Robot-assisted renal tumor enucleo-resection in patients with a solitary kidney

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CALAWAY AC, GUPTA GN, BHANDARI A, EUN D, BORIS RS. Robot-assisted renal tumor enucleo-resection in patients with a solitary kidney. *Can J Urol* 2015;22(4):7907-7913.

Introduction: *Nephron-sparing surgery is most crucial for patients with a small renal mass in a solitary kidney. Historically, a minimally invasive approach in this setting has been discouraged. Tumor enucleo-resection, long established in the management of hereditary renal tumor syndromes, is currently being evaluated as a viable surgical technique in the sporadic renal cell carcinoma (RCC) population. This approach may significantly reduce or eliminate the need for hilar clamping. We sought to evaluate our experience with robot-assisted enucleo-resection partial nephrectomy (EN-RAPN) in patients with solitary kidneys.*

Materials and methods: *Records of patients with a solitary kidney requiring partial nephrectomy performed with robot-assisted enucleo-resection technique at four academic institutions between 2010 and 2013 were reviewed. Baseline demographic, perioperative and pathological data were collected. Functional and early operative outcomes were analyzed.*

Results: *Twelve patients underwent EN-RAPN with a median age of 68 years (range 55-80) and follow up duration of 12.55 months (IQR: 5.25, 18.88). Median warm ischemia time was 5.5 minutes (IQR: 0, 13.25) with 6/12 (50%) done off-clamp (zero warm ischemia). Ten (83.3%) patients were pT1a and clear cell was the predominant pathology (9 patients, 75%). Surgical margins were negative in all patients. No patient experienced renal loss or required dialysis. Pre and postoperative estimated glomerular filtration rate (eGFR) at last follow up was similar (54.3, 48.9, Δ-7.0%; p = 0.313).*

Conclusions: *Robot-assisted enucleo-resection partial nephrectomy in patients with a solitary kidney appears safe and feasible in our early experience. This approach may be utilized to maximize renal preservation and minimize hilar clamping in this setting.*

Key Words: solitary kidney, robotic surgery, partial nephrectomy, enucleo-resection

Introduction

Nephron-sparing surgery in patients with small renal masses has become the gold standard surgical intervention. The benefits of renal parenchyma preservation with improved long term renal function have been championed without compromise to oncological outcomes. The presence of a small renal mass in a solitary kidney is an absolute indication for nephron-sparing surgery to limit the morbidity associated with renal replacement therapy.

Historically, open partial nephrectomy (OPN) has been the recommended surgical approach for this challenging patient population supported by maximal preservation of renal function using cold ischemia while maintaining encouraging long term cancer-free survival.[1] More recently, however, studies have investigated the role of minimally invasive surgical approaches for this high risk cohort.[2-8] Although safety and feasibility of robotic-assisted partial nephrectomy (RAPN) in patients with a solitary kidney has been demonstrated, long term data is still lacking and concerns regarding the potential for extended warm ischemia in this patient population remain.[5]

Accepted for publication May 2015

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Renal tumor enucleo-resection is an operative technique used in both open and minimally invasive surgery in which the surgeon enters the pseudocapsule plane between the renal tumor capsule and surrounding renal parenchyma in order to remove the tumor, thus theoretically minimizing renal parenchyma loss during surgery.[9] An additional potential benefit of this approach is the ability to perform many of these resections without requiring hilar clamping in an effort to further prevent loss of renal function.[10]

In this study, we aim to determine the overall safety and feasibility of robotic-assisted enucleo-resection in patients with a solitary kidney using a multi-institutional cohort. We also present early oncological and functional outcomes of our initial results.

Materials and methods

Study population

After Institutional Review Board approval at each institution, we retrospectively reviewed records of patients undergoing RAPN at four high-volume centers across the United States from 2010-2013. Patients presenting with a solitary kidney and who underwent robot-assisted partial nephrectomy using enucleo-resection techniques were identified and their preoperative demographics and perioperative outcomes were assessed. All operative dictation notes were reviewed and analyzed cases included the term "enucleation" or "enucleo-resection" in the report. The "intention-to-treat" principle was utilized in that when enucleation techniques were attempted but aborted (poorly visualized planes, tumor violation) and a standard healthy margin partial was performed these patients remained in our analysis as enucleation surgeries.

Preoperative evaluation included abdominal and chest imaging and routine laboratory analysis. Imaging studies were generally repeated postoperatively at 3 months and 1 year however there was some variation in follow up on an institutional basis. Renal function was evaluated with routine basic metabolic profiles. Estimated glomerular filtrate rate (eGFR) using the MDRD equation was utilized.9,11 The percentage change in renal function was calculated comparing the preoperative eGFR and the eGFR at the time of last follow up. Preoperative and postoperative presence of chronic kidney disease (CKD) was assessed using the clinical guidelines for CKD.[12] Postoperative complications were defined according to the Clavian-Dindo classification.[13]

Surgical technique

All tumors were removed by a technique previously described for hereditary renal disease at the National Institutes of Health for both open and robotic approaches.[9,14] Briefly, a transperitoneal laparoscopic robotic-assisted technique was utilized in all cases. The tumor pseudocapsule was identified and a plane was developed between the tumor and the renal parenchyma. The tumor was inspected intracorporeally to ensure an intact pseudocapsule. Permanent or frozen biopsy of the resection base was performed at the surgeon's discretion. Typically, hilar occlusion was initiated when bleeding during tumor extraction became excessive or limited the ability to see dissection planes. If tumor integrity was poor and/or planes could not be safely visualized, enucleation was aborted and a standard "healthy" margin partial nephrectomy was performed. Closure was typically performed in two layers closing initially any visualized collecting system defects or open vessels followed by capsule renorrhaphy in either an interrupted or running fashion. After closure was complete, clamps (if used) were removed and the defect was inspected for hemostasis. A 15 mm Jackson-Pratt drain was placed at the completion of the case.

Results

Twelve patients from four institutions were identified and included in the analysis. The median age was 68 (IQR: 64, 72). The patients were equally split between sex and laterality of tumor. Pre-existing hypertension and diabetes were present in 10 (83.3%) and 3 (25%) patients, respectively. Median preoperative creatinine and eGFR as determined by MDRD equation was 1.16 (IQR: 1, 1.31) and 54.3 (IQR: 47.6, 58), respectively. R.E.N.A.L nephrometry score, used to standardize tumor complexity, was estimated to be 7 (6, 8). Concomitant surgery including a renal cyst decortication and a robot-assisted prostatectomy were performed in two patients of the analyzed cohort.

Median operative time and estimated blood loss were 148 minutes (IQR: 122-152) and 200 cc (IQR: 110, 262.5), respectively. Six patients (50%) required hilar clamping at some point during tumor enucleation. Median warm ischemia time was 5.5 minutes (IQR: 0, 13.25) for the overall cohort. In patients who required hilar clamping the median warm ischemia WIT) was 14.5 minutes (IQR: 12, 20.75 minutes). The median R.E.N.A.L nephrometry score of the six patients who underwent a clampless procedure and the six patients who had some degree of warm ischemia was 6 and 7.5, respectively ($p = 0.06$). One surgeon elected not to perform cortical renorrhaphy in one of the cases.

One intraoperative complication occurred when a segmental renal artery was partially transected requiring robotic sutured repair without further sequellae. This same patient experienced a multitude of postoperative complications including COPD exacerbation, temporary acute renal failure, and pyelonephritis. This was graded as a Clavian 4b complication; however, the patient ultimately made a full recovery and is disease free with an eGFR of 28.7 (compared to 39.9 preoperatively, Δ-28%). No patient experienced a postoperative urine leak or bleeding event. No patients required a blood transfusion during or following surgery.

Pathological data confirmed diagnosis of renal cell carcinoma in all patients with clear cell histology most common in 83% of cohort. In patients with prior contralateral nephrectomy for renal cell carcinoma (RCC) (8, 67%) there was histologic concordance in 100% of patients. The median pathologic tumor size was 3 cm (IQR: 2-3.8). Ten patients were pathologic T1a, 1 T1b, and 1 T3a and 16.7% of tumors were high grade (Fuhrman 3-4). All patients had negative surgical margins.

The median follow up duration for the entire cohort was 12.55 months (IQR: 5.25, 18.8) with eight patients (66.7%) having been seen greater than 1 year after surgery. There was no evidence of tumor recurrence during follow up. One patient in the group died 4 months after surgery secondary to malnutrition. Her surgery itself and postoperative course as well as 6 week follow up were uneventful.

The median eGFR at the time of the last follow up was 48.8 (IQR: 42.1, 59.9) which resulted in a -7.0% in eGFR. There was no significant difference with respect to preoperative and postoperative eGFR ($p = 0.313$). No patient experienced temporary or permanent renal replacement. According to the current CKD classification system, two patients in our cohort were classified as CKD II and ten were considered CKD stage III prior to surgery. Postoperatively, at the time of last follow up, 10/12 (83.3%) patients remained in the same CKD classification and two patients progressed from CKD III to CKD IV.

Discussion

Renal tumors in patients with a solitary kidney present a therapeutic challenge. A safe, nephron-sparing approach should be strongly considered whenever possible to remove the tumor and maintain the renal remnant to avoid dialysis and renal transplantation for this high risk patient population.[15] Alternative management options for this unique patient cohort include active surveillance as well as laparoscopic and percutaneous cryotherapy and radiofrequency ablation. Surveillance options are traditionally deferred for patients with good life expectancy, minimal comorbidities, or concerning tumor radiographic or pathologic characteristics and/or non-stable growth kinetics. Concerns with ablative procedures include the potential for incomplete treatment (higher long term failure rates) as well as challenges with interpretation of post-treatment imaging and surveillance protocols.[2,7] Historically, open partial nephrectomy has been the favored surgical approach for patients with a tumor in a solitary kidney.[1] As both patients and surgeons strive for improvements in patient convalescence, increasingly complex renal masses have been approached with minimally invasive techniques with encouraging results.[3-5,8,16] Performing robot-assisted partial nephrectomy for patients with tumors in a solitary kidney has seldom been evaluated.

Outcomes comparing open versus minimally invasive partial nephrectomy in patients with a solitary kidney have been evaluated sparingly in the literature. Lane et al compared initial results of laparoscopic partial nephrectomy versus open surgery in patients with a solitary kidney showing that although cancer specific survival was similar, laparoscopy was associated with longer WIT, increased need for dialysis, and higher complication rates.[8] Recently, robotic-assisted surgery has been adopted as the preferred minimally invasive surgical approach for small renal masses secondary to improved 3-D visualization and surgical dexterity over traditional laparoscopy, without compromising functional or oncological outcomes.[17] Comparisons of laparoscopic and robotic techniques for partial nephrectomy in patients with solitary kidneys demonstrate shorter operative times, reduced WIT, and shorter hospital stays in the robotic group.[4] A multi-institutional review by Hillyer et al describing 26 solitary kidney patients undergoing robotic-assisted partial nephrectomy demonstrated an average WIT of 17 minutes. Five patients (19%) in their series did not require hilar clamping. Surgical margins were positive in one patient who subsequently went on to develop recurrent disease.[5] More recently, the same authors expanded the study population and compared their cohort to a matched open partial nephrectomy series of solitary kidneys.[16] Although the open approach tended to be utilized for increasingly complex tumors, the authors concluded perioperative, functional, and early oncological outcomes were similar. When comparing the aforementioned study by Hillyer et al to the current series of enucleated tumors in solitary kidneys, early results are encouraging. Details of the two patient cohorts are outlined in Table 1. Similar to the prior robotic series, the enucleation procedures were completed with a similar safety profile and excellent surgical margin status. Additionally, WIT was reduced in the enucleation cases

TABLE 1. **Comparing HM-RAPN versus EN-RAPN enucleo-resection partial nephrectomy**

	Kauok et al[5]	Our group
Patient #	26	12
Preop GFR, MDRD (IQR)	58.9 (43.6, 73.2)	54.3 (47.6, 58)
Postop GFR, MDRD, (IQR)	43.9 (37.1, 58.7)	48.8 (42.1, 59.9)
Δ in GFR	-15.5%	-7.0%
Follow up duration, months (IQR)	6 (5, 9.7)	12.5 (5.25, 18.8)
Warm ischemia time, minutes (IQR)	17 (12, 28)	5.5 (0, 13.25)
Clampless-procedures, # (%)	5 (19.2)	6 (50%)
Postoperative complications, # (%)	3 (11.5)	1 (8.3)
Positive margins, # (%)	1 (4)	0 (0)
Recurrences, # (%)	1 (4)	0 (0)

HM-RAPN = healthy-margin robotic assisted partial nephrectomy; EN-RAPN = enucleo-resection robotic assisted partial nephrectomy; GFR = glomerular filtrate rate

to 5.5 minutes with half of the cases able to be completed without hilar clamping. Whether or not this was directly attributable to our enucleo-resection technique remains unknown. Nevertheless, exploring this approach in a patient cohort were parenchyma preservation is paramount is warranted.

The technique of tumor enucleo-resection was initially described when surgically managing patients with known hereditary renal syndromes due to their propensity for developing multi-focal bilateral renal masses.[9] The approach is predicated upon entering into the natural tissue plane between the renal tumor pseudocapsule and the healthy renal parenchyma and "rolling" or "enucleating" the tumor out of the kidney, ideally in a relatively bloodless plane. Champions of this technique argue that this approach allows significant reduction of hilar clamping thus limiting WIT and normal renal parenchyma loss.[9,14] Opponents of this approach describe concerns with intraoperative visibility of tumor tissue planes and the possibility of unwarranted positive margins. Recently, several Italian series have investigated performing tumor enucleation for sporadic renal masses with encouraging results, however, the data remains preliminary to this point.[18-21] To our knowledge, this is the first study to look at the role of tumor enucleation for the renal mass in a solitary kidney. Surgeons in our study were well versed in both open enucleation for hereditary renal masses as well as complex robotic surgery and were successfully able to transfer these skill sets to this unique patient cohort. We were able to identify the pseudocapsule plane in all 12 cases, avoid any positive surgical margins, and obviate hilar clamping in half of the patients. Delayed clamping was initiated if bleeding became significant or the tumor/parenchymal plane could not be safely entered or identified. In the six cases where warm ischemia was required we remained able to successfully complete tumor enucleation and preserve as much surrounding parenchyma as possible. Enucleo-resection may be ideally suited for this patient population in attempt to significantly reduce overall ischemia to the kidney.

The benefit of limiting WIT on preservation of renal function has been extensively reported. Thompson et al concluded "every minute counts" during hilar clamping. In their study evaluating 362 patients undergoing open (319) and laparoscopic (43) partial nephrectomy in a solitary kidney, results demonstrated increasing warm ischemia time was associated with acute renal failure, decreased eGFR, and new-onset stage IV chronic kidney disease during follow up.[22] The authors suggest a cut off of 25 minutes as the maximal allowance of WIT in this patient cohort. Other authors have suggested that in fact < 20 minutes WIT is preferable.[23] Comparing WIT versus no ischemia during partial nephrectomy in a solitary kidney, Thompson et al concluded that patients with WIT were significantly more likely to develop acute renal failure and chronic kidney disease.[24] These results have been confirmed in subsequent studies from Wszolek et al demonstrating the association of hilar clamping and the development of delayed declining eGFR compared to a clamp-less procedure.[6] In the present study, the median WIT of 5.5 minutes (IQR: 0, 13.25 minutes) was well within the aforementioned safe range of < 25 minutes. Overall ischemia time of patients who required hilar clamping was 14.5 minutes

(IQR: 12, 20.75), also well within range. Although the zero ischemia we achieved in half of cohort did not demonstrate a significant preservation of renal function compared to our patients who required hilar clamping, (p = 0.47) the fact that we were able to achieve this safely without oncologic compromise is encouraging. Longer follow up will be useful in assessing the presence or absence of delayed functional decline in both the clamp and non-clamp groups.

Recent studies have suggested that the amount of renal parenchyma preserved may be a superior benchmark over WIT in predicting renal function preservation during partial nephrectomy.[25] Correlating volume loss and postoperative renal function in a solitary kidney model, authors have suggested that preoperative volume assessment may be useful and predictive prior to partial nephrectomy. Recently, multiple groups evaluated patients undergoing partial nephrectomy and concluded that the amount of parenchymal volume preserved was the primary contributor to the preservation of renal function, even when including ischemia time.[26,27] Unfortunately, in the present cohort, postoperative cross-sectional imaging or identical-modality pre and post imaging (preop and postop CT scan) was not available for a large number of our patients making 3D volume calculations to measure volume loss unavailable. Hypothetically, minimal margin partial nephrectomy using enucleo-resection should maximize preservation of surrounding renal parenchyma although ischemia time and renorraphy technique may also impact these measurements. We are currently calculating volume loss between healthy margin and enucleo-resection partial nephrectomy to evaluate the possible impact of technique on renal preservation.

A major consideration of performing enucleo-resection partial nephrectomy in a solitary kidney patient population is the potential increased risk of positive surgical margins. As we continue to study the properties and integrity of the tumor pseudocapsule in RCC, we acknowledge that there may be unique characteristics depending on the stage, grade, and/or histology of the tumor in question. If invasion of the tumor into or through the pseudocapsule occurs anywhere along the tumor margin, then performing enucleation, in theory, may create iatrogenic positive margins that may not occur with a standard "healthy-margin" partial nephrectomy. This concept has been addressed in several reports from Minervini et al from Italy which have described extremely low positive margin rates in over 300 patients undergoing this technique.[28,29] In analyzing the pseudocapsule of varying tumor histology for T1 RCC at our institution we revealed that papillary RCC was most likely to demonstrate tumor capsular invasion and that clear cell RCC consistently demonstrated the thickest, most complete pseudocapsule with minimal tumor invasion suggesting that clear cell RCC was the ideal tumor for enucleation.[30] Fortunately, in the present study no patient had a positive surgical margin on final pathology. Whether this can be explained by the lack of tumor capsule invasion in this cohort, the small sample size, the high percentage of clear cell RCC, or the safety of the technique remains unknown. Even in the event of a focal positive margin, the direct clinical consequence of this untoward occurrence is not fully understood.[31] Without question, the balance of maximizing renal preservation and minimizing a positive surgical margin must be weighed before selecting a surgical technique, especially in the solitary kidney patient population frequently presenting with a metachronous lesion. Although we have initially used this approach without tissue acquisition prior to partial nephrectomy, consideration of preoperative biopsy may be utilized to help select certain tumors (low grade, clear cell) that may be best suited for tumor enucleation.

Historically, surgical complications during partial nephrectomy are relatively more common than during radical nephrectomy, however this may be impacted heavily by both tumor complexity and patient morbidity.[32] Some large institutions have reported that in most circumstances performing partial nephrectomy does not significantly increase complication risk.[33] When evaluating complication rates for minimally invasive partial nephrectomy (laparoscopic and robotic), early series suggested more complications compared to open partial nephrectomy, however rates appear to be minimized with larger case volume and increasing surgical experience.[34] Comparing complications during open and robotic partial nephrectomy in patients with a solitary kidney, authors found no difference in perioperative or postoperative complications between the two operative techniques.[16] Complication rates in our present cohort (1/12, 8.3%) are comparable with results from previous series documenting complications in sporadic RAPN, OPN in solitary kidneys and RAPN in a solitary kidney.[5,8,35] The single patient sustained an intraoperative segmental renal artery injury that was repaired with robotic techniques. Postoperatively, related or unrelated to the initial event, the patient developed acute renal failure and e. coli pyelonephritis. Fortunately, the patient did not require renal replacement and his renal failure resolved with expectant management. Another patient died in the early postoperative period just beyond the initial 90-day postoperative period. The patient was older (80 years old), had other comorbidities, and the details of her death were never fully characterized but not believed to be due to her renal surgery, which was uneventful. Overall, robotic-assisted enucleo-resection in patients with a tumor in a solitary kidney appears to be a safe and well-tolerated procedure with similar complication rates to other surgical approaches for partial nephrectomy reported in the literature.

Regardless of the surgical technique utilized (i.e open versus minimally invasive; healthy margin versus enucleo-resection), proper patient selection is paramount. Previously, R.E.N.A.L nephrometry scores have been validated as predictor of renal tumor complexity and used as a surrogate to predict the difficulty of tumor resection.[36] Overall, there are few cases based on nephrometry scoring or tumor location that would preclude robotic consideration for an experienced minimally invasive surgeon. Surgeons should utilize caution with large multifocal disease when patients may be at risk for extended warm ischemia time. Additionally, patients who have had multiple abdominal surgeries, intra-abdominal mesh or a known history of extensive abdominal adhesions may not be suitable candidates for a transperitoneal approach. Retroperitoneal robotic partial nephrectomy is an emerging technique that can be applied successfully in these scenarios.[37] Completely endophytic tumors are challenging in any partial nephrectomy as the surgeon is often required to cruciate or split the renal parenchyma down to the level of the tumor. This can be achieved both with robotic or open techniques. For challenging tumors it is not unreasonable to begin initially with a minimally invasive approach, isolate the hilum and renal tumor using robotic assistance and assess the feasibility of a robotic resection with laparoscopic ultrasound. If unsatisfied with tumor visualization, a safe and controlled conversion to an open approach prior to hilar clamping can be easily achieved with minimal sequellae.

Our study is not without limitations. The study is retrospective and the cohort is small. Because of the limited number of patients undergoing robot-assisted partial nephrectomy in a solitary kidney we were unable to make direct comparisons between enucleo-resection and standard healthy margin techniques in this patient population. Most, but not all, of the surgeons who contributed to this study were fellowship-trained on enucleation techniques and this may have impacted our results. Functional outcomes were evaluated based on equations to assess eGFR based on serum creatinine measurements, which has obvious limitations (i.e. hydration status). Twenty-four hour measurements of urine creatinine is a more accurate method of determining renal function and could be considered for future studies. Despite these limitations this is the first series to evaluate the role of robot-assisted enucleo-resection in patients with a tumor in a solitary kidney. Ultimately, a prospective trial investigating the various partial nephrectomy approaches with longer follow up will be needed to better delineate the ideal approach to the surgical management of this unique cohort. Better understanding the role and impact of warm ischemia time, renorraphy, and renal volume loss will better elucidate the potential benefit of performing enucleo-resection patients with a solitary kidney in the future.

Conclusions

Robotic-assisted enucleo-resection partial nephrectomy in patients with a tumor in a solitary kidney is safe and feasible in our early experience. This minimal margin approach appears to maximize renal preservation and may obviate or minimize the need for hilar clamping without compromising surgical margin rates. Larger cohorts and longer follow up is better needed to support these initial findings. □

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