Surgical Management of Renal Cell Carcinoma

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Abstract

Keywords

- renal cell carcinoma
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- radical nephrectomy
- nephron-sparing surgery

Surgical resection of renal cell carcinoma (RCC) is the benchmark for long-term cure of the disease. Although open or laparoscopic radical nephrectomy is considered the gold standard for stage T1b-T4 tumors, nephron-sparing surgery is the preferred operative modality for small renal masses demonstrating equivalent oncologic efficacy and improved renal function outcomes compared with complete nephrectomy. With the advance of minimally invasive surgery, nephron-sparing procedures can safely be conducted laparoscopically with or without robotic assistance. RCC with intravenous tumor thrombus presents a surgical challenge, but multidisciplinary surgical approaches can provide long-term benefit in these patients. The role of cytoreductive nephrectomy and metastasectomy in patients with metastatic RCC (mRCC) is controversial, but seems to be beneficial for patients in the era of targeted therapy.

Objectives: Upon completion of this article, the reader will be able to describe the current surgical management of renal cell carcinoma.

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Renal cell carcinoma (RCC) is estimated to be responsible for more than 90% of 65,150 newly diagnosed kidney cancer cases and 13,680 cancer deaths in 2013.¹ Due to increased utilization and availability of computed tomography (CT) and magnetic resonance imaging (MRI), more renal masses are being identified and a concomitant stage migration has occurred, such that renal masses are being identified at

much earlier stages before symptoms suggest advanced disease.^{2,3} Incidentally discovered renal masses currently comprise 48 to 66% of tumors, compared with only 3 to 13% in the 1970s.⁴ Nevertheless, approximately 20 to 30% of patients have metastases at initial presentation. Even after surgical resection for clinically localized disease, 20 to 40% of patients will relapse and have a poor prognosis with respect to long-term survival.^{5,6} Even with the new targeted systemic therapies being developed and approved in the last decade, rarely do they provide complete or long-term responses. The only possibility of long-term cure and survival of RCC involve surgical interventions including radical nephrectomy, partial nephrectomy (PN), ablative techniques, and, in selected cases, metastasectomy in combination with multimodal treatment approaches.⁷ This article will review the current surgical management of RCC for clinically localized, locally advanced, and metastatic conditions.

Radical Nephrectomy

Since first described by Robson et al in 1969, open radical nephrectomy (ORN) has been the gold standard of treating malignant renal masses with a curative intention for decades.⁸

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In contrast to previously described pericapsular nephrectomy, radical nephrectomy included the en bloc resection of the entire kidney as well as the surrounding perinephric fat, the ipsilateral adrenal gland, and the regional lymph nodes.⁸ This improved overall survival (OS) significantly at that time to around 65% for localized RCC.⁸ Surgical access to the kidney can be achieved through several means, including a retroperitoneal approach with a flank incision, transperitoneal access by a midline or subcostal incision, or in case of large, upper pole tumors by a thoracoabdominal approach.

With technical advantages of cross-sectional imaging and the widespread use of CT and MRI, the detection of incidental small tumors has increased significantly and changed the surgical approach to RCC.⁹ Minimally invasive techniques have been developed and nephron-sparing surgery (NSS) has been added to the possible treatments.^{10,11} These innovations, critical discussion about conventional ORN arose, and the benefit of routine removal of the adrenal gland and regional or extended lymphadenectomy was questioned.

Several studies demonstrated the low incidence of adrenal metastasis in final pathologic ORN specimens, with detection rates around 4 to 6% primarily in upper pole tumors or with advanced T stages (40, 7.8, and 0.6% probability of adrenal spread in T4, T3, and T1–2 tumors, respectively).^{12–14} Also high sensitivity and specificity of presurgical imaging was confirmed, so that routine removal of the adrenal gland is not recommended any longer for low-stage tumors without any sign of adrenal involvement clinically or by cross-sectional imaging.¹⁴

The role and extent of regional lymphadenectomy is yet to be elucidated, even though lymphadenectomy provides the most accurate method of staging and detecting lymph node metastasis. If not clinically and radiographically suspected, incidence of lymph node involvement is as low as 4 to 14%. Further, lymphadenectomy does not consistently improve overall or cancer-specific survival in localized RCC (T1–2).^{15,16} Since the risk of lymph node involvement increases with increasing T stage (1.1, 4.5, and 12.3% for T1, T2, and T3, respectively), mostly patients with locally advanced stages (T3–T4) profit from regional or even extended lymph node dissection (resulting in longer disease-specific survival).^{17,18} The anatomy of renal lymphatic drainage is quite variable. Only 7% of patients drain primarily in the ipsilateral hilar area while more commonly the para-aortic nodes are the drainage sites (approximately 27%), which makes lymphadenectomy approaches difficult to standardize.¹⁹

In the 1990s, minimally invasive approaches to radical nephrectomy were developed, and subsequently laparoscopic radical nephrectomy (LRN) has become a widely adopted procedure.²⁰ LRN be performed by transperitoneal, retroperitoneal, and hand-assisted approaches. Due to equivalent oncologic control with lower morbidity, improved complication profile, and faster convalescence than ORN, LRN is now considered standard in a patient population not amenable to NSS and with tumor stages up to T1–3, N0, M0.^{21–24} Multiple studies demonstrated improved perioperative and postoperative outcomes such as decreased blood loss, decreased operative time, shorter

hospital stay, less need for analgesia, and faster recovery to normal physical activity.^{25,26}

Radical nephrectomy approaches (ORN and LRN) have been shown to be associated with the development of chronic kidney disease (CKD) and related morbidity, such as necessity of hemodialysis, cardiovascular disease, and cardiovascular-related mortality.^{27–29} It is for this reason that is why ORN and LRN have been questioned as the procedure of choice for small renal tumors otherwise amenable to nephron-sparing approaches, such as PN.^{30,31}

Partial Nephrectomy

After initial descriptions in the 19th century, PN or NSS was rarely used until approximately two decades ago; this was due largely to the high morbidity and mortality linked to these procedures at that time. The basic principle of PN is to excise the tumor with a rim of normal renal parenchyma, usually using temporary occlusion of the vascular pedicle, closure of any open collecting system and vessels, and finally capsular reconstruction. Initially, PN was reserved for patients with imperative indications, including anatomical or functional solitary kidney, bilateral tumors, predisposing syndromes such as von Hippel Lindau disease, and patients with CKD or general predispositions to CKD such as diabetes, renal artery stenosis, and nephrosclerosis, to prevent anephricity or high risk for dialysis.³² With improvements in radiological imaging, surgical technique, knowledge about ischemic effects on the kidney, and downstream effects of CKD after RN, PN has resurfaced as an attractive alternative to RN (see **Fig. 1**). PN has been adopted as standard procedure for small renal masses even in patients without an imperative indication, due to the benefit of preserving renal parenchyma and thus renal function with equivalent oncological outcomes.^{30,33} Various studies have demonstrated equal oncologic outcomes (5-year disease-specific survival up to 96%) for patients with T1a (up to 4 cm) tumors treated with PN compared with patients treated with RN.^{33,34} A recent population-based analysis comparing outcomes for PN and RN for T1a tumors indicates that a virtually perfect disease-specific survival rate (97.5% or better) was achieved by PN.³⁵ There is evidence the same appears to be true for select T1b (4–7 cm) tumors in terms of oncologic outcome (5-year disease-specific survival rate of 98%), with superiority of PN as for preventing CKD and preserving renal function, thereby preventing secondary causes of morbidity and mortality such as cardiovascular disease.^{27,36,37} In highly selected patients, PN seems oncologically effective and safe even in patients with higher tumor stages (T2 [> 7 cm but confined to kidney]; T3a/b [spreading to perinephric fat/renal vein or infradiaphragmatic inferior vena cava, IVC]).³⁸ There remains some debate regarding the unequivocal benefit of NSS for small renal masses, primarily because a randomized, prospective trial failed to demonstrate a clear benefit to PN compared with RN. However, this study had significant limitations that led the authors to interpret the results with caution.³¹

The role of margin width, its implication for prognosis, and the concern for local recurrence of RCC after PN are also

Figure 1 (A) Radiologic image and (B) intraoperative view of a left renal tumor amenable to partial nephrectomy (arrow, A).

debated. Margin width seems to have no effect on oncologic outcome and survival when the final margin is negative, and the risk of recurrence seems to be negligible even when margins are slightly positive.^{39–41} Fortunately, local recurrences after PN are rare and range between 0 and 10% overall, and data demonstrate even lower recurrence rates for T1a tumors (0–3%) in patients undergoing elective PN.³⁰ In addition to the oncologic equivalence between RN and PN, patients after PN have a better quality of life compared with patients who undergo RN.⁴²

Vascular clamping during PN is frequently used to improve hemostasis and visibility during the procedure to enable precise closure of the collecting system, vascular structures, and the parenchymal defect. Ischemia time during PN and the percentage of kidney preserved have a tremendous effect on renal function of the remnant kidney after surgery. The surgery can be performed with warm, cold, and no ischemia. Warm ischemia time should not exceed 20 to 25 minutes to prevent renal damage and progression to severe CKD.⁴³ If PN does not seem feasible with a warm ischemia time around 20 minutes, cold ischemia should be used. Cutoff times to avoid impairment of renal function are not clearly defined but should not exceed 35 minutes.⁴⁴ Recently suggested improvement of ischemia technique involves early unclamping after initial parenchymal suture to reduce ischemia time.⁴⁵ Generally, but especially in patients with a solitary kidney or other imperative indications for PN, the surgery should be per-

formed without ischemia whenever technically feasible due to better postoperative glomerular filtration rate, lower likelihood of acute renal failure, and lower rates of new onset or worsening CKD.⁴⁶

In recent years, centers of excellence have improved surgical techniques, and laparoscopic (LPN) as well as robotic-assisted (RAPN) techniques have been adopted for PN with equivalent short-term oncological results in experienced hands.^{47,48} Complication rates, including urine leaks, blood loss, and others have been decreased to an equal level for PN, LPN, and RAPN, whereas RAPN seems to be associated with less ischemia time compared with LPN.^{49–51}

PN displays definitive advantages in functional outcomes with equal oncological outcomes for locally confined RCC and is gaining traction in clinical practice. Still, there is a general underuse of PN because PN is a demanding and technically challenging procedure and surgeons as well as patients seem to favor LRN over any kind of PN in certain settings. There is a higher chance of undergoing PN in teaching or tertiary care centers.⁵²

Surgical Management of RCC with Venous Tumor Thrombus

Uniquely, RCC demonstrates a frequent pattern of intraluminal growth into venous structures. This can involve the renal vein or the IVC and can progress as far as the right atrium.

Figure 2 (A) Radiologic image of a tumor thrombus (arrows) and (B) a specimen including an inferior vena cava thrombus (arrow).

Surgically, this represents a complex challenge, increasing with the level of tumor thrombus (confined to the renal vein, infradiaphragmatic IVC, and supradiaphragmatic IVC). IVC thrombus is present in 4 to 10% of cases of RCC⁵³; therefore, preoperative imaging to detect and assess the exact extent of tumor thrombus is essential (see ►Fig. 2). To date, MRI is the preferred diagnostic modality at many centers to demonstrate the presence and degree of venous involvement, with equal performance to a multidetector CT.⁵⁴ RN in the presence of a renal vein thrombus is not significantly different from the typical procedure; however, IVC thrombi change the pattern of RN drastically. This includes mobilization of the liver and control of the supra- and infrarenal IVC, the contralateral renal vein, lumbar veins, porta hepatis, and other tributary veins for subdiaphragmatic thrombi. In cases with thrombus extension above the diaphragm, venovenous bypass or cardiopulmonary bypass with or without deep hypothermic circulatory arrest are required, and thereby necessitate a multidisciplinary approach. Usually, thrombi of RCC are not adherent to the venous wall and can be mobilized; when wall invasion into the IVC occurs, aggressive management is required with the necessity of venous wall reconstruction or replacement.⁵⁵ RN with tumor thrombectomy is associated with a high morbidity and mortality, with perioperative mortality rates of 2 to 4%, early complication rates of 15% and late complication rates of up to 25%. These potential complications make appropriate patient selection vital.^{56,57} However, surgical extirpation of the kidney and tumor thrombus provides the only long-term cure possible in these patients, with 5-year OS rates between 40 and 65% in patients without metastasis and poorer survival of 5 to 25% in patients with metastases.^{58–60}

Cytoreductive Nephrectomy

Cytoreductive nephrectomy (CN) is used in patients with RCC who initially present in a metastatic RCC(mRCC) setting. Two prospective randomized trials demonstrated superior progression-free survival and OS in patients undergoing CN followed by immunotherapy compared with immunotherapy

alone.^{61,62} In a combined analysis, patients treated with CN and immunotherapy had a survival benefit of 13.6 versus 7.8 months in patients undergoing immunotherapy alone.⁶³ This is the reason that CN for patients with mRCC has been widely adopted, although only patients with good overall performance status were included and some poor prognostic metastatic sites (brain) were excluded, introducing a selection bias. CN is significantly more complicated than standard RN, with in-hospital mortality rates of 5%, indicating the need for careful patient selection.⁶⁴

In the era of targeted therapies, the benefit of CN has been questioned again. To date, there are no prospective randomized controlled trials to answer this question, and other evidence is limited. Recent retrospective series suggest better outcomes for patients treated with CN before targeted therapy compared with targeted therapy alone, but again selection bias in these series limits conclusions.^{65,66} Two prospective randomized controlled trials are underway to provide Level-1 evidence regarding this matter.

Metastasectomy in Patients with mRCC

It should be reiterated that complete surgical resection is the only chance for cure in patients with RCC, including patients with mRCC, even though cures are uncommon in this latter group. Metastasis site has a significant impact on survival after metastasectomy, favoring lung and adrenal metastasis with 5-year OS rates of around 40 and 60% for single site metastasis, respectively, compared with bone and liver metastases (5-year OS rates around 15%).^{67,68} The single most important factor for long-term success in case of single or even multiple metastasectomies is complete resection.⁶⁹ Patients with complete resection of lung-only metastasis have a 5-year cancer-specific survival (CSS) rate of 73% compared with 19% without complete resection. In patients with nonlung-only metastasis, the difference in survival is also significant with a 5-year CSS rate of 33% with complete resection and only 12% without. In the era of targeted agents there is still limited evidence, but it seems as if the above-mentioned results can be transferred to the patient

Figure 3 (A) Radiologic image of a resectable systemic metastasis (arrow) and (B) radiologic image of a resectable local recurrence (arrow).

population undergoing targeted therapy as well, and emphasize the important role of multimodal and multidisciplinary approaches in mRCC (see ►Fig. 3A).⁷⁰

The same benefit as resection of a systemic metastasis is suggested to be true for isolated local recurrence of RCC. Likewise, aggressive and complete surgical resection can provide durable local tumor control, and a multimodal approach with thoughtful integration of systemic therapy should be considered in these patients (see ►Fig. 3B).⁷¹ However, these patients face a significant risk of developing systemic disease, despite aggressive surgery and the need to be monitored closely.

In conclusion, surgical resection represents the standard of care for managing patients with renal masses. Radical nephrectomy is the gold standard for larger renal masses, whereas nephron-sparing PN is the preferred treatment modality for T1a tumors. The role of CN and metastasectomy/extirpation of local recurrence in advanced RCC is yet to be defined in the era of targeted therapies, but to date does represent the only opportunity for cure.

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