Chronic Kidney Disease in Patients With Renal Cell Carcinoma

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Renal cell carcinoma (RCC) is diagnosed in over 65,000 Americans annually, and earlier detection and advances in surgical techniques have resulted in improved oncological outcomes. Given that diabetes and hypertension are independent risk factors for the development of RCC, it is not surprising that diabetic nephropathy or hypertensive nephrosclerosis are commonly encountered in these patients. Data support that at least one third of the 300,000 kidney cancer survivors in the United States have or will develop CKD; however, the effect of CKD in this clinical setting has largely evaded the attention of the medical community. It is likely that CKD which develops from postsurgical therapy for RCC may limit long-term outcomes by increasing the risk for cardiovascular morbidity and mortality. To further improve the clinical outcomes for kidney cancer patients, better recognition and management of CKD, which requires coordination among urologists, pathologists, and nephrologists, will be essential.

Key Words: Nephrectomy, Non-neoplastic kidney disease, Urology, Nephrology, Pathology

Introduction

The substantial burden and harmful effect of CKD in kidney cancer patients has largely evaded the attention of the medical community. Urologists who remove kidney tumors and the pathologists that evaluate these tumor nephrectomy specimens primarily have been focused on the potentially fatal effects of kidney malignancies. Although nephrologists have the expertise to manage CKD, they have not been included in the routine pre- and postoperative care of kidney cancer patients.

Many recent developments allow us to re-evaluate the current state of affairs. Nephron-sparing surgery (NSS), which encompasses radiofrequency ablation, cryoablation, and partial nephrectomy (PN), is now a minimally invasive, safe, effective, and routine procedure for kidney tumor resection. Similar oncologic outcomes can be achieved for early-stage renal cell carcinomas (RCCs) that are removed by PN or radical nephrectomy, but PN has demonstrated improved clinical outcomes because of the significant preservation of kidney function[1,2] and maintenance of blood pressure,[3] especially for small renal masses (SRMs). Therefore, a wide surgical margin is not only unnecessary, but it likely harms the patient because of the loss of kidney function. In addition, several recent studies have demonstrated the prevalence of common non-neoplastic kidney diseases in kidney cancer patients (especially diabetic nephropathy and hypertensive nephrosclerosis), and most diagnoses are not identified in the initial pathologic evaluation of the tumor nephrectomy specimen although they might be present.[4-6] This burden of CKD becomes readily apparent after surgical removal of any significant portion of functioning nephron mass and may negatively affect long-term outcomes.

This review will focus on the prevalence, harmful effect, and optimal management of CKD in the setting of kidney cancer; recent trends in the surgical removal and active surveillance of kidney masses; and the prevalence of non-neoplastic kidney diseases found during the pathologic evaluation of tumor nephrectomy specimens. It is hoped that significant gains in the clinical outcomes of kidney cancer patients can be obtained through improved management of CKD. At the core, the optimal management of kidney cancer patients requires increased communication and the coordination of clinical care among urologists, nephrologists, and pathologists.

CKD in Kidney Cancer

The harmful effects of CKD are well established and recognized. Huang and colleagues were the first to demonstrate that 26% of kidney cancer patients had CKD on the basis of the Modification of Diet in Renal Disease equation before tumor nephrectomy.[7] After surgery, 39% had an estimated glomerular filtration rate (GFR) of less than 60 mL/minute, but 70% of the patients underwent a radical nephrectomy. Hypertension[8,9] and diabetes[10] are independent risk factors for developing RCC. The risk of kidney cancer in ESRD patients is increased up to 100 times.[11] There are limited data that CKD may lead to a similar, albeit smaller, increased risk of kidney cancer.[12]

According to the U.S. National Cancer Institute, more than 65,000 cancers of the kidney and renal pelvis will be diagnosed in 2013, with 13,680 estimated deaths.[13] Over the last 2 decades, there has been a notable migration toward the diagnosis of early-stage kidney cancers in the

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United States. According to 1 study, 43% of kidney cancers were Stage 1 in 1993 and currently comprise over 60% of tumors.[14,15] Approximately 20% to 25% of these SRMs are benign (oncocytoma or angiomyolipoma).[16,17] For the remaining tumors that consist of RCC, the 5-year survival exceeds 90% to 95% in most studies. There are currently more than 300,000 kidney cancer survivors in the United States. Given the excellent oncologic outcomes for most kidney tumor patients, the attention has now shifted toward the preservation of kidney function and should also include the management of CKD. The urological community has spearheaded this effort as minimally invasive surgical approaches are more widely adopted. The American Urological Association in 2009 and the European Association of Urology in 2010 released position statements that PN should be considered for all clinical T1 (less than 7 cm) kidney tumors.[18,19]

Although there are data regarding the clinical outcome of kidney function postsurgery in kidney cancer patients, almost all of these studies did not specifically analyze the pathologic specimens for the presence or absence of a non-neoplastic kidney disease. Therefore, there are abundant opportunities for future translational and clinical research on this topic to better define the degree of CKD in patients with RCC.

CLINICAL SUMMARY

- CKD involves at least 25% of RCC patients even before nephrectomy.
- Of 300,000 RCC survivors in the United States, at least 45,000 have an underlying kidney disease (most commonly diabetic nephropathy or hypertensive nephrosclerosis).
- Improved coordination of care among urologists, pathologists, and nephrologists will result in better outcomes for RCC patients.

Less is Sometimes More (or at Least Better)

The incidence of SRMs has increased approximately 2% year after year.[20] Consequently, the management of SRMs (<4 cm) has evolved significantly in the recent past (Table 1). Although advanced RCC is often lethal, surgically treated localized tumors less than 4 cm (T1a) carry an excellent prognosis with a greater than 90% 10-year recurrence-free survival rate. The era of radical nephrectomy as a "1-size fits all" strategy has been replaced by biopsy to confirm the diagnosis followed by nephron-sparing treatment for many and selective surveillance for some. Therefore, a discussion of RCC in the context of CKD is pertinent to the management of SRMs and the treatment of large advanced tumors in which the effect on kidney function is clearly greater because of loss of more kidney mass.

PN has been a treatment option for years, but it was mostly applied in instances such as disease in a solitary kidney, bilateral kidney tumors, or in the setting of CKD, in which more radical surgery would clearly result in ESRD. The evidence supporting "elective" PN for SRMs emerged in the 1990s with equivalent 10-year oncologic outcomes between PN and more radical approaches.[21] However, the adoption of PN had been slower than expected.[22,23] Various reasons have been hypothesized, and there are data to suggest that the introduction of laparoscopic radical nephrectomy impeded the uptake of PN.[24] Although the long awaited results of a European Organization for Research and Treatment of Cancer randomized clinical trial showed similar oncologic outcomes, it failed to demonstrate a survival advantage for PN over radial nephrectomy.[25,26] However, given some study design limitations,[27] PN remains the first-line treatment for localized RCCs less than 4 cm.[18,19] PN may be performed in the conventional open manner or laparoscopic or robot-assisted laparoscopic. Despite minor differences in techniques, the goal of PN is to achieve complete tumor removal with a negative margin in an efficient manner such that ischemia times are kept to a minimum and consequent kidney damage is minimized.

A less invasive option for T1a RCC and in particular tumors less than 3 cm is percutaneous probe ablation. This is most commonly in the form of radiofrequency ablation or cryotherapy.[28] Given that it is performed percutaneously as an outpatient procedure, this modality has been a welcome addition to the "surgical" armamentarium, in particular for older patients and patients with significant comorbities. These techniques are most effective in treating tumors less than 3 cm in size located a distance from major vessels, which could act as an energy sink and lessen the effectiveness of therapy.[29] Success rates are inferior to PN, but they are considered acceptable at greater than 90% recurrence-free rates; however, these rates vary depending on the study population and definition of failure.[30-32]

Although many patients presenting with contrast enhancing SRMs go directly to some form of treatment, there is a growing experience and acceptance with percutaneous kidney tumor biopsy and active surveillance for SRMs. In centers with experience, the diagnostic rates of kidney tumor biopsy are greater than 80% with a very low complication rate (<5%) and a benign histology rate of greater than 25%.[17] Given that upward of 25% of solid-enhancing SRMs are benign, some have adopted the practice to biopsy all lesions before treatment. Furthermore, repeat biopsy after a nondiagnostic biopsy is successful 80% of the time.[33] Lastly, the concordance rates between biopsy results and surgical pathology approach 100% for SRMs.[34]