Renal Cell Carcinoma: Risks and Benefits of Nephron-Sparing Surgery for T1 Tumors

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Renal cell carcinoma is the most common cancer of the kidneys that is primarily treated with surgery, including removal of part or all the involved kidney depending on size and tumor, complexity, and patient characteristics. Partial nephrectomy historically was restricted to cases of solitary kidney or bilateral tumors. It was then started for masses smaller than 4 cm and currently is even studied and justified in tumors smaller than 7 cm if surgically feasible. Although partial nephrectomy preserves kidney tissue and, therefore, delays or prevents the new onset of CKD and ESRD, radical nephrectomy is still overused even for the small tumors. Studies have shown that although this practice is driven by an easier complete removal of the kidney especially in the era of minimally invasive surgery, partial nephrectomy is successful in curing cancer and achieving excellent cancer-specific survival in addition to its benefits on cardiovascular health. Nowadays interest in preserving healthy kidney tissue is increasing to the level of studying the impact of larger volume removed around the kidney and the histopathology of that non-neoplastic tissue to predict kidney function behavior postoperatively.

Key Words: Renal cell carcinoma, Radical nephrectomy, Partial nephrectomy, CKD, ESRD

INTRODUCTION

Renal cell carcinoma (RCC) is essentially a surgical entity because the gold standard for treatment of stage T1 (tumors <7 cm) is surgical resection. A significant increase in the incidence of RCC has occurred in the United States since about 1950, reaching an estimated 61,000 new cases and 14,000 deaths in 2015.[1,2] This increase has been attributed to the increased use of abdominal imaging for unrelated symptoms. In turn, this has resulted in earlier diagnoses at lower stages and a change in the natural history of RCC to a surgically curable disease in most cases. Surgery for RCC entails violation of the kidney system and removal of a variable number of nephrons.

Until relatively recently, radical nephrectomy (RN) was the treatment of choice,[3] and nephron-sparing surgery was only performed in extremely selected cases of bilateral synchronous tumors and functional or anatomic solitary kidneys. In contrast, there is now consensus that partial nephrectomy (PN) is preferable for small tumors whenever feasible even in the presence of contralateral normal kidney. This represents an attempt to preserve normal kidney tissue and avoid progression to CKD and ESRD. RN remains the gold standard treatment for larger tumors.[4,5]

EMERGENCE OF PARTIAL NEPHRECTOMY—IMPACT ON ONCOLOGICAL OUTCOMES

The phrase "nephron-sparing" was first used in 1993 to reflect the desire to preserve kidney parenchyma, in the context of both a raising incidence of RCC and medical sequelae of CKD. An encouraging 95% survival rate at a median follow-up of 3 years was then reported.[6] Although subject to selection and observer biases, additional early observational studies added further evidence in support of PN and its oncological equivalence to RN in the treatment of T1a tumors, defined as smaller than 4 cm (Table 1).[8-11] A Cleveland Clinic cohort study, where 39% of patients had kidney insufficiency preoperatively, revealed an 88% cancer-specific survival at 5 years and investigators concluded that PN is an equivalent alternative to RN.[12] McKiernan and colleagues[13] reported in 2002 the kidney functional outcome after PN and RN for masses smaller than 4 cm. There was a substantially higher risk of developing a creatinine of 2.0 mg/dL in the RN group compared with the PN group. This conclusion, along with the suggested equivalency in oncological outcome between PN and RN, led to further use and to an expansion of the indication as discussed subsequently. All these studies were outcome analysis retrospective studies that arguably limit the strength of the evidence.

EXPANDING THE ONCOLOGICAL APPLICATION OF PARTIAL NEPHRECTOMY

Historically, PN was considered to be absolutely indicated in cases of bilateral tumors or functional or anatomic solitary kidney, to be suggested for patients with potential kidney conditions that could affect the long-term kidney function or genetic predisposition for RCC such as in Von Hippel-Lindau disease and optional for small localized tumors with a normal contralateral kidney (Table 2).[14] As the stage migration of recently diagnosed RCC has continued with a higher incidence of smaller and asymptomatic lower stage tumors because of widespread use of abdominal imaging, the urological community has increasingly recognized the medical importance of preserving kidney parenchyma to prevent or delay the onset of ESRD and, thereby, improve the overall survival (OS). As a result, the practice of oncological restriction of nephron-sparing surgery to tumors smaller than 4 cm has been questioned. Several reports

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mainly from Memorial Sloan Kettering and Mayo Clinic from 2002 to 2006 showed equivalent oncologic outcomes of PN and RN for tumors between 4 and 7 cm.[15-17] A joint report from both centers in 2009 strengthened the evidence. At median follow-up of 4.8 years, there was no difference in cancer-specific survival or OS between 286 patients treated with PN and 873 patients treated with RN ($P = 0.8$).[18] This conclusion was supported in 2010 by data from the Cleveland Clinic, where a propensity score model was used to control for the effect of age, comorbidities, and tumor size and pathological stage on survival in both surgical groups. Elective PN was associated with a significantly better OS in this cohort because RN was associated with postoperative CKD (odds ratio 3.4, 95% confidence interval 2.1 to 5.6).[19]

SURGICAL APPROACHES FOR KIDNEY TUMORS

Historically, PN was considered a more complex and less well-tolerated surgery than RN because of the increased risk of ischemic kidney injury caused by clamping of kidney vessels during operation, immediate and delayed bleeding from the resected tumor bed, and urinary fistulas. In early series, severe hemorrhage (>1 L) was 2.5-fold higher in the PN group, and urinary fistula occurred only with nephron-sparing surgery.[20] Operative techniques have improved since, and rates of complications have dropped to low or manageable levels, depending on the center, the level of expertise, the surgical approach, and the complexity of tumor.

CLINICAL SUMMARY

- Renal cell carcinoma is the most common cancer of the kidneys and is primarily treated with surgery.
- Partial nephrectomy is currently acceptable in tumors smaller than 7 cm with excellent cancer-specific survival.
- Partial nephrectomy preserves kidney tissue and, therefore, delays or prevents the new onset of CKD and ESRD.
- Partial nephrectomy may also offer benefit for cardiovascular health because of the link between CKD and cardiovascular disease when patients are adequately selected for this surgery.

One of the advancements in operative techniques is laparoscopic nephrectomy. Laparoscopic RN and PN were first reported in 1991[21] and 1993,[22] respectively. Laparoscopy consists of operating in a video-assisted fashion through several small incisions that allow introduction of surgical instruments manipulated from outside the body. It has been widely adopted in surgery as it confers less pain and smaller surgical incisions, earlier recovery, and lower estimated blood loss.[23,24] Gill and colleagues[25] reported 100 consecutive laparoscopic RNs for T1-T3a tumors with a mean surgical time of 2.8 hours and hospital stay of 1.6 days. All specimens were extracted intact with negative surgical margins. Compared with laparoscopic RN, laparoscopic PN can be more complex because of the mobility of the kidney, the potential for bleeding, and the need to limit ischemic time during which the artery is clamped. The introduction of robotic-assisted laparoscopic technology has allowed surgeons to match the operative time, ischemic time, percent change in glomerular filtration rate (GFR), rate of adverse events, surgical margins, and lengths of hospitalization to those achieved by laparoscopic PN.[26] However, the selection of the surgical approach in kidney surgery should be secondary to the decision of whether nephron-sparing or radical surgery is needed.

TUMOR COMPLEXITY: ELIGIBILITY FOR PARTIAL NEPHRECTOMY

Neoplasms in the kidney can grow in any parenchymal location; they can be exophytic or centrally located and surrounded by normal tissue. Tumors can also occur in close proximity to critical structures, such as kidney vessels, liver, spleen, duodenum, or pancreas, depending on the side. These among other anatomic variables dictate the complexity of tumors in the kidney and, thus, the difficulty of their removals. Although specialized urological oncologists may perform PN safely and effectively for tumors larger than 7 cm if optimally located (exophytic and polar),[27] RN is imperative for much smaller tumors when invading the kidney artery or vein at the hilum.

In 2009, Kutikov and Uzzo[28] from Fox Chase Cancer Center described the first reproducible and standardized scoring system. The "RENAL nephrometry score" quantitates the anatomic complexity of kidney masses based on radius, exophytic/endophytic properties, nearness to the collecting system, anterior/posterior descriptor, and the location relative to the polar line. This quantification of tumor anatomical complexity gained popularity rapidly. Each unit increase in RENAL score was associated with a 35% increased odds of urinary leak ($P = 0.009$).[29] Subsequent studies[30-33] supported this association and validated this scoring system. In 2011, the Fox Chase group went on to include the proposed nephrometry score in a nomogram to predict the malignant and high-grade potential of tumors.[34] Other scoring systems have been proposed, but the R.E.N.A.L model continues to be the most widely used by urologists.

BENEFIT OF NEPHRON-SPARING SURGERY

Kidney function preservation has significant implications; reduced kidney function increases the risk of cardiovascular disease in addition to the increased morbidity and mortality associated with CKD and ESRD.[35] The risks of RN have been compared with the risks of losing a kidney through living donor transplant nephrectomy. Many longitudinal studies of living kidney donors with impressive follow-up durations have indicated that long-term kidney function is well preserved, likely because of compensatory hypertrophy of the remaining kidney.[36-40] Increases in rates of hypertension and proteinuria have been observed in donors in some series, but these findings have not been thought to be clinically meaningful.[40-43] However, in a more recent study, Muzaale and colleagues[41] questioned this paradigm.