Deferred Systemic Therapy in Patients With Metastatic Renal Cell Carcinoma

Aaron P. Mitchell,[1] Bradford R. Hirsch,[1,2] Michael R. Harrison,[1] Amy P. Abernethy,[1,2] Daniel J. George[1]

Abstract

We analyzed a retrospective cohort of 60 patients with metastatic renal cell carcinoma who did not receive systemic therapy within the first year after diagnosis. Reasons for delayed therapy included surgical or other local management, and an active surveillance approach. The 5-year survival was 59%, suggesting that deferred therapy may be an appropriate strategy in selected patients.

Background: With the advent of small-molecule "targeted" therapies, the prevailing treatment paradigm for metastatic renal cell carcinoma (mRCC) is that all patients who are able to tolerate systemic therapy should receive it. However, oncologists often defer the initiation of systemic therapy for patients with mRCC. The outcomes of and clinical reasoning behind the initial management of patients with mRCC without systemic therapy have not been well described. **Methods:** We conducted a retrospective cohort study of all patients with mRCC treated within the Duke University Health System and diagnosed from January 1, 2007, to January 1, 2011. We defined our cohort as patients who did not receive systemic therapy during the first year after mRCC diagnosis. The clinical rationale for the lack of immediate treatment was ascertained by manual chart review. **Results:** A total of 60 of 268 patients (22%) with mRCC managed without initial systemic therapy were included in our study. The median age was 61.2 years, the median duration from diagnosis of localized RCC to development of mRCC was 41.9 months, and 91% of patients had Eastern Cooperative Oncology Group functional status of ≤ 1. Of the patients, 60% were managed with surgical metastasectomy alone, 12% received multiple local treatment modalities, 13% received active surveillance, 7% were managed supportively, and 8% were categorized as "other." **Conclusions:** The majority of patients in our cohort had favorable disease characteristics and experienced favorable outcomes with surgery alone. Our results suggest that this population could represent 20% of patients with mRCC in tertiary care settings. Prospective data are needed to evaluate deferred systemic therapy as a management strategy.

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Introduction

Between 17% and 30% of patients with renal cell carcinoma (RCC) have metastatic disease at the time of diagnosis,[1-3] and another 20% to 40% of those who undergo a potentially curative nephrectomy for localized disease will later develop metastatic disease.[1,4-6] For those who are diagnosed with metastatic RCC (mRCC), a number of systemic treatment options exist, including 7 new agents approved by the US Food and Drug Administration from December 2005 to February 2012.[7]

[1]Division of Medical Oncology, Duke University Medical Center, Durham, NC
[2]Center for Learning Health Care, Duke Clinical Research Institute, Durham, NC

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Address for correspondence: Daniel J. George, MD, DUMC 102002, Durham, NC 27710
E-mail contact: Daniel.george@duke.edu

The management of patients with mRCC with oligometastatic disease using surgery alone has long been an accepted strategy and is a recommended option in National Comprehensive Cancer Network guidelines.[8] However, with the new availability of effective and well-tolerated treatments, the prevailing view is moving toward offering systemic therapy for a greater number of patients. The potential role of targeted agents as adjuvant therapy in this setting, currently under investigation,[9] may be a factor. Physicians also may be less comfortable managing mRCC without systemic therapy because of the relative lack of data; the study of mRCC generally occurs within the context of therapeutic trials or postmarketing studies, which include only patients who receive systemic therapy.

As a result, the cohort of patients with mRCC who elect to defer—or never receive—systemic treatment often go unrecognized and unstudied. The size of the cohort, patient and disease characteristics, and clinical outcomes are unknown, especially in the era of

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targeted therapies. Anecdotally, some patients with mRCC achieve favorable outcomes for prolonged periods without systemic therapy; a more complete understanding of this group would inform treatment decisions and potentially avoid drug toxicity in those unlikely to benefit.

Physician recommendations, in addition to patient preferences, certainly influence a patient's decision to defer therapy. However, the clinical reasoning behind the initial management of mRCC without systemic therapy has not been well described. Is this strategy recommended to patients who are surgical candidates or to those perceived as unlikely to tolerate systemic therapy? To address this void and to understand the appropriateness of such an approach with currently available treatments, we describe the experience at one academic medical center of patients who did not receive initial systemic treatment in the context of available targeted therapies.

Materials and Methods

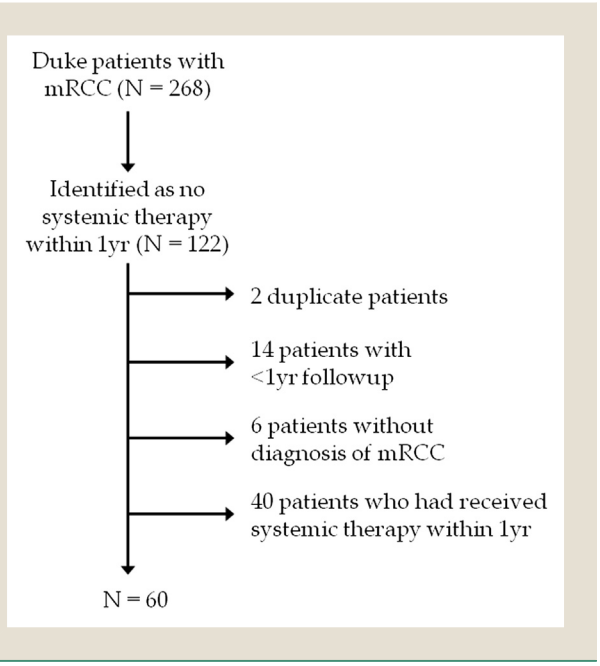
This retrospective cohort study received a waiver of informed consent from the institutional review board at Duke University. Eligible cases included all adult patients (aged > 18 years) with mRCC who received some portion of their mRCC care in the Duke University Health System. All patients were diagnosed with mRCC between January 1, 2007, and January 1, 2011, with the last data collection occurring in May 2013. Cases were initially identified by searching the Duke patient database using International Classification of Diseases, 9th Revision codes and were then confirmed by research coordinators.

Study data were extracted from the Duke data warehouse (demographics, laboratory results, treatments) and supplemented by manual chart abstraction using a standardized case report form (histology, grade, metastatic burden, supplemental treatment history). Completed case report forms underwent quality review before entry into a secure study-specific data repository.

The resulting registry contained 268 patients (Figure 1). The cohort of interest was defined as those patients who did not receive any systemic therapy before 1 year of follow-up had elapsed or death had occurred. Thus, patients who received systemic therapy within 1 year of diagnosis of mRCC were excluded, and those who went at least 1 year without receiving therapy or died in less than 1 year without receiving therapy were included. In addition, patients with insufficient documentation to confirm absence of systemic therapy before death or 1 year of follow-up were excluded, narrowing the cohort to 82 patients. During subsequent manual chart review, 22 patients were excluded from the analytic cohort; 14 had less than 1 year of follow-up, 6 did not have a pathologic diagnosis of mRCC, and 2 were duplicates. Sixty patients remained in the final analytic cohort. Dates of death were confirmed for all patients by searching the public record.

A detailed review of clinical notes was used to define why each patient did not receive systemic therapy (eg, patient refusal, hospice referral). Patients were divided into the following 5 categories according to the treatment strategy during the first year after diagnosis with mRCC: (1) surgical metastasectomy; (2) multiple local treatment modalities (eg, surgery, radiofrequency ablation, cryoablation); (3) active surveillance (defined as patients with known disease for whom treatment was deferred pending evidence of progression or other clinical changes); (4) deemed not a candidate for therapy and managed with best supportive care alone or referral to hospice care; and (5) other. Those patients in group 1, who received surgical metastasectomy, were subdivided according to further treatments received during the first year after diagnosis: (1a) followed with no evidence of disease, (1b) had recurrence and underwent 1 or more additional metastasectomies, and (1c) had recurrence and an active surveillance strategy was used. Recorded Karnofsky status was converted to Eastern Cooperative Oncology Group functional status according to previously published recommendations[10] where appropriate.

Figure 1 Cohort Selection



Abbreviation: mRCC = metastatic renal cell carcinoma.

Results

The cohort included 37 men and 23 women for a total of 60 patients, representing 22% of all patients with mRCC treated (Table 1). Median age at diagnosis was 61.2 years. Median time from date of RCC diagnosis to the diagnosis of mRCC was 41.9 months, including 5 patients (8%) who were already metastatic at time of RCC diagnosis. Most patients had favorable or intermediate risk disease by Memorial Sloan Kettering Cancer Center criteria, at 40% and 35%, respectively. Some 91% of the 44 patients with recorded functional status had an Eastern Cooperative Oncology Group score of 0 to 1. Disease burden was low, with 83% patients having a single metastatic site at the time of mRCC diagnosis.

Of the 60 patients, 36 (60%) were initially managed with surgical metastasectomy alone (Table 2); of these 36, 22 (37% of cohort) received a single metastasectomy within 1 year of diagnosis and were thereafter followed with no evidence of disease, 9 patients (15%) received multiple metastasectomies within the first year of diagnosis, and 5 patients (8%) elected for an active surveillance approach after recurrence. The anatomic site of metastasectomy for these