Rationale and Relevance of Risk Assessment in Advanced Renal Cell Carcinoma:

A Review for Community Oncologists

C. Lance Cowey, MD

Genitourinary Oncology and Melanoma Programs
Baylor Charles A. Sammons Cancer Center
Texas Oncology, PA
Dallas, Texas

Thomas E. Hutson, DO, PharmD

Director, Genitourinary Oncology Program
Professor of Medicine and Co-Chair, GU Research
US Oncology
Baylor Charles A. Sammons Cancer Center
Texas Oncology, PA
Dallas, Texas

Introduction

In 2010, cancer involving the kidney afflicted more than 58,000 patients in the United States and resulted in more than 13,000 deaths.[1] Most of these patients had renal cell carcinoma (RCC) of the clear cell type and were diagnosed with localized disease.[2] Although surgical resection can be curative for localized disease, a risk for recurrence and distant spread is present with all stages of localized disease. Once RCC has metastasized it is considered incurable for the vast majority of patients[3]; however, several systemic agents that can affect clinical outcomes have been introduced during the past 5 years.[2,4-8]

Several risk-scoring systems have been formulated to help determine prognosis for patients who have developed metastatic disease. These validated risk measurement tools are important for the community oncologist to employ since they can aid with prognostic discussions and may help formulate treatment decisions. In the case of metastatic RCC, community oncologists should be mindful of the fact that performance status is just one factor in assessing risk; in addition, age is not a prognostic factor and should not alter treatment options when considered by itself. A discussion of various criteria and prognostic factors is offered below, as well as ways to incorporate them into routine clinical practice in the community setting.

Evaluating Prognosis In Metastatic RCC

Prognostic Risk Factors Based On Memorial Sloan-Kettering Cancer Center Data

Despite many recent additions to the therapeutic armamentarium for metastatic RCC, the development of this stage of the disease is almost uniformly fatal. However, patients with metastatic RCC can follow a variety of clinical paths, with some patients receiving single or multiple treatment courses, or even none at all. A set of prognostic risk factors based on data from Memorial Sloan-Kettering Cancer Center (MSKCC) was developed to help determine the prognosis of subsets of metastatic RCC patients and to aid in patient selection for clinical trials.[9] These original MSKCC data identified patient factors that contribute to outcome, such as elevated lactate dehydrogenase (LDH; >1.5 x upper limit of normal), elevated corrected calcium (>10 mg/dL), poor performance status (Karnofsky Performance Status <80%), anemia (below lower limit of normal), and absence of prior nephrectomy.[9] If present at initial diagnosis, these factors each held negative prognostic significance. Patients with no risk factors were deemed to have good risk, 1 to 2 risk factors have intermediate risk, and 3 or more risk factors indicate poor risk.[9] Median survival for patients with good-, intermediate-, and poor-risk RCC was 19.9, 10.3, and 3.9 months, respectively.[9]

After the original MSKCC data were published, 2 Phase III randomized trials highlighted the importance of primary tumor removal (debulking nephrectomy) in the outcomes of patients with systemic therapy.[10,11] A longer survival time in patients after undergoing nephrectomy was found to be linked to a disease-free interval in those patients who had undergone surgical resection for a localized tumor and then had relapsed. This prompted a review of the model of prognostic assessment from the original MSKCC data, with the presumption that most patients would undergo debulking nephrectomy prior to systemic interferon or other cytokine therapy.[12] This led to a revised set of prognostic risk factors, commonly referred to as the Motzer criteria, which included elevated LDH; elevated calcium; anemia; poor performance status; and an interval of less than one year from initial RCC diagnosis to initiation of systemic therapy.[12] With these updated criteria, patients in good-, intermediate-, and poor-risk categories had 29.6, 13.8, and 4.9 months median survival with interferon systemic therapy.[12]

External validation of these extended criteria was performed by Mekhail et al at the Cleveland Clinic Foundation, in which all risk factors held up under multivariate analysis with one exception: performance status.[13] Additionally, 2 other prognostic risk factors were found to be significant: number of sites of metastasis (≥2), and history of radiotherapy (Table).[13]

TABLE. Prognostic Factors Among Validated Prognostic Scoring Systems for Metastatic RCC

	Original Published MSKCC Data	Modified MSKCC (Motzer Criteria)	Extended Criteria (Mekhail)
Karnofsky Performance Status score (<80)	X	X	
Corrected calcium (>10 mg/dL)	X	X	X
LDH level (>1.5 times upper limit of normal)	X	X	X
Hemoglobin level (<lower limit of normal)	X	X	X
Absence of prior nephrectomy	X		
Time from diagnosis to systemic Rx (<1 year)		X	X
Sites of metastasis (≥2)			X
History of radiotherapy			X

LDH, lactate dehydrogenase; **MSKCC,** Memorial Sloan-Kettering Cancer Center; **RCC,** renal cell carcinoma
Based on references 9, 12, and 13.

Clinical Application of Motzer And Mekhail Criteria

Although the Motzer criteria and the extended Mekhail criteria were developed in the cytokine era, the pivotal Phase III trials evaluating vascular endothelial growth factor (VEGF) and mammalian target of rapamycin (mTOR) inhibitors used one of these risk assessment schema in selecting patients for enrollment in their clinical trials.[4-7] Most trials limited enrollment to patients with good or intermediate risk, as per these criteria. Based on Phase III trial data, level 1 evidence exists for use of targeted therapeutics in certain RCC patients depending on their risk status and history of prior therapies; however, the optimal sequence and drug selection for patients remain to be defined.[14] Patients with metastatic clear cell RCC and adequate organ function can be considered for high-dose interleukin-2 therapy, although in a recent prospective multicenter study no single pretreatment clinical factor was associated with improved outcome.[15]

The recently approved VEGF or mTOR-targeted agents were almost exclusively studied in the clear cell RCC population in their registrational trials.[2] However, data have been collected on non–clear cell RCC patients showing some activity for both classes of agents in this population.[16-18] However, these patients should still be referred to a clinical trial when possible since the optimal management of non–clear cell RCC remains to be defined.

Other Features Commonly Considered in RCC Management

In another evaluation of prognostic factors that correlate with survival, Heng and colleagues examined the outcomes of 645 patients treated with VEGF pathway inhibitors.[19] In this study, 4 prognostic risk factors based on the published MSKCC data were found to be associated with poorer outcomes: anemia, hypercalcemia, elevated LDH, and performance status. In addition, neutrophilia (> upper limit of normal) and thrombophilia (> upper limit of normal) also were found to be important prognostic risk factors.[19] Although neutrophilia and thrombophilia may be signs of more aggressive disease, currently these findings should not affect treatment decision-making as they have not been prospectively validated.

Implementing Risk Assessment In the Community Setting

Prognostic risk scoring, specifically with the validated Motzer criteria, should play an important role in the medical oncologist's evaluation of patients with metastatic RCC. It is important to recognize that patients were selected for the recent Phase III trials based on this prognostic scoring system and it still applies to patients today. The Motzer risk scoring evaluation is simple and consists of laboratory assessment—including measurement of complete blood cell count (CBC), LDH, and serum calcium—and a clinical history to assess performance status, nephrectomy status, and interval from diagnosis to initiation of systemic therapy. These assessments should be considered standard of care, so fortunately no additional costs are incurred.

It is important to recognize that using performance status alone *does not equate to a proper assessment* in terms of prognostic impact. Each finding (low hemoglobin, elevated LDH, elevated calcium, poor performance status, time from diagnosis to systemic therapy <12 months) is assigned one point in the Motzer risk factor scoring system, with zero total risk factors considered good risk, 1 or 2 total risk factors considered intermediate risk, and 3 or more total risk factors considered poor risk.

As with any clinical risk score, comfort comes with frequency of clinical use. Practical employment of clinical risk evaluation may include memorization of the risk scoring system, creation of a clinical worksheet for nursing staff to help complete, or use of an online tool. After receiving a proper risk assessment, patients can then get appropriate therapy for their metastatic RCC.

Conclusion

The prognostic risk factors based on the Motzer criteria and the extended criteria (the Mekhail criteria) remain clinically relevant in the modern era of targeted therapies. These risk factors include anemia, hypercalcemia, elevated LDH, poor performance status, and time from nephrectomy to initiation of systemic therapy within 12 months. Additionally, the number of sites of metastasis and absence of nephrectomy may also be prognostic risk factors. Also of clinical interest are histology and a review of comorbidities, outlined in the sidebar.

Regularly using these risk factors helps determine the clinical course and is a useful guide to the art of drug selection for these patients. Although level 1 evidence exists for the management of patients with good or intermediate prognostic risk factors as well as those with poor prognostic risk, many treatment options are available and optimal sequencing of agents is still being determined.

Proper risk evaluation in the community setting is simple: It should include patient history, including comorbidities, and physical exam; laboratory assessment, including CBC, LDH, and calcium; and radiographic evaluation—such as CT imaging—to assess for location of metastatic sites. Physicians should also take into account RCC histology, as the clinical course can vary given the particular histologic subtype.

Performance status is, by itself, never a surrogate for a formal risk assessment. Patients should be considered for cytoreductive nephrectomy when appropriate, given the available data supporting improved outcomes with systemic therapy. And finally, proper risk factor assessment is important for clinical studies, which must be undertaken in order to continue to improve clinical outcomes in RCC.

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Additional Clinical Considerations

Histology

While the Motzer criteria were designed for clear cell RCC patients,[1] it is important to note that the histologic subtype of RCC also plays an important role in risk assessment. RCC is a heterogeneous group of tumors with different genetic defects and clinical courses. The most common RCC subtype is clear cell RCC, which makes up 75% to 80% of cases. Non–clear cell papillary RCC (types 1 and 2) make up the next most common type, occurring in about 15% to 20% of RCC cases, with the papillary type 2 variant having a more aggressive course than type 1. Chromophobe RCC accounts for about 5% of all cases and has an excellent prognosis. Less common are renal oncocytoma (benign neoplasms) and renal medullary carcinoma (very aggressive). Although renal pelvis carcinoma is often lumped in with RCC in epidemiologic tabulations, these cancers are more histologically similar to urothelial cell carcinomas, such as bladder cancer.

Several studies have shown that clear cell RCCs portend a slightly worse outcome for patients than non–clear cell RCCs.[2,3] Sarcomatoid dedifferentiation (which can occur in any histologic subtype), medullary, and Xp11.2 translocation carcinomas all tend to have the worst outcomes.[4]

Comorbidities

Although it is logical to consider comorbidities when planning treatment, no specific comorbidities have been associated with prognosis. While VEGF inhibitors can cause hypertension and cardiac-related events, and mTOR inhibitors can lead to hyperglycemia and hyperlipidemia, these agents may safely be administered to patients with these pre-existing conditions in conjunction with careful monitoring and vigilant side-effect management.

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