Evolving Understanding and Surgical Management of Renal Cortical Tumors

Several factors, including tumor stage migration, an improved understanding of the histologic subtypes, and new surgical treatment strategies, are simultaneously affecting the surgical management of renal cortical tumors. The article by Lau and colleagues\(^1\) in this issue of *Proceedings* is both timely and important as we approach the surgical management of renal tumors today.

**Stage Migration**

The historical presentation of renal cancer—flank pain, abdominal or flank mass, and hematuria—is distinctly uncommon today (<5% of cases) and has been replaced by the incidentally discovered solid renal mass. Abdominal ultrasonography, magnetic resonance imaging, and computed tomographic (CT) scanning are ordered increasingly to assess nonspecific abdominal complaints, to assist in evaluation of the extent of disease in patients with other cancers, and to be performed during routine cancer follow-up. At Memorial Sloan-Kettering Cancer Center, approximately 90% of such solid renal masses represent renal cortical tumors.\(^2\) Consequently, the frequency of incidental detection of renal tumors has been increasing.\(^5\) At our center, in 70% of patients operated on for renal cancer, the cancer has been diagnosed incidentally. Although 25% of patients present with large, locally advanced, or metastatic tumors, an excellent overall prognosis is now anticipated, with long-term survival in more than 75% of patients undergoing surgical management. With longer survival expected after treatment of the index tumor, patients with sporadic renal cancers remain at risk for comorbid medical illness as they age (ie, diabetes, hypertension, nephritis), which can adversely affect overall renal function. In addition, even in nonfamilial cases of renal cancer, a small but real risk of approximately 4% exists for development of a tumor in the contralateral kidney.\(^2\)

### Understanding Histologic Variants of Renal Cortical Tumors

For many years, clinicians and pathologists have viewed solid renal masses as a single clinical entity termed broadly “hypernephroma” or “renal cell carcinoma.” Little attempt was made to organize observed histologic variants or gauge the potential impact of these variants on clinical outcome. Two decades of research have now replaced this single view of renal tumors with clearly defined, distinct histologic subtypes of renal cortical tumors with varying metastatic potential.\(^3\) The sporadic renal cortical tumors also display different histologic subtypes broadly fitting into 4 major categories. These categories include the most potentially metastatic conventional clear cell carcinoma (65%), the intermediate-risk papillary (14%) and chromophobe (8%) tumors, and the virtually benign oncocytoma (10%). Preoperative attempts to reliably diagnose tumor histologic subtypes by standard imaging modalities or percutaneous biopsy techniques have to date been unsuccessful.

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Intensive research into kindreds of patients with hereditary or familial forms of renal cancer, which account for less than 5% of patients with renal cortical tumors, led to the discovery of distinct molecular genetic defects.\(^7\) For example, mutations in the von Hippel-Lindau tumor suppressor gene (3p25) can lead to multiple and recurrent conventional renal cell carcinoma along with a spectrum of other tumors, including central nervous system and retinal hemangioblastoma, pheochromocytoma, pancreatic cystadenoma, epididymal cystadenoma, and islet cell tumors.\(^8\) Multiple partial nephrectomies of a single kidney, often repeated on several occasions, are required when renal tumors reach 3 cm in diameter (well before metastatic potential is realized). Every attempt is made to retain enough functional kidney parenchyma to avoid dialysis for as long as possible.\(^9\) Familial clear cell carcinoma is associated with translocations involving chromosomes 3 and 8. In hereditary

Address reprint requests and correspondence to Paul Russo, MD, Department of Urology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021 (e-mail: russop@mskcc.org).
papillary renal cell carcinoma, tumors that are commonly multifocal and bilateral, consistently observed genetic defects include trisomy involving chromosomes 7, 16, and 17 and loss of chromosome Y in males. Mutation in the MET oncogene (7q31-34) is also identified in 80% of patients with hereditary papillary renal cell carcinoma. Recently a familial form of oncocytoma has been reported, although the cytogenetic defects involved remain to be elucidated.

The insight gained from these molecular studies is stimulating research, using both radiologic and pathologic strategies, to develop a means to diagnose histologic subtype preoperatively. The idea of tailoring a surgical procedure based on the preoperative determination of histologic subtype is appealing and may allow for even more widespread use of kidney-sparing operations.

**Changing Surgical Management of Renal Tumors**

The traditional operation for localized kidney cancer, the perifascial radical nephrectomy, and its component parts of ipsilateral adrenalectomy and regional lymph node dissection are viewed by many urologic surgeons as the "gold standard" treatment for renal tumors, particularly in the presence of a normal contralateral kidney. However, the component parts of this operation have never been tested in a prospective randomized trial. Current information from centers with a large clinical experience in renal cancer surgery, including our own, cannot demonstrate any therapeutic effect from either lymphadenectomy or ipsilateral adrenalectomy. Metastatic involvement in either of those sites is associated with a median survival of 9 months or less. For practical purposes, radical nephrectomy is still appropriately performed when the primary tumor is large and effectively replaces too much renal parenchyma for a kidney-sparing approach to be considered.

With the detection of many renal tumors at an earlier, more curable stage, the indications for kidney-sparing surgery have expanded. In the last 10 years, accumulated clinical evidence from several major American and European centers has shown the effectiveness and safety of kidney-sparing surgery (partial nephrectomy) in the treatment of renal tumors measuring 4 cm or smaller. Although most elective partial nephrectomies are performed in tumors measuring 4 cm or smaller, larger tumors in the polar regions of the kidney can also safely be resected by using partial nephrectomy. Common criticisms voiced by many surgeons regarding partial nephrectomy are that the potential for recurrent disease within the kidney (1%-4%) is great and that radical nephrectomy eliminates that concern. However, as has been the experience in von Hippel-Lindau disease, patients who have had partial nephrectomy are under careful surveillance, and should the tumor recur, repeated partial nephrectomy could again be offered to the patient with no anticipated decrease in survival. During kidney-sparing surgery, the entire kidney surface is de-fatted and carefully inspected, both visually and with use of intraoperative ultrasonography, in search of satellite renal tumors that have escaped detection by preoperative CT scanning or ultrasonography. These small tumors can be millimeters in diameter, have histologic features identical to the larger, more clinically obvious tumors, and may enlarge to detectable recurrent disease. Identification of a small satellite renal tumor that can be excised completely should not contraindicate kidney-sparing surgery.

Patients with small, incidentally detected tumors are attractive candidates for laparoscopic and hand-assisted laparoscopic nephrectomy. As with many laparoscopic procedures, the dividends of reduced hospital stay, reduced analgesic requirements, smaller incisions, and faster return to work are offset by increased operating room time, concerns regarding specimen entrapment and tumor spillage at the time of removal, access to training centers of excellence, the steep learning curve for laparoscopy, and quality assurance. Laparoscopic total nephrectomy is being practiced widely, yet laparoscopic partial nephrectomy is under clinical investigation and attempted most enthusiastically for removal of small exophytic tumors in selected centers committed to minimally invasive surgery. Also under investigation in this good prognostic group of patients are alternative treatments for small renal tumors such as percutaneous or laparoscopically guided cryosurgery. Whether improvements in instrumentation, laparoscopic ultrasonography, and continued clinical experience with minimally invasive surgery will allow for partial nephrectomy to be done laparoscopically in more complicated central or subcortical tumors remains to be seen. The role of cryosurgical ablation needs to be studied in a randomized prospective trial with a control group of comparably sized renal tumors treated with partial nephrectomy.

**Radical Nephrectomy vs Kidney-Sparing Surgery**

The article by Lau et al is an important contribution to the urologic oncology literature from a number of vantage points. First, this is a large study of nephrectomy in the management of renal cancer that spans more than 3 decades, although 70% of the patients in their database were entered in the 1990s. Using valid statistical methods and closely matching 164 patients with renal tumors treated by partial or radical nephrectomy, the authors found no differences between the groups in relation to overall survival, cancer-specific survival, contralateral recurrence, perioperative complications, or the occurrence of metastatic disease. The most important observation in this well-done retrospective analysis is that patients treated by partial nephrectomy have a decreased cumulative incidence of...
chronic renal insufficiency, as defined by a serum creatinine level of greater than 2 mg/dL (11.6% of those who had partial nephrectomy vs 22.4% of those who had radical nephrectomy at 10 years) and a decreased risk of proteinuria (34.5% in patients who had partial nephrectomy vs 55.2% in the patients who had radical nephrectomy). Although more elaborate methods such as 24-hour urine collections for creatinine clearance and protein and nuclear renal scans could have strengthened the authors’ case, the identified differences in serum creatinine levels and proteinuria certainly raise our concern that the liberal use of radical nephrectomy can be deleterious to the long-term health of the patient. In addition, as patients age, their overall muscle mass decreases, and the serum creatinine level underestimates overall renal function. The data presented by Lau et al do not display a difference in overall rates of dialysis between the partial and total nephrectomy patient groups. This lack may simply be due to the fact that 70% of the patients were operated on in the 1990s; these patients have not had enough years at risk for the development of overt renal failure.

The principal observation that renal function may be preserved in patients undergoing partial nephrectomy without sacrificing the effectiveness of the cancer operation is in contradistinction to what many urologic surgeons have been trained to believe, namely, that 1 kidney can effectively support an otherwise healthy patient for the duration of that patient’s life. The commonly cited evidence to support radical nephrectomy and to oppose the liberal application of kidney-sparing surgery is that donor nephrectomy patients do not lose renal function over time. This donor population is not directly comparable since the median age of the donor is 37.5 years and the median age of the nephrectomy patient is 61.7 years. This 24-year difference likely accounts for the observations by Lau and colleagues relative to proteinuria and a rising serum creatinine level in patients undergoing radical nephrectomy. Whether a radical nephrectomy is done for a small renal tumor by partial nephrectomy, coupled with the fact that 35% of all renal cortical tumors carry a reduced or nonexistent metastatic potential, will make functional renal preservation a goal equal to local tumor control in the contemporary management of renal tumors.

Paul Russo, MD
Department of Urology
Memorial Sloan-Kettering Cancer Center
Weill School of Medicine
Cornell University
New York, New York