The Changing Face of Renal-Cell Carcinoma

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Abstract

The present decade can be credited with the improved understanding of renal-cell carcinoma (RCC), its local and systemic management, and various controversies from diagnosis to types of various available interventions. The old paradigms and dogmas are no longer accepted as “the best way” without evidence, and many “old” principles are cautiously questioned. These notions have resulted in new knowledge, questions, arguments, and treatment options. This article will describe the “changing face of RCC” over the past several years and will briefly summarize the major changes and issues in the field of renal oncology. The discussed topics include improved molecular understanding of RCC, management of small renal masses, the safety and accuracy of renal mass biopsy, the emerging role of molecular imaging, the importance of maximal renal preservation, and the evolving role of laparoscopy, robotics, and ablation.

Introduction

RENAL-CELL CARCINOMA (RCC) remains the third most common genitourinary malignancy and one of the major healthcare concerns worldwide. In 2009, kidney cancer was diagnosed in more than 57,000 patients and claimed the lives of almost 13,000 in the United States.¹ In Europe, an additional 63,000 patients will be diagnosed and 26,000 will die from RCC. RCC incidence appears to be steadily rising by 3% per year in the United States and most of the European countries.² The increase in cross-sectional imaging and detection of renal masses can only partly be responsible for the rising incidence of RCC. The steady rise in RCC mortality over the past decade suggests that some other factors may also play an important role responsible for the rise in RCC incidence and its aggressiveness.

The present decade can be credited with the improved understanding of RCC, its local and systemic management, and various controversies from diagnosis to types of various available interventions. The old paradigms and dogmas are no longer accepted as “the best way” without evidence, and many “old” principles are cautiously questioned. These notions have resulted in new knowledge, questions, arguments, and treatment options. This article will describe the “changing face of RCC” over the past several years and will briefly summarize the major changes and issues in the field of renal oncology, such as the following:

- (1) Improved molecular understanding of RCC
- (2) Management of small renal masses (SRMs)
- (3) The safety and accuracy of renal biopsy
- (4) The role of conventional and molecular imaging

- (5) The importance of maximal renal preservation
- (6) The evolving role of laparoscopy, robotics, and ablation
- (7) Advances in systemic treatments for metastatic RCC

Recent Advances

One of the major achievements can be attributed to recognizing that RCC is not a single disease but a compilation of different histologic types, each caused by different genetic mutations affecting different molecular pathways.^{3–6} In fact, four distinct genes have now been well described as a cause for the different types of RCC.^{7,8} Understanding of these genetic alterations and pathways has resulted in several new medications approved for use in the treatment of metastatic RCC and many more in clinical trials at the present time.^{9–11}

Perhaps, understanding of the von Hippel-Lindau (VHL) pathway allowed for the most breakthroughs in the systemic treatments. As we have learned about the role of VHL as a tumor suppressor gene, we have gained a deeper insight in the mechanism of renal carcinogenesis. We learned that under normoxic conditions, the VHL protein forms a complex with other proteins to target hypoxia-inducible factor (HIF) for ubiquitin-mediated degradation. The loss of VHL results in over accumulation of HIF, which acts as a transcriptional activator of downstream genes, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), glucose transporter-1 (GLUT-1), and erythropoietin (EPO). Therefore, loss of VHL results in dysregulated levels of HIF, leading to increased angiogenesis, growth, and cellular proliferation. The new agents specifically target various parts of

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the VHL pathways. Similar to dissecting the VHL pathway, understanding of *MET*, *BHD*, and *FH* genes in renal carcinogenesis will result in new and promising molecular targeting.¹²

Small Renal Masses

With our improved understanding of the molecular pathways and natural history of RCC, we also recognize that not every patient with a renal mass must undergo surgical intervention. The concept of management of "SRMs" is now at the forefront of many manuscripts, conferences, and discussions. Although the concept of the observation of SRMs has been used at the National Cancer Institute for the past two decades^{13,14} in patients with familial RCC, the role of active surveillance in sporadic RCC has only recently gained enough attention and popularity.¹⁵⁻¹⁷ The most recent meta-analysis by Chawla et al¹⁸ has shown that the majority of SRMs can safely be observed in most patients for an average of 34 months, with metastatic rate of only 1% of cases (3 out of 286 patients).

There are several observations and concepts that have emerged leading to active surveillance of SRMs. Understanding that not all SRMs are "created equal," many may be benign, may not exhibit interval growth, and will have no long-term sequelae to patients. This allowed urologic surgeons to entertain the idea of close surveillance of those with small tumors of the kidney.¹⁹ Additionally, recent epidemiologic data by Kaplan et al²⁰ revealed that in the elderly, the competing causes of death far outweigh the risk of mortality due to the diagnosis of RCC. Although the 5-year death rate from all causes is nearly 25% in patients over 75 years of age and 55% in patients over 85, RCC is only responsible for 0.24% and 0.12% of the cause of mortality in these patients, respectively.²⁰ In the present time, when the majority of renal masses are small at diagnosis and found incidentally during the work-up for unrelated causes,² the need for immediate definitive surgical intervention has been questioned.^{21,22} On the other hand, the role of active surveillance of renal masses is being continuously examined against minimally invasive interventions and in patients who are older or have larger masses.²³ O'Malley et al²⁴, for example, cautioned the role of surveillance in elderly, indicating that the age was an independent predictor of malignancy and high stage. Similarly, higher tumor size increased the risk of higher grade of malignant renal lesions. Other authors found a higher rate of growth and more advanced disease in patients with renal lesions greater than 4 cm.²⁵

The interim analysis of the ongoing Prospective Multi-Center Canadian Uro-Oncology Group Trial studying the active surveillance of SRMs demonstrated a 1.5% rate of metastatic disease at 15 months follow-up.²⁶ The long-term results may help answer the question of who may or may not be a candidate for active surveillance in the future.

Renal Biopsy and Imaging

One of the evolving concepts in the management of renal masses and RCC is the role of the renal biopsy.²⁷⁻²⁹ The "old dogma" that a patient with a renal mass has a greater than 90% chance of harboring a RCC is no longer the case. Several recent studies demonstrated that a substantial proportion of SRMs are benign and the rate of malignancy increases with the tumor size.^{30,31} Concerns about the safety and accuracy of renal biopsies have recently been addressed in two independent reviews by Lane et al³² and Volpe et al.³³ Both reviews

have demonstrated a low risk of periprocedural complications, a negligible rate of tumor seeding, and a high overall accuracy rate in excess of 90%. The proponents of biopsy argue for its utility in potentially altering the management of the patient, whereas the opponents feel that renal biopsy rarely changes the management of the young patients and may be unnecessary in those who are older and may benefit from active surveillance without additional risks or morbidity of the biopsy. In attempt to potentially avoid the biopsy, Jeldres and colleagues³⁴ found that statistical models are unreliable in determining a grade of a tumor and cannot safely be substituted for renal mass biopsy. Meanwhile, recent biopsy literature suggests a strong correlation of histological subtype determined by preoperative biopsy and final specimen but cautions its accuracy in cases of large renal masses and the ability to correctly identify the grade of the tumor.^{35,36} Further improvement of and work in our ability to identify key prognostic serum or urine markers preoperatively or via biopsy may help in identifying those patients who will benefit from aggressive surgical approach versus those who may be safely observed.

As the management of RCC is becoming more precise, the knowledge and skills of radiologists and interventionalists is closely integrated in the management of patients with renal masses. Although the importance of differentiating among various histologic subtypes and the identification of advanced disease noninvasively are not new concepts, some recent publications suggest that MRI could identify the histology with a reasonable degree of accuracy.^{37,38} Use of diffusion-weighted MRI also allowed separation of clear RCC and nonclear RCC.³⁹ Additionally, dynamic contrast-enhanced MRI was able to detect vascular changes induced by sunitinib in xenograft renal tumors, demonstrating the potential utility of dynamic contrast-enhanced MRI in selecting the dose and schedule of angiogenic compounds.⁴⁰ Guimaraes et al⁴¹ have shown the ability to identify metastatic lymph node in renal carcinoma using lymphotrophic nanoparticle-enhanced MRI. Although the sample size in their study was small, the sensitivity of 100% and the specificity of 95.7% are encouraging. Additionally, perfusion-computed tomography monitoring may have a utility in the follow-up of renal tumors treated by ablation.⁴²

One of the most promising directions, however, appears to be the use of molecular imaging. Recently, using the iodine-124-labeled antibody chimeric G250, Divgi and colleagues⁴³ were able to correctly identify 15 out of 16 clear RCCs. This study not only underscored the importance of molecular imaging but also emphasized the need for deeper knowledge of the molecular pathways responsible for the imaging characteristics and the biologic behavior of different types of renal masses.

Meanwhile, as our field has evolved in the diagnosis and imaging of renal masses, much progress has been done in the management of renal masses. One of the most important concepts was recognition of the adverse effects of renal insufficiency and the importance of maximal renal preservation. Although no randomized prospective studies exist at this time, retrospective analysis revealed that incremental increase in renal insufficiency is associated with incremental increase in all-cause hospitalization, cardiovascular morbidity, and all-cause mortality.⁴⁴ Additionally, several other authors demonstrated close association of renal insufficiency with cardiovascular disease,^{45,46} whereas others have suggested

that those patients treated with radical nephrectomy had shorter overall survival when compared with those treated with a partial nephrectomy.⁴⁷ The above findings supported aggressive preservation of renal function and led to expansion of the indications of nephron-sparing surgery.

Evolving Role of Renal Preservation

One of the major changes in RCC management is the acceptance of partial nephrectomy as a treatment of choice (2009 American Urological Association guidelines)⁴⁸ for T1 renal masses and the extension of nephron-sparing surgery beyond the traditional 4 cm cutoff size. It is no longer necessary to treat a patient with a solitary kidney, severe renal insufficiency, or history of renal calculi to offer a partial nephrectomy for a T1 renal mass. In fact, while radical nephrectomy may still be a standard of care for T1b tumors, partial nephrectomy should now be discussed as an alternative standard of care, even in the presence of a normal contralateral kidney.⁴⁸ Recent study of over 1000 patients from Mayo Clinic and Memorial Sloan-Kettering Cancer Center showed that the overall and cancer-specific survival is not compromised when partial nephrectomy is done for 4- to 7-cm renal cortical tumors.⁴⁹ Of importance, the argument that most renal donors do well long term with a solitary renal unit is no longer supported by the data. The recent findings by Koenig and colleagues⁵⁰ demonstrated that those with RCC are significantly more likely to have an underlying renal insufficiency than the healthy donor population. In addition, several centers have now reported equivalent oncologic outcomes of partial and radical nephrectomy performed for patients with RCC measuring over 4 cm.^{51–53} The recent data presented at the 2009 Annual American Urological Association Meeting suggests equivalent oncologic outcomes for partial and radical nephrectomy even beyond the clinical T2 stage.⁵⁴

With the evolution of our appreciation for the importance of nephron-sparing surgery, there are a parallel improvement and advances in minimally invasive options for RCC management. Laparoscopic partial nephrectomy is no longer considered experimental, although the technical demands of the procedure and versatility with intracorporeal suturing may limit its use to centers of laparoscopic expertise.^{55,56} To compensate for the difficulty of laparoscopic reconstruction there has been a recent trend of increased utilization of a robot-assisted platform in partial nephrectomy.⁵⁷ Several centers have reported similar outcomes and potentially slightly improved warm ischemia times utilizing robot assistance, when compared with conventional laparoscopy.⁵⁸ Of importance, however, none of these series are prospective, and more definitive studies will need to be performed to show the superiority of one technique over the other. Kural et al⁵⁹ pointed out the need for an experienced assistant and the cost associated with robot-assisted partial as of the disadvantages of robotic surgery. Nevertheless, the role of robotic assistance should not be ignored, as it may allow a larger group of urologic surgeons to perform more complex renal surgeries and more renal units may be saved. Recently, robotic assistance has been used in the management of multiple renal masses in the same setting.⁶⁰

Another forefront of minimally invasive options is filled with a variety of ablative techniques. Unfortunately, a small number of patients from each individual institution, absence of controlled trials, and absence of long-term follow-up limit

one's ability to select one modality over another. In most recent publications, Stern and colleagues⁶¹ suggested that radiofrequency ablation of small renal cortical tumors may be a reasonable modality in healthy adults, and Malcolm et al⁶² demonstrated promising oncologic and functional outcomes in patients treated with cryotherapy at intermediate follow-up. Although recent meta-analysis suggests higher recurrence rates with radiofrequency ablation and cryotherapy when compared with partial nephrectomy, there may still be a role for ablation in well-selected patients.²² Additionally, the paucity of pathologic material after ablation and the reliance of ablation success on postablation imaging may potentially be skewing the data for or against ablation. As our ability to better select patients for active surveillance, surgical extirpation, or ablation improves, the care and outcomes of our patients are likely to improve as well.

Finally, advances in the current systemic options for metastatic RCC are truly groundbreaking. In the past 4 years, six new medications were approved by the Food and Drug Administration for the treatment of patients with advanced renal cancer. Sorafenib, sunitinib, bevacizumab, and pazopanib target components of the previously described VHL pathway, whereas temsirolimus and everolimus act on another important pathway for renal carcinogenesis regulated by mammalian target of rapamycin.^{63–70} Although the mechanism of action and specifics of each trial leading to approval of these agents are beyond the scope of this article, suffice it to state that these new agents have been shown to significantly prolong progression-free survival, and in the case of some agents, overall survival.

Conclusions

In summary, the past several years have resulted in much progress in the field of renal oncology. With combined efforts of basic scientists, diagnostic and interventional radiologists, and medical and urologic oncologists, the RCC is remaining a rapidly moving and evolving field.

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G. Bratslavsky and Z. Kirkali declare that no competing financial interests exist.

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Abbreviations Used

EPO = erythropoietin
 GLUT-1 = glucose transporter-1
 HIF = hypoxia-inducible factor
 MRI = magnetic resonance imaging
 PDGF = platelet-derived growth factor
 RCC = renal-cell carcinoma
 SRM = small renal mass
 VEGF = vascular endothelial growth factor
 VHL = von Hippel-Lindau