Robotic nephron-sparing surgery for renal tumors: Current status

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ABSTRACT

There have been a number of advances in robotic partial nephrectomy (RPN) for renal masses. We reviewed these advances with emphasis on the evolution of technique and outcomes as well as the expanding indications for RPN. Literature in the English language was reviewed using the National Library of Medicine database. Relevant articles were extracted, and their citations were utilized to broaden our search. The identified articles were reviewed and summarized with a focus on novel developments. RPN is an evolving procedure and is an emerging viable alternative to laparoscopic partial nephrectomy and open partial nephrectomy with favorable outcomes. The contemporary techniques used for RPN demonstrate excellent perioperative outcomes. The short-term oncologic outcomes are comparable to those of laparoscopic and open surgical approaches. Further studies are needed to assess long-term oncologic control.

Key words: Outcomes, partial nephrectomy, renal cell carcinoma, robotic surgery

INTRODUCTION

Over the last two decades, the incidence of renal cell carcinoma (RCC) has increased annually by 2% in North America and Europe,\textsuperscript{[1,2]} primarily reflecting an increase in the incidental detection of small renal masses (SRMs) by abdominal imaging.\textsuperscript{[3,4]} Approximately, 75% of newly diagnosed renal masses are asymptomatic, incidentally detected and <4 cm in size.\textsuperscript{[5]}

The current treatment options for SRMs include active surveillance, partial nephrectomy (PN), ablative techniques and rarely, radical nephrectomy (RN).\textsuperscript{[6]} The decisions regarding the optimal treatment of incidentally diagnosed SRMs are complex and depend on tumor characteristics, including size, location and local or distant spread, and on patient factors, including age, comorbidities, renal-function, and preference.

Active surveillance is reserved for SRMs in patients with limited life expectancy and multiple comorbidities.\textsuperscript{[6-8]} Thermal ablation (TA) techniques, including cryoablation and radiofrequency ablation, have emerged as alternative nephron-sparing treatments for SRMs.\textsuperscript{[9,10]} However, the long-term efficacy of TA is unknown, and a recent worldwide analysis suggests that the local SRM recurrence rate may be higher than those of PN and RN.\textsuperscript{[11]} Historically, clinically stage I renal masses have often been treated with RN.\textsuperscript{[12]} However, the increased recognition of chronic kidney disease (CKD) as a worldwide public health problem and an independent risk factor for cardiovascular events, hospitalization and death\textsuperscript{[13]} has led to the increased use of nephron-sparing surgery, which is performed with the ultimate goal of achieving the PN “trifecta” that is, negative surgical margins, functional preservation and complication-free recovery.

The recently published prospective randomized phase three trial from the European Organization for Research and Treatment of Cancer and several other large retrospective nonrandomized studies have shown comparable oncologic efficacy for PN and RN in the treatment of low-stage renal tumors.\textsuperscript{[14-17]} Nephron-sparing surgery is now accepted as a standard of care for most stage T1a renal masses.\textsuperscript{[6]}
Although open PN (OPN) remains the reference standard for clinically localized cases,[18] laparoscopic PN (LPN) has recently emerged as a viable, minimally invasive approach that provides similar intermediate oncologic outcomes and faster postoperative recovery compared with open surgery.[19] Recently, robotic PN (RPN) has emerged as an alternative to LPN. Given the enhanced dexterity and three-dimensional vision afforded by the robotic platform and the relatively shorter learning curve compared with LPN,[20] a rapidly increasing number of PNs are being performed robotically. Worldwide, in 2008, RPN was the fastest growing robotic procedure among all surgical specialties.[21] Subject to the availability of the technology and expertise, it is also becoming the technique of choice for treating most stage T1a tumors. In addition, its feasibility has been demonstrated for highly complex renal masses.[22] This review summarizes the current status of RPN, focusing on the evolving indications, technical advancements, and current outcomes data.

INDICATIONS FOR PARTIAL NEPHRECTOMY

Although the traditional absolute indications for PN include bilateral tumors, renal insufficiency, and a solitary functional kidney, extensive data indicate equivalent cancer-specific and metastasis-free survival between patients treated with PN and RN for T1a lesions.[23,24]

The indications for nephron-sparing surgery now encompass most tumors <4 cm in patients with a normal contralateral kidney. Furthermore, Leibovich et al. demonstrated the oncological equivalency of treating T1b tumors with PN, which provided a 5-year cancer-specific survival (CSS) of 98% for tumors 4–7 cm in size.[25]

Partial nephrectomy has also been endorsed by the American Urological Association as the treatment of choice for clinical stage T1a and selected T1b renal tumors.[6]

Patients considered for PN should be evaluated with high-quality cross-sectional triphasic abdominal computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI), chest radiography, and serum chemistries including electrolytes, renal-function and liver-function tests, and coagulation studies.

PARTIAL NEPHRECTOMY FOR T1B TUMORS

Although most urologists and guideline committees currently support elective PN for T1a tumors, the expansion of PN to larger tumors (T1b/T2) has been increasingly advocated by many to optimize renal preservation. There are also lifelong concerns about tumor formation (2–5%) in the contralateral kidney.[26] The expansion of elective PN to T1b and T2 tumors is subject to important selection factors, including patient age and medical condition, tumor location and proximity to critical structures and the experience of the surgeon.

Over the last decade, PN has generally been favored, with many believing that PN should be performed whenever technically feasible, even for larger tumors in the presence of a normal contralateral kidney. For T1b renal masses, PN and RN result in equivalent cancer-specific outcomes.[25,27–31] In the largest study to date, Badalato et al. analyzed a retrospective dataset that included 11,256 patients who underwent PN and RN for T1b masses, with 1047 who underwent PN, with a median follow-up of approximately 3 years. After controlling for several factors, no difference was found in CSS or overall survival between the PN and RN treatment groups. Stratification by tumor size and patient age did not affect the findings.[27] Lane and Gill reported the long-term oncological outcomes of LPN and OPN for T1 tumors; at 7-year, the CSS for T1a tumors was 95% in both cohorts. In addition, both procedures resulted in similar 7-year CSS for T1b tumors.[32]

We believe that RPN should be performed for carefully selected T1b or larger tumors that are technically amenable. The tumor size alone does not fully reflect its complexity. Furthermore, these procedures should be performed at a center of excellence by an experienced robotic surgeon.

ROBOTIC PARTIAL NEPHRECTOMY

Despite advances in LPN, it has not been universally embraced due to the technical demands it places on the surgeons. The limited degree of freedom of nonarticulating laparoscopic instruments makes tumor excision and reconstruction under the time constraints of warm ischemia demanding. RPN overcomes this technical deterrent and facilitates adoption of minimally invasive PN among urologists compared with LPN.

A number of published reports have demonstrated the safety and feasibility of RPN for hilar, completely endophytic and multiple tumors.[33,34] Even in the setting of a solitary kidney, where the preservation of renal-function was previously thought to be best achieved by an open procedure,[35] novel techniques that minimize or completely eliminate warm ischemia time (WIT) have enabled RPN to be performed safely with excellent functional results.[36,37]

A transperitoneal or retroperitoneal approach is chosen depending on the tumor location, patient surgical history and surgeon preference [Figures 1 and 2]. The transperitoneal approach is the most widely used for RPN. Although safe and effective when performed by an experienced surgeon, the retroperitoneal approach is potentially more challenging because of its confined workspace and relatively fewer anatomic landmarks.[38] In addition, this procedure is unforgiving in the event of bleeding and large amounts of sticky fat.
The retroperitoneal approach is best suited for posteromedial tumors and a hostile peritoneal cavity. It has several advantages over the transperitoneal technique. The retroperitoneal approach avoids bowel manipulation and allows direct exposure of the renal hilum. The relative contraindications of this approach include prior major retroperitoneal surgery, dense perirenal inflammation/fibrosis, musculoskeletal limitations that preclude proper positioning, large tumors with extensive collaterals and abundant perinephric fat with extensive stranding.

WARM ISCHEMIA TIME

An important consideration in evaluating surgical options for RCC is WIT. Traditionally, during PN, the renal hilar vessels are clamped before tumor excision. In contrast to OPN, which is often performed under renal hypothermia to minimize ischemic insult to the clamped kidney, minimally invasive techniques for achieving renal hypothermia during renal hilar clamping have failed to achieve widespread application.

Although the exact WIT threshold beyond which irreversible kidney injury occurs is controversial, <30 min of WIT has long been postulated to provide acceptable postoperative kidney function, as demonstrated by the glomerular filtration rate (GFR). In a single-institution series of 102 patients who underwent LPN or RPN, Wang and Bhayani reported a decreased WIT (19 vs. 25 min) and shorter hospital stay (2.5 vs. 2.9 days) for the RPN cohort, but no difference in complication rates between the two groups. A recent multicenter analysis that examined surgical outcomes for three experienced robotic surgeons showed significantly shorter WIT for RPN compared with LPN (19.7 vs. 28.4 min, \( P < 0.0001 \)). This study showed that RPN had a benefit with respect to WIT, even with complex tumors (25.9 min for RPN vs. 36.7 min for LPN). Furthermore, the authors demonstrated that in patients who required collecting system repair or had multiple tumors, the mean WIT was still <30 min. For tumors > 4 cm, the patients had a significantly longer WIT compared with patients with a tumor size <4 cm, but once again, both groups had <30 min of WIT.

With the recognition of the potential impact that even a short duration of WIT may have on renal function, variations in surgical technique have been attempted to minimize or eliminate ischemic insult to the kidney. One such technique is early-unclamping, which involves releasing the hilar clamp after controlling the transected intrarenal blood vessels within the sinus fat. Thus, parenchymal reconstruction (cortical approximation) is performed off-clamp. The early-unclamping technique resulted in a 50% reduction in ischemia time (31 vs. 14 min).

Further pushing the envelope, a novel “zero-ischemia” technique has been developed to eliminate global renal ischemia. In this technique, the surgeon identifies and controls only the tertiary or higher-order arterial branches that feed the “tumor plus margin”, and thus, no ischemia is experienced by the renal remnant. After devascularizing the tumor in a highly selective manner, RPN is performed while maintaining an uninterrupted blood flow to the rest of the kidney. Neurosurgical micro bulldog clamps can be used if needed to control the specific arterial branches feeding the tumor. In a study of 100 patients who underwent anatomical zero-ischemia PN, the median operative time (OT) was 275 min, the estimated blood loss was 200 mL, and 20% of the kidney was excised; all the patients had negative tumor margins. These early data support the safety and feasibility of the zero-ischemia approach.

Reports of zero-ischemia RPN from other institutions indicate that the technique is reproducible by surgeons with expertise in minimally invasive kidney surgery.
TECHNICAL CONSIDERATIONS

Functional preservation

From a technical perspective, PN is among the most challenging procedures undertaken by urologists. PN outcomes are ultimately dictated by surgically modifiable and nonmodifiable factors. Nonmodifiable factors refer to the quality and quantity of the nephrons, and the kidney quantity that can be preserved depends on tumor characteristics including size, location and depth. Surgically modifiable factors include the ischemia duration, surgical margin width, maximal preservation of vascularized parenchyma by eliminating deep sutures and technical imprecision leading to complications.

The volume of the preserved renal parenchyma fundamentally determines postoperative renal function. Accordingly, it is important for surgeons to minimize the amount of kidney tissue excised during nephron-sparing surgery by adopting the “minimal margin” or even an “enucleation” approach. Renal tumor enucleation is a nephron-sparing technique in which the tumor is excised by dissection in the natural plane between the peritumor pseudocapsule and the renal parenchyma, without removing a visible rim of normal parenchyma. Significant data support this approach as an oncologically sound procedure. Preoperative assessment with high-quality cross-sectional CT is crucial for planning tumor excision. Real-time intraoperative ultrasonography is an important adjunct, as it can accurately delineate the tumor from the normal kidney. The stereoscopic visualization and enhanced dexterity afforded by the robotic platform facilitate a tightly contoured tumor excision.

Super-selective arterial clamping in anatomic partial nephrectomy

The anatomic PN technique is built on the “artery first, tumor second” philosophy. This concept underlies seminal technical innovations such as vascular micro-dissection (VMD), in which the specific arterial branch(es) feeding the tumor is (are) identified. Using the patient’s preoperative three-dimensional CT arteriogram as a roadmap, VMD is performed radially from the hilum outward to identify the specific arterial branch(es) supplying the tumor. A radial nephrotomy incision may be required to carry the dissection intrarenally; in these instances, defining the parenchymal surface where the vessels enter as the starting point is critically important. Mini vessel loops can be used to encircle higher-order vessels as dissection proceeds. Neurosurgical aneurysm micro bulldog clamps (Bear™ disposable vascular clamps) are applied to achieve tumor-specific devascularisation. The preservation of the perfusion of all the nontumor-bearing parenchyma is confirmed with color Doppler ultrasonography or intravenous indocyanine green when a robot with infrared visualization is employed. Tumor excision is performed with a combination of electrocautery and cold scissors. Hem-o-lok clips® (Weck Surgical Instruments, Teleflex Medical, Durham, NC) are applied to small vessels projecting into the tumor from the resection bed, and these clips are ultimately under-sewn to prevent their migration into the pelvicalyceal system (PCS). Any PCS entry is repaired in a water-tight fashion. Recognizing that indiscriminate whip-stitching of the PN bed may induce ischemia in the underlying normal parenchyma, only point-specific hemostatic suturing is performed. Typically, no surgical bolster is required, thereby eliminating potential pressure ischemia on the renal remnant. Clearly, this anatomic approach lends itself well to complex, perihilar tumors. However, tumors located at a significant transparenchymal distance from the hilum, particularly those with a large parenchymal contact surface area, are generally unsuitable for this technique.

Minimal margin partial nephrectomy

Super-selective arterial clamping, as described above, transforms hilar-unclamped, minimally invasive PN into a clean and controlled procedure. However, this technique maintains a controlled environment, even during the total elimination of vascular clamping and minimal volume loss. We recently adapted our technique with these features in mind, rendering both hilar preparation and VMD with micro bulldog application unnecessary in many cases. The technique is still grounded in anatomic concepts. Specifically, we propose the following: (1) The natural architecture of the kidney and its vasculature is radially oriented; (2) this architecture is largely preserved in the setting of neoplastic growth if the tumor is well-encapsulated; (3) the parenchyma immediately adjacent to the tumor is histologically altered, perhaps by compressive effects exerted by the tumor; and (4) the vessels in this histologically altered zone are generally smaller in caliber. Therefore, the most amenable resection plane for a totally unclamped PN is very close to the pseudocapsule, which we termed the “minimal margin” plane. Notably, this term does not refer to the final pathologic margin width but rather to our intent to excise the tumor along the closest plane dictated by the natural kidney architecture.

In technical terms, minimal margin PN begins with a radial nephrotomy tangential to the tumor. Being radially oriented, this initial incision should be relatively bloodless. Using a fine spreading motion with robotic forceps, the natural radial plane adjacent to the tumor is developed bluntly. The plane is extended superficially in a circumferential manner and then deepened with a combination of blunt dissection, in which the tumor is gently nudged off the parenchyma using the backside of the robotic forceps, and high power electrocautery (cautery setting at 100 W), which controls small vessels near the tumor. Larger vessels projecting into the tumor are defined and controlled with Hem-o-lok clips. If the tumor is not sufficiently mobilized off the parenchymal bed to dissect out these vessels, both clip placement and suture ligation will fail. In this instance,
the vessel is transected to further release the tumor, and the bedside assistant’s suction apparatus is used to compress the vessel until suturing is performed. As such, having two available suction apparatuses is prudent: One for judicious suction and irrigation and one for compression only. Once the tumor is completely excised, point-specific hemostatic suturing and PCS repair are performed as needed. Bolster application is rare. The minimal margin technique is most applicable to perihilar and polar exophytic tumors; treating peripheral tumors with large contact surface areas remains challenging with this approach.

**RENAL FUNCTION AFTER PARTIAL NEPHRECTOMY**

As discussed above multiple factors influence renal function after PN, including baseline function, amount of parenchyma preserved, and WIT. These factors have recently been the focus of debate as well as intense clinical and laboratory research.

Critics of segmental ischemia techniques note that post-PN functional outcomes are driven by remnant kidney volume and baseline kidney function, not WIT. We agree that kidney volume and quality are the fundamental determinants of ultimate function. However, the following points merit attention. First, WIT is important; a multivariate analysis that adjusted for volume and quality factors showed that a WIT of 25 min was significantly associated with acute kidney injury and new-onset stage IV CKD (CKD; hazard ratio = 2.27; P = 0.049). Second, the kidney volume excised and WIT are inherently correlated: More complex tumors predict greater volumes of excised kidney and longer WITs. Third, kidney volume and quality are largely determined by tumor characteristics, patient characteristics, or both; therefore, they are surgically nonmodifiable to a large extent. Conversely, WIT is definitely modifiable via surgery.

From our perspective, it is difficult to determine whether preserving more kidney parenchyma or minimizing ischemia is more important because each factor affects the other.

During larger kidney resections, a greater volume of parenchyma is removed and the ischemia time is longer. Currently, the ultimate goal is to both preserve more kidney parenchyma and minimize ischemia.

**COMPLICATIONS OF ROBOTIC PARTIAL NEPHRECTOMY**

As minimally invasive techniques in PN have evolved, procedural complications have decreased, and the complication rates in contemporary RP series, even those including large, complex tumors, remain low (8.6–20.0%).

In a single-institution series of 102 patients who underwent LPN or RPN, Wang and Bhayani reported a decreased WIT (19 vs. 25 min) and shorter hospital stay (2.5 vs. 2.9 days) for the RPN cohort but no difference in complication rates between the two groups. A recent study comparing 118 patients who underwent LPN with 129 patients who underwent RPN also found similar rates of postoperative complications between study arms (10.2% vs. 8.6%). In a multi-institutional study of 450 patients who underwent RPN, complications were stratified using the Clavien-Dindo classification system. Overall, 71 patients experienced a complication (16%), with 8 intraoperative and 65 postoperative complications; 54 complications were classified as Clavien Grade I or II (12%), which required conservative management only, whereas 17 were Clavien Grade III or IV (4%) and necessitated subsequent intervention.

The rates of postoperative hemorrhage after minimally invasive PN are relatively low (<5%) and are similar between laparoscopic and robotic series, with a rare need for angioembolization (0.4%). The majority of delayed postoperative hemorrhages arise from arterial pseudoaneurysms or the formation of arteriovenous fistulas. As expected, with increasing tumor centrality and the involvement of major vascular structures during resection, the risk of vascular anomalies also increases. Angioembolization can readily control the source of postoperative PN hemorrhage if recognized quickly and can obviate the need for operative re-intervention, which carries a significant risk of RN. In any patient who presents with postoperative bright red hematuria, significant anemia or hemodynamic instability after PN, a high index of suspicion and a low threshold for angiointervention are necessary.

Several techniques have been used during LPN and RPN to improve hemostasis and reduce the risk of postoperative hemorrhage. These methods include the use of a deoxidized cellulose bolsters during renorrhaphy to provide compressive hemostasis; the use of a gelatin matrix thrombin sealant, which has been reported to reduce postoperative hemorrhage from 11.8% to 3.2%; the use of “sliding-clip” renorrhaphy, which involves the application of Hem-o-lok® clips to the reconstruction sutures to provide the appropriate tension to the kidney repair; and the use of barbed V-Loc® sutures (Covidien, Mansfield, MA) during reconstruction, which allow the even distribution of tension across the surgical bed to control transected vessels and reduce the likelihood of postoperative bleeding.

Anatomical zero-ischemia PN can minimize the bleeding risk because it permits the methodical identification of feeding vessels with individual, point-specific suture ligation. Because the kidney remains perfused during resection, there is no time constraint for ischemia. Tumor resection can proceed deliberately with the specific control of individual blood vessels as they are encountered, enabling continuous
hemostasis assessment. By intentionally minimizing the amount of normal parenchyma resected, the entry into larger renal blood vessels is reduced.

Urine leakage is a recognized PN complication, but its incidence remains low. In the largest series performed to date comparing LPN with OPN, urine leakage was comparable between the groups (3% and 2.3%, respectively). Several RPN series with smaller cohorts have shown urine leakage rates of 1.6–2.3%, similar to those obtained with laparoscopic procedures. Predictors of postoperative urine leakage include tumor centrality, tumor size, collecting system entry, and a higher nephrometry score.

Several techniques can reduce the risk of urine leakage. A retrograde ureteral catheter can enable methylene blue injection to identify urine leakage and aid its visualization during water-tight repair. This method is particularly useful for central tumors and those necessitating large resections, such as heminephrectomy. Alternatively, the collecting system can be closed by mechanical compression with a bolstered renorrhaphy, without a ureteral catheter. If urine leakage occurs, most cases can be managed conservatively. Persistent or clinically symptomatic urine leakage can be addressed with ureteral stenting or percutaneous urinoma drainage. A percutaneous nephrostomy tube may be required in recalcitrant cases for better proximal diversion.

LIMITATIONS OF ROBOTIC PARTIAL NEPHRECTOMY

Despite the many advantages of the robotic platform, some limitations remain. First, there is loss of tactile feedback, which might result in tissue trauma or suture breakage, an issue that is particularly pertinent for surgeons with limited experience. However, the loss of haptic feedback can be overcome using learned visual cues. Currently, efforts are underway to develop methods of providing feedback through grip force, potentially allowing haptic information integration in the future.

Despite the widespread adoption of robotic surgery in the United States, there has been a more tempered acceptance of the robotic platform throughout the rest of the world. The higher costs associated with robotic surgical systems largely account for their limited adoption. However, the purported benefits of robotic surgery, including widespread applicability for surgeons, operative efficiency, decreased hospital stays and minimal complications, might translate into lower overall costs to the hospital.

TRIFECTA OUTCOMES

The concept of a “trifecta” outcomes of robotic or LPN has been recently introduced. These outcomes are negative tumor margins, functional preservation and no urologic complications. Trifecta outcomes were evaluated in 534 patients who underwent RPN or LPN for renal tumors over a 12-year period. The patients were divided retrospectively into four chronological eras, referred to as the discovery era (September 1999 to December 2003; n = 139), the conventional hilar-clamping era (January 2004 to December 2006; n = 213), the early-unclamping era (January 2007 to November 2008; n = 104) and the zero-ischemia era (March 2010 to October 2011; n = 78). Renal-function decline was defined as a >10% estimated GFR reduction, as predicted after surgery based on the kidney percentage preserved, which was subjectively assessed by the surgeon during the procedure after tumor excision. Over the four eras, the tumors trended toward being larger (2.9, 2.8, 3.1 and 3.3 cm for the discovery, conventional hilar-clamping, early-unclamping and zero-ischemia eras, respectively; P = 0.08), but the estimated percentage of kidney preserved was similar (89%, 90%, 90%, and 88%, respectively; P = 0.3). More recent eras were associated with increasingly complex tumors than earlier eras, with tumors more likely to be >4 cm in size (P = 0.03), centrally located (P < 0.009) or hilar (P < 0.0001). Nevertheless, the WITs decreased serially at 36, 32, 15 and 0 min, for the discovery, conventional hilar-clamping, early-unclamping and zero-ischemia eras, respectively (P < 0.0001). The renal-function outcomes were superior in the contemporary eras, with fewer patients experiencing declines (P < 0.0001). The negative tumor margin rates were uniformly low (P = 0.7), and urologic complications tended to be fewer in the more recent eras (P = 0.01). Trifecta outcomes were achieved more commonly in the recent eras and were 45%, 44%, 62%, and 68% for the discovery, conventional hilar-clamping, early-unclamping and zero-ischemia eras, respectively (P = 0.0002). The authors concluded that despite increasing tumor complexity, the trifecta outcomes of RPN and LPNs improved significantly over the past decade. Thus, the trifecta should be a routine goal during PN surgery.

CONCLUSIONS

Robotic partial nephrectomy is a welcome extension of LPN, and it represents a viable alternative to laparoscopic and open surgery. The use of robotic assistance can also aid surgeons with limited laparoscopic experience, given the shorter learning curve. Published series of RPN have demonstrated that it is safe and feasible, with perioperative outcomes comparable to laparoscopic and open surgical approaches. In addition, short-term analyses of functional and oncologic outcomes demonstrate comparable results. Further studies are needed to assess long-term oncologic control. The experience with RPN is likely to grow and mature with the aim of providing the trifecta outcomes of negative tumor margins, minimal renal-function decrease and no urologic complications.
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