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Optimal management of localized renal cell carcinoma: Surgery, Ablation or Active Surveillance

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Abstract

Radical nephrectomy is historically accepted as the standard treatment for localized renal cell carcinoma (RCC). However, the presentation of RCC has changed dramatically over the last three 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.

Keywords

renal cell carcinoma; treatment; surgery; ablation; surveillance

INTRODUCTION

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 deaths resulted from RCC.[1] Historically presenting with symptoms such as a palpable flank mass, hematuria, pain, or weight loss, the majority of today's cases are identified by chance. This change is attributed to the increased frequency of cross-sectional diagnostic imaging, and an asymptomatic, incidental renal mass now accounts for at least 48–66% of RCC diagnoses.[2] Over the last three decades, there has been a steady increase in the incidence of RCC with downward stage migration, and a matching increase in the rate of RCC interventions.[3]

An evolution of treatment options has accompanied this differing presentation of RCC. Surgery remains the mainstay of treatment for localized RCC, although open radical nephrectomy (ORN) arguably is no longer the gold standard. ORN 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. We compare the data regarding these treatments and the role for each intervention.

OPEN RADICAL NEPHRECTOMY

Robson is credited with establishing ORN 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

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with those undergoing the prior practice of pericapsular nephrectomy and made ORN results the benchmark for comparison with later treatments.[4] For patients of the pre-CT era who would present with symptoms of advanced RCC, these elements of ORN were needed.

Based on Robson's experience and other follow-up studies, ORN 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 ORN 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 those components have no clearbenefit over nephrectomy alone for treating localized renal masses in the absence of abnormal imaging (ie, adenopathy or adrenal mass), and these features of the operation are now performed selectively.[5, 6]

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

LAPAROSCOPIC RADICAL NEPHRECTOMY (LRN)

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 ORN, this approach initially met with great resistance from the general urologic community. In the years since its first report, LRN has gained acceptance as equivalent to ORN, supported by favorable long-term outcomes. Although not directly compared in randomized prospective trials, multiple retrospective studies have shown the efficacy of LRN to be equal to ORN (Table 1).

Although overall patient outcomes are similar for ORN and LRN, the latter, because it is minimally invasive, shows better perioperative parameters such as decreased blood loss and hospital length of stay, as well as a reduction in morbidity with less pain and more rapid patient convalescence.[10, 11] With surgeon experience, LRN is possible for nearly all organ-confined RCC that would traditionally undergo ORN; LRN has been successfully completed with very large but localized tumors and in patients who have undergone prior surgery.[12, 13] Although through a different surgical approach, LRN fulfills the basic tenets of ORN and can fully replicate its critical principles. Although the LRN approach can be either transabdominal, retroperitoneal, and hand-assisted, these different methods show similar results.[14, 15]

In summary, LRN demonstrates equal outcomes for RCC as ORN, but offers the patient the advantage of lower blood loss, shorter hospital stay and pain medicine requirements, improved cosmesis, and faster return to work and normal activities. These short-term benefits with similar long-term results make LRN is clearly preferable to ORN, and it has been suggested to be the new gold-standard treatment.[16]

NEPHRON-SPARING SURGICAL (NSS) RESECTION

The development of LRN has occurred concurrently with advances in 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 today found asymptomatic, relatively small, and localized; and 2) sensitive modern imaging, which can show in detail the anatomic relationships between tumor and adjacent normal tissue. OPN 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 OPN has been conducted for more relative indications, such as for patients with a unilateral tumor and baseline renal insufficiency, or having concurrent medical disease such as renal artery stenosis, hypertension or diabetes. In this population, OPN has been applied in order to reduce the potential of developing future renal failure. From these initial scenarios where dialysis is an immediate or future risk, OPN 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 OPN 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 OPN with similar results.[20, 21]

OPN, when compared with ORN or LRN, is a more complex operation demanding advanced surgical skills. OPN 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, as prolonged ischemia time is recognized to affect renal function recovery.

Because of its greater complexity, OPN has a higher rate of complications, most often involving hemorrhage, urinary fistula formation, ureteral obstruction, acute renal insufficiency, and infection.[18] Compared with ORN and LRN, which have estimated overall complication rates of 10–20%, OPN has a reported complication rate as high as 30%, although this is suggested to lessen with time and greater clinical volume. At experienced centers, the complication rate for ORN, LRN and OPN are all generally similar (10–15%).[18, 22] Although the risk for complication with OPN is influenced by surgeon experience and patient medical condition, additional factors impacting the potential for postoperative complication include tumor size and location, which dictate the complexity of resection. More difficult tumors to successfully perform NSS are larger (> 4 cm), located centrally or at the renal hilum, and the risk of complications may be considerably higher.

To reduce the morbidity of OPN, LPN has been performed and offers a minimally invasive approach for NSS. However, LPN has been infrequently conducted given its added complexity. This procedure is more demanding than either LRN or OPN and can challenge even skilled and experienced laparoscopic surgeons. With traditional laparoscopic instrumentation, LPN is recognized to be particularly difficult regarding the reconstruction and closure of the kidney defect. Few centers have significant clinical experience with LPN. Its early and intermediate oncologic outcomes appear similar to OPN, 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, OPN or LPN can be considered for any patient with any indication for renal preservation. OPN has been advocated as the preferred treatment for localized RCC given its equivalent oncologic outcomes and its benefit of preserving the uninvolved kidney.[20] For masses less than 4 cm, which are found benign or indolent in 20–30% of cases,[25, 26] OPN also addresses the risk of 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 shows improved long-term overall survival because of lower renal morbidity in patients who undergo OPN compared with those who undergo radical nephrectomy, suggesting that total nephrectomy is ultimately deleterious.[19, 28] These results show OPN and LPN for localized RCC provide unique benefits and may be superior to radical nephrectomy. Although

NSS may potentially have a higher rate of complications, OPN or LPN should be initially considered in the treatment of incidental RCC when technically feasible.

TISSUE ABLATIVE THERAPY—RADIOFREQUENCY ABLATION (RFA)/CRYOABLATION

Because OPN and LPN 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 less 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. 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 id-1990's.[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 via 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 OPN or LPN.

Although these approaches are appealing given their relative ease of performance, favorable patient tolerance, and perceived low risks, they have several limitations and disadvantages. As there is a fixed area of ablation beyond each probe, these treatments are best suited for smaller renal masses (<3 cm), whereas larger tumors require multiple probes and have a greater risk of incomplete ablation. Because these approaches do not provide complete pathologic staging, the ability to estimate prognosis is imperfect and based primarily upon the results of a percutaneous biopsy, whose accuracy with RCC remains 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 OPN, with a short median follow-up period of only 16–18 months, showed cryoablation associated with a 7.5-fold increased risk of local recurrence and RFA an 18-fold increased risk (Table 2). Although a few single-institution series do 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 surgical resection is particularly high-risk or contraindicated.

ACTIVE SURVEILLANCE (AS) 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 the RCC and overall death rates have paradoxically also increased.[37] These and other data suggest that many incidentally detected RCC may not be aggressive or lead to mortality and, contrary to traditional belief, may not require treatment.[38] Several retrospective series of AS have suggested the behavior of small renal masses is mostly indolent, with the average growth being roughly 3 mm/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 AS is the risk for progression to metastatic disease; in a recent meta-analysis, that occurrence during AS with a mean follow-up of nearly 3 years was quite low and is equivalent to that for patients who were treated with definitive excision or ablation.[41]

AS 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 AS 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 co-morbid 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

ORN remains the most frequent RCC treatment, occurring in roughly 70–90% of recent US cases, suggesting overuse.[43] Although situations remain in which a renal mass requires treatment using ORN because of its size or complexity, this intervention should occur less commonly in the future given currently available and preferable alternatives. LRN and OPN 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 LRN or OPN instead of ORN 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, LRN 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 LRN since its introduction in 2003 showed that after 13 years, this procedure was used to treat fewer than 15% of RCC cases in the US.[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 LRN's greater complexity, the learning curve for LRN remains a considerable barrier to greater application.

Although OPN 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 OPN or LRN over ORN, ORN remains the most common treatment because most urologists are unable or reluctant to proceed with any alternative.

Perhaps the ideal definitive treatment might be LPN, combining the advantages of OPN and LRN, 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 LPN 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 LPN, showing operative parameters such as renal ischemia time, blood loss, and complications to be similar or better than OPN,[46] and the use of this tool will probably hasten LPN adoption in the future.

For example, with the daVinci system, radical prostatectomy in the US 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 LRN and LPN 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 ORN. The increasing presentation of incidental RCC enables a greater proportion to be amenable to OPN or LPN. 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 treatment should be possible in the future using LPN, offering the potential for similar surgical results similar to those of OPN and reduced morbidity.

For tumors not amenable to NSS due to either size or location, radical nephrectomy remains an appropriate option but should be preferentially performed using LRN because of its lower morbidity compared with the open techniques. ORN 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, AS may be preferable. AS seems to show equivalent outcomes to excision and ablation for small renal masses during the first 24–36 months after diagnosis, while avoiding treatment-related morbidity. Tissue-ablative treatment, with limited long-term efficacy data, may an option in highly selected patients.

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Table 1

Outcomes for surgery for localized stage I RCC

ORN efficacy—Author (year)	n	% 5-yr 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)	**n**	**% 5-yr survival**
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)	**n**	**% 5-yr survival**
Jacobs et al[55] (1980)	51	84%
Morgan & Zincke[56] (1990)	104	89%
Belldegrun et al[57] (1999)	146	93%

Table 2

Collective published data on management of patients with small renal masses. (Adapted from Kunkle et al 2008[41])

	OPN	Cryoablation	RFA	AS
Case Series (N)	40	16	19	9
Total Tumors (N)	4583	406	521	315
Mean f/u (months)	54.0	18.3	16.4	33.3
Risk of 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.