Comparison of clamping technique in robotic partial nephrectomy: does unclamped partial nephrectomy improve perioperative outcomes and renal function?

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Introduction: *Partial nephrectomy without renal vascular occlusion has been introduced to improve outcomes in patients undergoing robotic partial nephrectomy (RPN). We prospectively evaluated unclamped RPN at our institution and compared this to other clamping techniques in a non-randomized fashion.*
Materials and methods: *Ninety-five consecutive patients who successfully completed RPN between June 2010 and October 2011 are included in this analysis. All RPNs were performed by a single surgeon. Clamping technique was artery and vein (AV), artery alone (AO) or unclamped (U) without hypotensive anesthesia. Clamping decision was based on surgeon preference and feasibility of minimizing ischemia. All patients had bilateral functional renal units.*
Results: ***E****ighteen (19%), 58 (61%) and 19 (20%) patients had AV, AO and U technique respectively. Preoperative characteristics including age (p = 0.43), body mass index (p = 0.40) and RENAL nephromety distribution (p = 0.10) were similar. In AV and AO, mean warm ischemia time were 19 and 17 minutes and similar between the two cohorts (p = 0.39). Mean glomerular filtration rate (GFR) and overall percentage decrease in GFR at time of at last follow up were (64, 69, 81, p = 0.12) and (6%, 6%,and 2%,p = 0.79) for AV, AO and U respectively. Median follow up for last serum creatinine was 113 days and was similar between all cohorts (p = 0.37). Complication rate (p = 0.37), positive margin rate (p = 0.84), and change in hemoglobin concentration postoperatively (p = 0.94) were similar between cohorts.*
Conclusions: *Unclamped partial nephrectomy is possible in patients undergoing RPN. In this study, it does not significantly alter perioperative or postoperative renal function or change rate of complications. Minimal ischemia, irrespective of clamping technique, in patients with bilateral renal units does not appear to adversely effect intermediate term renal function in these patients.*

Key Words: kidney, robotics, laparoscopy, nephrectomy, partial nephrectomy, nephron sparing surgery, ischemia, kidney cancer

Introduction

Incidentally diagnosed renal masses continue to be identified with increasing frequency.[1,2] While there are several treatment options for management of these lesions, surgical extirpation provides the most definitive treatment for patients deemed appropriate surgical candidates. Partial nephrectomy or nephron sparing surgery has produced similar long term oncologic control to radical nephrectomy while preserving renal function, and when technically feasible, has become the treatment option of choice.[3,4]

As indications and adoption of partial nephrectomy have increased, there has been an improved understanding of changes in renal function. Some

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authors have noted that even short duration ischemia can produce impairment in glomerular filtration rate (GFR).[5] Since long term renal dysfunction is associated with impaired survival outcomes,[6] experts in the field of minimally invasive partial nephrectomy have consistently moved to decreasing the total duration of ischemia during partial nephrectomy.[7] Institutions of excellence have initiated unclamped techniques for minimizing any ischemia to the kidney. This has been initially described in open series,[8] but has since been adopted in patients undergoing minimally invasive partial nephrectomy.[9]

However, conflicting reports concerning renal functional changes following renal ischemia, particularly warm ischemia, have been described.[10] Here, we evaluated the role of minimizing ischemia by performing unclamped robotic partial nephrectomy (RPN) in a select cohort of patients with functional contralateral renal units and compared this group to a contemporaneous consecutive patient population with artery and vein, or artery alone clamping.

Materials and methods

All data was prospectively collected and entered into our institutionally review board approved database. Inclusion criteria included all patients undergoing RPN for suspected renal masses. All patients in this cohort had functional contralateral renal units. Decision to perform unclamped (U) versus renal artery only (AO) or renal artery and vein (RAV) clamping was made intraoperatively by the attending surgeon and based on tumor location and size, depth or renal mass invasion and ability to individually clamp the renal vessels. The attending physician had previously performed more than 80 RPNs at this institution.

Our technique of RPN has been described previously.[11,12] Briefly, the tumor is located with intracorporeal ultrasound and the margins are scored with electrocautery. Indocyanine green dye (Akorn, Lake Forest, IL, USA) is used with near-infrared spectroscopy and is used to identify tumor margins and pertinent renal vasculature. All patients had tumor excision without performing enucleation with a goal of obtaining at least a 1 mm margin. Rennoraphy is completed in two steps: first, a closure of pelvicaliceal collecting system when opened, ligation of vessels at the base of excised renal parenchyma with one or two 3-0 poliglecaperone continuous sutures; at this point we remove vascular clamps where these were used then renal parenchyma and capsular repair is performed with 1-0 poliglecaperone or polyglycolic acid interrupted sutures or Barb continuous suture and then perirenal adipose tissue is covered over the defect. All procedures were performed using a transperitoneal approach. Resident or fellow involvement in the case involved certain aspects of the procedure based on experience and level of training. As trainees progressed, they assumed more responsibilities consistent with their level of training.

Follow up data was obtained by patient interviews and/or review of medical records. All complications were graded according to the Clavien-Dindo grading system.[13] Renal function was evaluated preoperatively, each morning while an inpatient and at the time of most recent follow up by serum creatinine measurements and calculation of the Modification of Diet in Renal Diseases equation.

Descriptive analysis was performed with JMP (8.0.1) (Cary, NC, USA). Comparison of outcomes was performed using analysis of variance (ANOVA) analysis for continuous variables or chi-squared for categorical variables.

Results

We identified a total of 95 patients who successfully completed RPN between June 2010 and October 2011. Eighteen (19%), 58 (61%) and 19 (20%) patients had RAV, AO and were unclamped, respectively. Preoperative characteristics are reviewed in Table 1. Patients were well matched according to age, sex, history of comorbidities, and body mass index. No patients in this cohort had a solitary kidney. In dividing patients into chronologic tertiles, the percentage of unclamped procedures increased from 1/32 (3%) to 8/32 (25%) to 10/31 (32%) which was statistically significant ($p = 0.0035$) for the trend. In this cohort, the RENAL nephrometry scores were similar as were the PADUA classifications. In fact, in patients with either > 50% endophytic tumors, 8 (44%), 29 (50%) and 7 (37%) ($p = 0.55$) had RAV, AO or U respectively.

Perioperative characteristics were similar in these cohorts, Table 2. Operative duration, which included incision, creation of pneumoperitoneum, adhesiolysis when necessary, specimen extraction and closure of skin incisions, was similar between all cohorts ($p = 0.24$). Estimated blood loss was similar in all cohorts ($p = 0.13$). The percentage decrease in hemoglobin was 15% across all cohorts ($p = 0.94$). The percentage of patients with renal malignancy identified on final pathology was similar between all three cohorts ($p = 0.47$). The overall rate of positive margin was 7.3% and the mechanism of clamping did not alter risk of positive margin ($p = 0.84$).

No patient required an intraoperative transfusion. Overall, three patients required postoperative

TABLE 1. **Preoperative patient demographics and characteristics**

	Artery and vein	Artery only	Unclamped	p value
Total patients	18	58	19	
Age	62.4 ± 2.9	60.2 ± 1.6	57.1 ± 2.9	0.43
Body mass index	28.9 ± 5.6	29.5 ± 5.4	31.3 ± 7.7	0.40
Number (%) male	7 (39%)	35 (60%)	11 (58%)	0.27
Nephrometry score				0.10
Low (4-6)	14 (78%)	31 (55%)	15 (79%)	
Mod (7-9)	3 (17%)	24 (43%)	4 (21%)	
High (10+)	1 (6%)	1 (2%)	0	
> 50% endophytic	8 (44%)	29 (50%)	7 (37%)	0.55
Anterior tumor	9 (50%)	27 (48%)	6 (32%)	0.39
Posterior tumor	7 (39%)	19 (34%)	9 (47%)	
Lateral tumor	0 (0%)	6 (9%)	3 (16%)	
Hilar tumor	2 (11%)	4 (7%)	1 (5%)	
PADUA score				0.13
Low (6-7)	10 (56%)	27 (48%)	15 (79%)	
Mod (8-9)	5 (28%)	22 (39%)	2 (11%)	
High (10+)	3 (17%)	7 (13%)	2 (11%)	
Tumor size (cm) Median (range)	3.0 (1.3-4.9)	2.9 (1-5.7)	1.6 (1-8.8)	0.001
ASA grouping				0.70
1	0	1 (2%)	1 (41%)	
2	7 (39%)	18 (33%)	7 (53%)	
3	11 (61%)	36 (65%)	9 (6%)	
History of prior surgery	9 (50%)	31 (53%)	9 (47%)	0.89
CKD stage III or greater	4 (23%)	15 (27%)	3 (16%)	0.60
Comorbidities				
Hypertension	10 (56%)	36 (62%)	13 (68%)	0.72
Diabetes mellitus	2 (11%)	10 (17%)	4 (21%)	0.70
COPD	1 (6%)	2 (3%)	1 (5%)	0.90

ASA = American Association of Anesthesia Score; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease

TABLE 2. **Perioperative and postoperative outcomes based on clamping technique**

	Artery and vein	Artery only	Unclamped	p value
Total patients	18	58	19	
Operative time (skin incision to closure) (min)	213 ± 10	220 ± 6	201 ± 10	0.24
Estimated blood loss (mL)	83 ± 20	74 ± 11	118 ± 19	0.13
Warm ischemia time (min)	19 ± 2	17 ± 1	n/a	0.39
% decrease in HgB on POD#1	15% ± 3%	15% ± 2%	15% ± 2%	0.94
Renal malignancy	15 (83%)	47 (81%)	13 (68%)	0.47
Positive margin	1 (6%)	5 (9%)	1 (5%)	0.84
Major complication (3+)	3 (17%)	6 (10%)	1 (5%)	0.52

HgB = hemoglobin concentration g/dL

transfusions (3%), one in the RAV cohort and two patients from the AO group (p = 0.47). A graded Clavien-Dindo complication occurred in 19 (20%) of patients overall, with 10 (10%) of these being major (≥ Clavien III.) Rates of overall (0.38) or major complications (0.52) were similar between all three cohorts. Overall length of stay was not statistically different. On patient in the RAV cohort had cardiopulmonary arrest on postoperative day 2 who had significant medical comorbidities preoperatively. He required intubation, eventual tracheostomy, developed hospital acquired pneumonia and eventually was discharged to a skilled nursing facility on postoperative day 47. There were no Clavien V complications. Nine of the patients required escalation of care with either telemetry or ICU monitoring. All of these were patients who had artery only clamping and had a history of cardiac disease besides other medical problems. The only two patients requiring urgent angioembolization of a bleeding renal vessel were in the artery only clamping cohort (one patient was on Lovenox and other patient had delayed bleeding after 2 weeks). One patient in the RAV group required JJ ureteral stent placement for urinoma postoperatively and an additional patient had a gastroduodenoscopy for intractable nausea postoperatively which was normal. The patient in the unclamped cohort with a major complication had a localized retroperitoneal collection from tiny colonic leak as patient presented at 2 weeks with history of fever. This was managed by placing percutaneous drain with antibiotic and no further intervention was required. All other major complications were cardiac in nature in patients with known cardiovascular disease preoperatively and resolved with medical therapy. In this follow up period, no patient was noted to have a recurrence of tumor and no patient require reoperation or retreatment for oncologic management.

Preoperative serum creatinine measurements were similar in all three cohorts (p = 0.66) and GFR, as measured by the MDRD equation was similar as well (p = 0.25.), Table 3. Change in serum creatinine measurements at the time of discharge was unchanged based on the clamping technique (p = 0.33). At an overall median of 113 days, 65 (68%) of patients had follow up serum creatinine measurements. There was no statistically significant difference in decreased GFR at this point in time (6% AV, 6% AO, 2% U, p = 0.79.) Overall, seven patients had increase in CKD stage, three in the RAV group, three in the AO group and one in the U cohort (p = 0.51.) Six patients were diagnosed with new onset stage 3 CKD, and one patient had increase from stage 3 to stage 4 CKD. The median percentage increase in serum creatinine in this cohort was 25% (range 6%-77%) and the median decrease in percentage GFR is 23% (range 7%-48%). Median follow up was similar for all three groups (p = 0.37).

TABLE 3. **Changes in renal function comparing clamping versus unclamped techniques**

	Artery and vein	**Artery only**	**Unclamped**	**p value**
Total patients	18	58	19	
Preoperative GFR	72 ± 6	77 ± 4	86 ± 6	0.25
Preoperative sCr	1.0 ± 0.8	1.1 ± 0.5	1.0 ± 0.8	0.66
% patients stage 3 CKD preoperatively (GFR < 60)	4 (24%)	15 (27%)	3 (16%)	0.60
% increase in sCR at discharge	17% ± 5%	10% ± 3%	4% ± 5%	0.22
% decrease in GFR at discharge	10% ± 5%	5% ± 3%	1% ± 5%	0.33
sCr at discharge	1.2 ± 0.9	1.1 ± 0.5	1.0 ± 0.9	0.23
GFR at discharge	62 ± 6	72 ± 3	84 ± 5	0.02
% increase in sCR at last follow up	13% ± 5%	8% ± 3%	3% ± 5%	0.33
% decrease in GFR at last follow up	6% ± 5%	6% ± 3%	2% ± 5%	0.79
Most recent sCr	1.2 ± 0.9	1.2 ± 0.6	1.0 ± 1.0	0.48
Most recent GFR	64 ± 6	69 ± 4	81 ± 6	0.12
% patients w/ increase in CKD stage	3 (19%)	3 (9%)	1 (7%)	0.51
Days to most recent serum Cr	128 ± 24	166 ± 17	136 ± 25	0.37

GFR = glomerular filtration rate; CKD = chronic kidney disease; ± SE when reporting means

Discussion

Minimizing renal dysfunction following extirpative procedures of the kidney is a laudable goal. The risks associated with chronic kidney disease continue to be demonstrated in large population based cohorts.[6] Chronic renal dysfunction is associated with increased risk of cardiovascular morbidity and decrease overall survival following management of renal neoplasms. Our understanding of minimizing renal ischemia and the dogma of the 30 minute rule continue to be passed down, however the data supporting this, particularly in the setting of a normal contralateral renal unit, has not been well established.[14-16]

Unclamped RPN is a technically difficult procedure to perform, even in the most experienced surgeon's hands. In this cohort of patients, it was performed at a much higher rate later in the cohort, likely due to increased familiarity with the procedure and progressing through the learning curve. In a recent series on zero ischemia a significant increase in rate of complications and transfusions have been reported.[9] For this technique to be adapted to community practices, with it's increase rate of complications and transfusions previously described, there should a definitive benefit associated with this.

We could not appreciate any significant improvement in renal function by performing an unclamped partial nephrectomy. In fact, there was no association with improvement in renal functions, based on clamping, or whether both vessels were clamped. While there was minimal decrease in the change in GFR at most recent follow up, this was not statistically significant between the cohorts. Clinical significance was also not different, as a similar percentage of patients in all cohorts were classified as worsening CKD stages. We did not identify any increased risk in either complications or positive surgical margins in this cohort, so likely performing this procedure did not harm, the patient, however if there is a benefit this wasn't elucidated. Anecdotally, hilar tumors and completely endophytic tumors were the most difficult tumors to perform unclamped procedures on, however as noted previously, we did not attempt unclamped RPN until later in our series and after having developed experience with the procedure.

Other groups have explored analyzing the technique of vascular clamping as an independent predictor of renal function. In one retrospective analysis of 1228 patients who underwent partial nephrectomy, patients where the artery and vein were clamped, were twice (HR 2.16) as likely to develop chronic kidney disease stage 3 or greater.[17] In a matched paired comparison, other authors have noted that artery only occlusion produced no change in postoperative renal function, however artery and vein occlusion demonstrated a significant decrease in both serum creatinine and GFR at postoperative day 1 and at latest follow up.[18] In contrast, another manuscript noted en bloc hilar clamping versus artery alone clamping was not associated with changes in renal scintography at follow up nor was it a predictor on multivariate analysis of change in renal function.[19] Clearly the role of hilar clamping has not been fully elucidated.

Other authors have demonstrated that unclamped partial nephrectomy does not improve renal functional outcomes, particularly in the setting of a normal contralateral kidney. While performing a retrospective comparison of GFR at follow up in patients undergoing minimally invasive partial nephrectomy, it has reported there is no significant difference in renal function at a mean of more than 14 months of follow up. These authors also could not appreciate any difference in differential function based on renal scans.[20] Another center of laparoscopic nephron sparing surgery excellence found that in 42 patients who underwent laparoscopic partial nephrectomy, there was no difference in change in renal function at 6 months when comparing them to patients with greater than 30 minutes of ischemia.[16] In the largest published series on this topic, another set of authors noted that in 1132 patients treated with partial nephrectomy with normal renal function and a normal contralateral kidney, neither zero ischemia nor duration of clamping was a significant predictor of renal function postoperatively.[21] Only quality of renal parenchyma (as measured by baseline GFR) and percentage of tissue preserved predicted postoperative change in renal function.[21] At our institution, senior author performs all cases of renal masses amenable to partial nephrectomy with robotic assistance. Open partial nephrectomy with and without cold ischemia is a standard of care and our practice pattern has evolved learning from open and laparoscopic partial nephrectomy before embarking our journey with robotic assistance. Larger studies have confirmed preservation of renal parenchyma provides the best long term renal function, more important than mechanism of partial nephrectomy, and we have adopted this into our practice patterns.[20]

Several important limitations must be recognized when evaluating the findings of this manuscript. Initially, patient selection for grouping was based on surgeon preference and not randomized. Additionally, this is only a median 4 month (range 1-13) follow up. Other groups have demonstrated that renal function following partial nephrectomy is essential unchanged between 3 weeks of follow up and longer

duration.[22] Here we have not obtained renograms or other functional imaging to evaluate if differential function has been altered by this procedure. We have calculated GFR based on the MDRD equation, which is accepted for patients following partial nephrectomy, however it does have flaws, particularly in calculating renal function in patients without CKD.[22] In addition, we are evaluating a snapshot of the postoperative renal function in these patients, and do not report longitudinal data with sequential serum creatinine measurements. Multiple evaluations of renal function postoperatively at varying time points would provide a more complete evaluation of the changes in renal function postoperatively. Based on sample size, it is possible that larger cohorts of patients may demonstrate a statistical significance to the data presented, however at present any beneficial effects of unclamped partial nephrectomy have not been demonstrated in this cohort. As all patients in this cohort had functional contralateral renal units, it is also possible that the effect of unclamped technique would be more pronounced in solitary kidneys, as other institutions have established.[8,23] Similar perioperative outcomes in the unclamped group, may also be associated with the learning curve encountered, as the majority of the unclamped procedures occurred in the final chronologic tertile of patients.

Conclusion

Unclamped robotic partial nephrectomy can be performed safely in patients with small renal masses, although with increased experience and technical difficulty. The effects on renal function at early follow up are minimal, and in patients with normal contralateral kidneys, may not produce significant clinical benefit. □

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