Original Article

Optimal Management of Localized Renal Cell Carcinoma: Surgery, Ablation, or Active Surveillance

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Key Words

Renal cell carcinoma, treatment, surgery, ablation, surveillance

Abstract

Radical nephrectomy is historically accepted as standard treatment for localized renal cell carcinoma (RCC). However, the presentation of RCC has changed dramatically over the past 3 decades. Newer alternative interventions aim to reduce the negative impact of open radical nephrectomy, with the natural history of RCC now better understood. This article discusses current surgical and management options for localized kidney cancer. (*JNCCN* 2009;7:635–643)

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Describe the most common presentation of renal cell carcinoma (RCC)
- Identify the components of open radical nephrectomy for RCC
- Describe the best techniques for laparoscopic radical nephrectomy
- Identify the recommended gold standard for the treatment of RCC
- List the disadvantages of cryoablation and radiofrequency ablation for the treatment of RCC

Renal cell carcinoma (RCC) accounts for approximately 3.5% of all malignancies and is the third most common cancer of the urinary tract. In 2008, an estimated 54,390 new cases were identified and 13,010

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deaths resulted from RCC.[1] Although historically patients presented with symptoms such as a palpable flank mass, hematuria, pain, or weight loss, most cases today are identified by chance. This shift is attributed to the increased frequency of cross-sectional diagnostic imaging; an asymptomatic incidental renal mass now accounts for at least 48% to 66% of RCC diagnoses.[2] Over the past 3 decades, a steady increase has been seen in the incidence of RCC with downward stage migration, along with a matching increase in the rate of RCC interventions.[3]

An evolution in treatment options has accompanied this differing presentation of RCC. Surgery remains the mainstay of treatment for localized RCC, although open radical nephrectomy is arguably no longer the gold standard; it has known procedure-related morbidity and can lead to renal insufficiency. Several alternatives have become available to reduce or avoid these inherent negative consequences.

This article reviews different surgical and management approaches for localized RCC, and compares the data and role for each intervention.

Surgery

Open Radical Nephrectomy

Robson[4] is credited with establishing open radical nephrectomy as the treatment for RCC, defining the key components as early isolation and ligation of the renal vessels, kidney removal with all surrounding perinephric tissues, resection of the ipsilateral adrenal gland, and regional lymph node dissection. His original report showed patients experienced improved outcome compared with those undergoing the prior practice of pericapsular nephrectomy, and made open radical nephrectomy results the benchmark for comparison with later treatments.[4] For patients of the pre-CT era who presented with symptoms of advanced RCC, these elements of open radical nephrectomy were needed.

Based on Robson's experience and other follow-up studies, open radical nephrectomy has been viewed as the standard operation for RCC, with its outcome well documented (Table 1). However, in recent decades, with increasing numbers of incidental and localized RCC identified with sensitive modern imaging, the need and application of these aspects of open radical nephrectomy have been questioned. For example, although adrenalectomy and lymphadenectomy may have a role in pathologic staging of patients with large or clinically advanced (≥ T2) tumors, evidence suggests that these components have no clear benefit over nephrectomy alone for treating localized renal masses in the absence of abnormal imaging (i.e., adenopathy or adrenal mass), and these features of the operation are now performed selectively.[5,6]

Despite its proven effectiveness for localized RCC, open radical nephrectomy has recognized drawbacks. Morbidity is inevitable from the incision through muscle and fascia, and recovery generally requires months. Additionally, with loss of an entire kidney, most patients experience a decline in renal function, and open radical nephrectomy is associated with future renal failure and dialysis.[7,8] Other interventions may be preferable to open radical nephrectomy for localized RCC.

Laparoscopic Radical Nephrectomy

Minimally invasive radical nephrectomy was first described by Clayman et al.[9] in the early 1990s. Given its novelty and increased technical demands compared with open radical nephrectomy, this approach initially met with great resistance from the general urologic community. In the years since its first report, laparoscopic radical nephrectomy has gained acceptance as equivalent to open radical nephrectomy, supported by favorable long-term outcomes. Although not directly compared in randomized prospective trials, multiple retrospective studies have shown the efficacy of laparoscopic radical nephrectomy to be equal to open radical nephrectomy (Table 1).

Although overall patient outcomes are similar for open and laparoscopic radical nephrectomy, the latter, because it is minimally invasive, shows better perioperative parameters, such as decreased blood loss and hospital length of stay, and a reduction in morbidity with less pain and more rapid patient convalescence.[10,11] With surgeon experience, laparoscopic radical nephrectomy is possible for nearly all organ-confined RCC that would traditionally require open radical nephrectomy; laparoscopic radical nephrectomy has been successfully completed with very large but localized tumors and in patients who have undergone prior surgery.[12,13] Although using a different surgical approach, laparoscopic radical nephrectomy fulfills the basic tenets of open radical nephrectomy and can fully replicate its critical prin-

ciples. Although the laparoscopic radical nephrectomy approach can be transabdominal, retroperitoneal, or hand-assisted, these different methods show similar results.[14,15]

In summary, laparoscopic radical nephrectomy shows equal outcomes to open radical nephrectomy for RCC, but offers patients the advantages of lower blood loss, shorter hospital stay, reduced pain medicine requirements, improved cosmesis, and faster return to work and normal activities. These short-term benefits with similar long-term results make laparoscopic radical nephrectomy clearly preferable to open radical nephrectomy, and it has been suggested as the new gold-standard.[16]

Nephron-Sparing Surgical Resection

The development of laparoscopic radical nephrectomy has occurred concurrently with advances in nephron-sparing surgical resection (NSS), in which resection is limited to the renal tumor and the uninvolved kidney is maintained. This approach is aided by 1) the downward stage migration of RCC, with most tumors now found when they are asymptomatic, relatively small, and localized; and 2) sensitive modern imaging, which can show in detail the anatomic relationships between tumor and adjacent normal tissue. Open partial nephrectomy has been the primary approach for NSS and was originally performed for patients with absolute indications, those with a solitary kidney and RCC, or those with bilateral RCC.[17]

Gradually, open partial nephrectomy has been conducted for more relative indications, such as patients with a unilateral tumor and baseline renal insufficiency or those with concurrent medical disease, such as renal artery stenosis, hypertension, or diabetes. In this population, open partial nephrectomy has been applied to reduce the potential of developing future renal failure. From these initial scenarios in which dialysis is an immediate or future risk, open partial nephrectomy has been further undertaken for solely elective indications in otherwise healthy individuals, such as patients with a single localized RCC, a normal contralateral kidney, and without particular increased risk for developing renal insufficiency.[18] Regardless of indication, treatment of isolated RCC with open partial nephrectomy seems to have equivalent results to radical nephrectomy (Table 1), with the former minimizing the degree of renal function change related to tumor resection.[7,19] These outcomes have been shown primarily in treating tumors of 4 cm or less, although recent data suggest that bigger tumors (≥ 7 cm) can also be addressed using open partial nephrectomy with similar results.[20,21]

Table 1 Outcomes for Surgery for Localized Stage I Renal Cell Carcinoma

ORN Efficacy (Author/Year)	n	5-y Survival
Robson et al.[49] (1969)	32	66%
McNichols et al.[50] (1981)	177	67%
Guinan et al.[51] (1995)	1048	75%
LRN Efficacy (Author/Year)		
Portis et al.[52] (2002)	64	81%
Saika et al.[53] (2003)	195	84%
Colombo et al.[54] (2008)	63	78%
OPN Efficacy (Author/Year)		
Jacobs et al.[55] (1980)	51	84%
Morgan and Zincke[56] (1990)	104	89%
Belldegrun et al.[57] (1999)	146	93%

Abbreviations: LRN, laparoscopic radical nephrectomy; OPN, open partial nephrectomy; ORN, open radical nephrectomy.

Open partial nephrectomy, when compared with open radical nephrectomy and laparoscopic radical nephrectomy, is a more complex operation demanding advanced surgical skills. Open partial nephrectomy requires establishing temporary vascular occlusion, performing complete tumor excision, potentially repairing the urinary collecting system, closing the kidney tissue defect, and obtaining hemostasis. The foremost objective is completing mass resection and renal reconstruction in a timely fashion and minimizing the period of renal artery clamping, because prolonged ischemia time is recognized to affect renal function recovery.

Because of its greater complexity, open partial nephrectomy has a higher rate of complications, most often involving hemorrhage, urinary fistula formation, ureteral obstruction, acute renal insufficiency, and infection.[18] Compared with open radical nephrectomy and laparoscopic radical nephrectomy, which have estimated overall complication rates of 10% to 20%, open partial nephrectomy has a reported complication rate as high as 30%, although this is suggested to lessen with time and greater clinical volume. At experienced centers, complication rates for open radical, laparoscopic radical, and open partial nephrectomies are all generally similar (10%–15%).[18,22] Although the risk for complica-

tion with open partial nephrectomy is influenced by surgeon experience and patient medical condition, additional factors impacting the potential for postoperative complications include tumor size and location, which dictate the complexity of resection. More difficult tumors to address using NSS are larger (> 4 cm), located centrally, or at the renal hilum, and the risk for complications may be considerably higher.

To reduce the morbidity of open partial nephrectomy, laparoscopic partial nephrectomy has been performed and offers a minimally invasive approach to NSS. However, laparoscopic partial nephrectomy has been infrequently conducted because of its added complexity. This procedure is more demanding than either laparoscopic radical nephrectomy or open partial nephrectomy and can challenge even skilled, experienced laparoscopic surgeons. With traditional laparoscopic instrumentation, laparoscopic partial nephrectomy is recognized to be particularly difficult regarding the reconstruction and closure of the kidney defect. Few centers have significant clinical experience with laparoscopic partial nephrectomy. Its early and intermediate oncologic outcomes seem similar to open partial nephrectomy, and although it offers faster recovery, the overall risk for complication is generally slightly higher.[23,24]

In summary, although originally restricted to patients at risk for renal failure, open partial nephrectomy or laparoscopic partial nephrectomy can be considered for any patient with any indication for renal preservation. Open partial nephrectomy has been advocated as the preferred treatment for localized RCC given its equivalent oncologic outcomes and the benefit of preserving the uninvolved kidney.[20] For masses smaller than 4 cm, which are benign or indolent in 20% to 30% of cases,[25,26] open partial nephrectomy also addresses the risk for overtreatment by avoiding a total nephrectomy for what may be a nonmalignant lesion. In addition to having a benefit on renal function and physical health, NSS has been shown to also improve patient satisfaction and psychosocial indicators of quality of life.[7,27] Lastly, recent data show improved long-term overall survival because of lower renal morbidity in patients who undergo open partial nephrectomy compared with those who undergo radical nephrectomy, suggesting that total nephrectomy is ultimately deleterious.[19,28] These results show that open partial nephrectomy and laparoscopic partial nephrectomy for localized RCC provide unique benefits and may be superior to radical nephrectomy. Although NSS may have a higher rate of complications, open partial nephrectomy or laparoscopic partial nephrectomy should be initially considered in the treatment of incidental RCC when technically feasible.

Tissue Ablative Therapy: Radiofrequency Ablation/Cryoablation

Because open partial and laparoscopic partial nephrectomy are currently applied in a minority of RCC cases, largely due to their greater technical demands, interest has been shown in developing NSS treatments that could be more readily performed and are associated with lower morbidity and risk. This has led to tissue ablative approaches, which use radiofrequency energy or cryoablation instrumentation to generate a level of heat or cold that is ultimately lethal to the target. Radiofrequency ablation (RFA) and cryoablation have been shown to effectively ablate different tumor sites, including liver,[29] lung,[30] and prostate,[31] and have been applied to RCC since mid-1990s.[32,33] Both approaches rely on a needle or probe placed into the target tumor. If the tumor can be accurately accessed, then ablation is possible. Depending on tumor location, ablation can be attempted through laparoscopy, or percutaneously using image guidance and requiring only sedation. RFA and cryoablation have the goal of eliminating RCC in situ, are nephron-sparing because the field of ablation is small and therefore most of the kidney is unaffected, and they avoid the more substantial potential complications associated with tumor resection that can occur with open partial or laparoscopic partial nephrectomy.

Although these approaches are appealing given their relative ease of performance, favorable patient tolerance, and perceived low risks, they have several limitations and disadvantages. Because each probe has a fixed area of ablation, these treatments are best suited for smaller renal masses (< 3 cm), whereas larger tumors require multiple probes and are associated with a greater risk for incomplete ablation. Because these approaches do not provide complete pathologic staging, the ability to estimate prognosis is imperfect and based primarily on the results of a percutaneous biopsy, whose accuracy with RCC re-

mains controversial.[34] Consensus is lacking regarding appropriate patient follow-up after tissue ablative therapy and how to measure and determine treatment success. Ultimately, the greatest drawback for tissue-ablation is that intermediate and long-term oncologic outcomes remain unproven. A recent meta-analysis comparing outcomes of tissue ablative therapy with those of open partial nephrectomy, with a short median follow-up period of only 16 to 18 months, showed cryoablation associated with a 7.5-fold increased risk for local recurrence and RFA an 18-fold increased risk (Table 2). Although a few single-institution series suggest the potential for long-term treatment efficacy with ablation,[35,36] tissue ablative therapy for RCC generally remains reserved for highly selected small renal masses in the elderly, sick, and infirm, for whom treatment is deemed necessary but standard surgical resection is particularly high-risk or contraindicated.

Table 2 Collective Published Data on Management of Patients With Small Renal Masses

	OPN	Cryoablation	RFA	AS
Case series (N)	40	16	19	9
Total tumors (N)	4583	406	521	315
Mean follow-up (months)	54.0	18.3	16.4	33.3
Risk for local recurrence (vs. OPN)	1.00	7.45	18.23	n/a

Abbreviations: AS, active surveillance; n/a, not applicable; OPN, open partial nephrectomy, RFA, radiofrequency ablation.
Adapted from Kunkle DA, Egleston BL, Uzzo RG. Excise, ablate or observe: the small renal mass dilemma—a meta-analysis and review. J Urol 2008;179:1227–1233.

Active Surveillance With or Without Delayed Intervention

A final option to consider relies on the growing evidence that many small renal masses may be clinically insignificant. The epidemiology of RCC over the past decades shows an increasing incidence with a corresponding rise in rate of treatments, but RCC and overall death rates have also paradoxically increased.[37] These and other data suggest that many incidentally detected RCCs may not be aggressive or lead to mortality and, contrary to traditional belief, may not require treatment.[38] Several retrospective series of active surveillance have suggested the behavior of small renal masses is mostly indolent, with the average growth being roughly 3 mm per year,[39] with up to one third of tumors having zero net growth at a median follow-up of 29 months.[40] Ultimately, the greatest concern about active surveillance is the risk for progression to metastatic disease; in a recent meta-analysis, occurrence during active surveillance with a mean follow-up of nearly 3 years was low and is equivalent to that for patients who were treated with definitive excision or ablation.[41]

Active surveillance may be beneficial in allowing avoidance of intervention except for patients whose tumors show brisk growth in follow-up. Increase in size is believed to indicate biologic behavior, and patients whose tumors show rapid change might be identified to need treatment. Retrospectively, delayed RCC intervention does not alter treatment options or carry greater risk for stage migration or developing metastases.[42] For a disease that may be overtreated, initial active surveillance followed by selective delayed intervention might better discriminate patients who benefit from treatment from patients with a clinically insignificant tumor. This management strategy could be most fitting for older patients with comorbid conditions, whose risk for death from other causes can be greater than the risk for death from metastatic progression of an incidentally detected RCC.

Treatment Selection

Open radical nephrectomy remains the most frequent RCC treatment, occurring in roughly 70% to 90% of recent United States cases, suggesting overuse.[43] Although situations remain in which a renal mass requires treatment using open radical nephrectomy because of its size or complexity, this intervention should occur less commonly in the future given currently available and preferable alternatives. Laparoscopic radical nephrectomy and open partial nephrectomy are established options with clear short- and long-term advantages for patient recovery or renal function preservation but remain underused, probably because of their technical difficulty. Studies examining the application of either laparoscopic radical nephrectomy or open partial nephrectomy instead of open radical nephrectomy have shown these operations to be concentrated at select hospitals with specific experienced

surgeons, with slow adoption in the broader urologic practice.[44] For example, laparoscopic radical nephrectomy requires a unique skill set and particular technology and instruments, and many urologists have inadequate minimally invasive surgical experience to perform this procedure.

A review of the uptake of laparoscopic radical nephrectomy since its introduction in 2003 showed that after 13 years, this procedure was used to treat fewer than 15% of RCC cases in the United States.[43] In contrast, within 3 years after introduction of laparoscopic cholecystectomy, this less-complex operation was adopted in 50% of all cases, approaching 70% within 4 years.[45] Because of the relative infrequent nature of RCC surgery (roughly 10 times less common than cholecystectomy) along with laparoscopic radical nephrectomy's greater complexity, the learning curve for laparoscopic radical nephrectomy remains a considerable barrier to greater application.

Although open partial nephrectomy has also gradually increased in frequency (now accounting for approximately 15% of national RCC cases),[43] it still tends to be applied mostly for absolute and relative indications and may not be adequately considered in general. In studying patterns of RCC treatment, surgeon preference primarily determined the type of operation performed, with tumor or patient features only weakly influencing the choice of treatment.[43] This suggests that, despite the evidence showing an advantage for either open partial nephrectomy or laparoscopic radical nephrectomy over open radical nephrectomy, open radical nephrectomy remains the most common treatment because most urologists are unable or reluctant to proceed with any alternative.

Perhaps the ideal definitive treatment might be laparoscopic partial nephrectomy, combining the advantages of open partial nephrectomy and laparoscopic radical nephrectomy, although its practice remains limited because of its technical difficulty. It has been the least common treatment, applied in only an estimated 3% of RCC cases nationally.[43] Recently, robotic-assisted laparoscopic partial nephrectomy was described, incorporating the daVinci surgical system (Intuitive Surgical, Inc), which facilitates operations that are technically difficult using traditional laparoscopic instruments. Preliminary reports describe favorable outcomes for robotic-assisted laparoscopic partial nephrectomy, showing operative parameters such as renal ischemia time, blood loss, and complications to be similar to or better than those of open partial nephrectomy,[46] and use of this tool will probably hasten laparoscopic partial nephrectomy adoption in the future.

For example, with the daVinci system, radical prostatectomy in the United States has converted in a decade from what was almost exclusively an operation performed in open fashion to what is now mostly performed using a robot-assisted laparoscopic approach.[47] A similar impact could occur with renal cancer surgery, wherein the daVinci system will enable more urologists to perform laparoscopic radical nephrectomy and laparoscopic partial nephrectomy with greater aptitude and increasing frequency than otherwise possible using standard laparoscopic tools.

Conclusions

Current evidence supports surgical resection of RCC and recognizes an advantage for NSS and minimally invasive approaches over open radical nephrectomy. The increasing presentation of incidental RCC enables a greater proportion to be amenable to open partial nephrectomy or laparoscopic partial nephrectomy. NSS should be an equally emphasized objective of RCC treatment to minimize the renal function loss resulting from radical nephrectomy, which is a recognized risk factor for noncancer cardiovascular-related mortality.[48] With increasing surgeon experience and aided by new technology, such as the daVinci system, a greater proportion of NSS treatments should be possible in the future using laparoscopic partial nephrectomy, offering the potential for surgical results similar to those of open partial nephrectomy and reduced morbidity.

For tumors not amenable to NSS because of either size or location, radical nephrectomy remains an appropriate option but should be preferentially performed using laparoscopic radical nephrectomy because of its lower morbidity compared with the open techniques. Open radical nephrectomy should be limited to extremely large primary tumors or RCC with significant locally advanced disease.

Lastly, for patients who are poor surgical risks or in whom surgery is contraindicated, active surveillance may be preferable. Active surveillance seems to show equivalent outcomes to excision and ablation for small renal masses during the first 24 to 36 months after diagnosis, while avoiding treatment-related

morbidity. Tissue-ablative treatment, with limited long-term efficacy data, may be an option in highly selected patients.

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Nephrectomy for Renal Cell Carcinoma

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1. Which of the following is currently considered the most likely presentation of renal cell carcinoma (RCC)?
   A. Hematuria
   B. Flank mass
   C. Incidental finding
   D. Weight loss
2. Which of the following procedures in open radical nephrectomy is considered most likely to improve outcomes in patients with localized RCC compared with nephrectomy alone?
   A. Perinephric tissue removal
   B. Ipsilateral lymphadenectomy
   C. Ipsilateral adrenalectomy
   D. All of the above
3. Which of the following laparoscopic radical nephrectomy approaches is associated with the best outcomes for localized RCC?
   A. Transabdominal
   B. Retroperitoneal
   C. Hand-assisted
   D. Similar outcomes for all
4. Which of the following procedures is suggested to be the new gold standard treatment for RCC due to improved short-term outcomes?
   A. Laparoscopic radical nephrectomy
   B. Nephron-sparing surgical resection
   C. Open partial nephrectomy
   D. Laparoscopic partial nephrectomy
5. Which of the following best describes the rate of local tumor recurrence associated with cryoablation and radiofrequency ablation (RFA) compared with open partial nephrectomy for the treatment of RCC?
   A. Both 7.5 times higher
   B. Both 18 times higher
   C. 7.5 times higher for cryoablation and 18 times higher for RFA
   D. 7.5 times higher for RFA and 18 times higher for cryoablation

Activity Evaluation

1. The activity supported the learning objectives.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
2. The material was organized clearly for learning to occur.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
3. The content learned from this activity will impact my practice.
   Strongly Disagree 1 2 3 4 5 Strongly Agree
4. The activity was presented objectively and free of commercial bias.
   Strongly Disagree 1 2 3 4 5 Strongly Agree

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