The median time from nephrectomy to recurrence was 8.3 years (range, 5.6-29.0 years). At relapse, the majority (83%) of patients had >1 site of metastatic disease, most often involving lung, bone, and pancreas. A majority of the cohort presented with favorable IMDC (Heng) scores (71%).

Table 1. Patient and Tumor Characteristics of Patients With Late-Relapse Metastatic Renal Cell Carcinoma (n=24)

Patient Characteristics	Value
Age at diagnosis, median years (range)	72 (60-94)
Male sex, n (%)	20 (83)
Patients receiving nephrectomy, n (%)	24 (100)
Time from nephrectomy, median years (range)	8.3 (5.6-29.0)
IMDC (Heng) risk factors/risk categories, n (%)	
Karnofsky Performance Scale score <80[a]	4 (17)
Hemoglobin <12 g/dL	2 (8)
Corrected calcium >10 mg/dL	3 (13)
Neutrophil count $>7\times10^9$/L	2 (8)
Platelets >400,000 units	1 (4)
Favorable (0 IMDC risk factors)	17 (71)
Intermediate (1-2 IMDC risk factors)	6 (25)
Poor (≥3 IMDC risk factors)	1 (4)
Tumor Characteristics, n (%)	
Clear cell histology	24 (100)
Number of metastatic sites	
1	4 (17)
>1	20 (83)
Metastatic sites	
Lung	19 (79)
Bone	8 (33)
Pancreas	8 (33)
Lymph nodes	7 (29)
Renal	7 (29)
Adrenal glands	4 (17)
Brain	3 (13)
Liver	2 (8)
Muscle	2 (8)
Bowel	1 (4)
Pleura	1 (4)
Abdominal wall	1 (4)

IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

[a]A score >80 on the Karnofsky Performance Scale indicates that the patient has only minor symptoms from his/her illness.

Treatment Response and Survival Outcomes

The estimated median overall survival time was 60.5 months after detection of metastatic disease (Figure). The 3-year overall survival rate after detection of metastatic disease was 71.78% (95% confidence interval, 47.98%-84.77%). All patients received targeted therapy; pazopanib, sunitinib, sorafenib, or cytokine therapy was used as first-line treatment in 11, 4, 6, and 3 patients, respectively (Table 2). Targeted therapies in the second-line setting were administered to 16 patients (67%). Median time to treatment failure on first-line therapy was 19.7 months (range, 0.5-

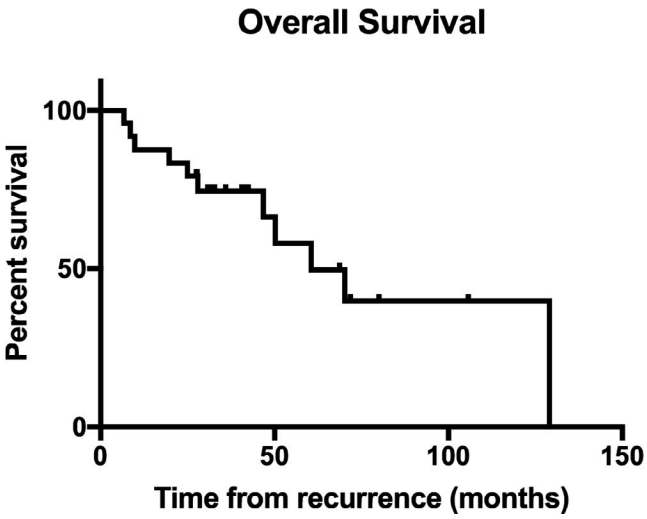

Figure. Overall survival in patients with late-relapse metastatic renal cell carcinoma from time of recurrence.

41.6). We found no significant difference in time to treatment failure between therapies.

The most common adverse events associated with treatment were fatigue (54%), diarrhea (33%), hypertension (29%), anorexia (29%), hair and skin changes (25%), increased liver function tests (21%), and nausea/vomiting (17%), with 95% of adverse events being grade 1 or 2.

DISCUSSION

Previous reports have suggested that the distribution of late-relapse mRCC is comparable to the distribution of early-relapse mRCC, although late-relapse mRCC is associated with a higher number of unusual metastases.[5,12] We observed this pattern in our study; metastases were most commonly detected in the lung, bone, lymph nodes, kidney, and pancreas, but disease was also commonly seen in the adrenal gland and occasionally in the bowel, pleura, muscle, and abdominal wall. This increased tendency of unusual metastases may be important when evaluating patients with late-relapse mRCC or when considering imaging modalities for surveillance.

Our study cohort had a high metastatic burden, with a majority (83%) of patients presenting with multiple metastases, including areas considered to confer a poor prognosis in mRCC such as liver and bone.[13] Furthermore, a noteworthy portion of our cohort (33%) developed pancreatic metastases that have been shown to be more common in the late-relapse population,[6] and the pancreas is a metastatic site known to be associated with extended survival in patients with mRCC.[14,15] Kalra et al found pancreatic metastasis to be independently associated with extended survival in a multivariate analysis accounting for number of metastatic sites, presence of lung metastases, and Heng risk category.[15] These authors speculate that this unique clinical phenomenon could be explained by host and tumor features representing a more indolent tumor phenotype in patients with late relapse than in patients with early relapse.

RCC is divided into 2 histologic subtypes: clear cell RCC, the most common histology, and non–clear cell RCC that encompasses several histologies including papillary RCC, chromophobe RCC, collecting duct carcinoma, and renal medullary carcinoma.[16] Clear cell mRCC has been shown to have a more favorable treatment response and prognosis than non–clear cell mRCC, and comparative reports on early-relapse RCC vs late-relapse RCC have shown that non–clear cell RCC is less common in the late-relapse population.[17] All 24 patients in our study had clear cell histology, possibly conferring an additional favorable prognostic characteristic.

Kroeger et al reported in 2014 that patients with late-relapse RCC have a better response to targeted therapy and increased overall survival compared to patients with early-relapse RCC.[5] Similarly, our late-relapse cohort demonstrated a high overall survival compared to historic controls treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors.[9,18]

Adamy and colleagues suggested that patients with late-relapse mRCC fall in better risk stratification categories compared to patients with early-relapse mRCC, a factor that may contribute to favorable outcomes.[6] Indeed, 71% of patients in our study presented with no IMDC (Heng) risk factors at relapse. Perhaps a prolonged disease-free and

Table 2. Evaluation of Overall Response to First-Line Therapy by RECIST v.1.1 Guidelines in Patients With Late-Relapse Metastatic Renal Cell Carcinoma (n=24)

First-Line Therapy and Response	Value
Pazopanib, n (%)	11 (46%)
CR	0
PR	2
SD	8
PD	1
TTTF, median months (range)	23.4 (4.0-41.6)
Sunitinib, n (%)	4 (17%)[a]
CR	0
PR	0
SD	2
PD	0
TTTF, median months (range)	19.7 (18.7-26.0)
Sorafenib, n (%)	6 (25%)
CR	0
PR	2
SD	4
PD	0
TTTF, median months (range)	23.7 (0.5-41.4)
Cytokine, n (%)	3 (13%)
CR	0
PR	0
SD	2
PD	1
TTTF, median months (range)	4.0 (2.8-4.1)

CR, complete response; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TTTF, time to treatment failure.
[a]Response criteria were not available for 2 patients.

treatment-free interval permits hematologic and immunologic recovery, allowing targeted therapy to be more effective. This concept is supported by Santoni et al who demonstrated that an elevated pretreatment neutrophil to lymphocyte ratio is a poor prognostic factor for patients with late-relapse mRCC treated with targeted therapy.[19]

Our study was retrospective, albeit composed of consecutive patients, and thus subject to all limitations inherent to this study design. Furthermore, our cohort size was relatively small, making comparisons difficult. Including more subjects with a longer follow-up would be beneficial to verify equivalence between first-line treatment responses in terms of objective response rate and time to treatment failure.

CONCLUSION

Late relapse is a known phenomenon in RCC and is associated with unusual metastatic sites such as the pancreas, adrenal glands, and soft tissue. Patients with late-relapse mRCC have increased time to treatment failure and overall survival when treated with targeted therapy because of their favorable prognostic features. These characteristics of late-relapse mRCC are relevant when considering long-term disease surveillance and informing patients of their prognosis.

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