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# Anatomic complexity quantitated by nephrometry score is associated with prolonged warm ischemia time during robotic partial nephrectomy

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## Abstract

**Objective—**To assess the association between Nephrometry Score (NS) and prolonged warm ischemia time (WIT) in patients undergoing robotic partial nephrectomy (RPN) for clinically localized renal masses.

**Methods—**We queried our prospectively maintained kidney cancer database to identify all patients undergoing RPN for localized tumors from 2007–2012. Patient and tumor characteristics were compared between complexity groups using ANOVA and Chi square tests. Multivariable logistic regression models were used to examine the relationship between NS complexity and warm ischemia >30 minutes.

**Results—**375 patients (mean age 59±11 years, mean CCI 1.0 ±1.3) undergoing RPN under warm ischemia for clinically localized renal tumors (mean tumor size 3.1±1.5 cm, mean NS 6.8±1.8) met inclusion criteria and had NS available. Stratified by complexity, groups differed with respect to age at surgery, tumor size, proximity to the hilum, collecting system entry, EBL, and operative time (all p values ≤ 0.05). Significant differences in mean warm ischemia time were observed when comparing low (19.4±12.1 min), intermediate (28.6±12.8 min) and high (36.1±13.7 min) NS complexity groups ($p<0.0001$). Adjusting for confounders, patients with intermediate (OR 2.1 [CI 1.2–3.9]) and high (OR 3.7 [CI 1.1–11.8]) NS complexity were more likely to require prolonged warm ischemia time when compared to patients with low complexity tumors.

**Conclusions—**In our large institutional cohort, quantification of anatomic complexity using the NS is associated with WIT greater than 30 minutes in patients undergoing RPN for localized renal tumors. This provides further evidence that standardized reporting of tumor anatomic complexity affords meaningful outcome comparisons.

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**Keywords**

Renal cell carcinoma; ischemia time; robotic surgery; partial nephrectomy; nephrometry score

## Introduction

Advances in nephron sparing surgery (NSS) have made partial nephrectomy (PN) the preferred treatment for small renal masses if technically feasible.[1] There is evidence to support the idea that the preservation of renal function is associated with benefits such as increased overall survival, decreased other-cause mortality, and decreased cardiovascular adverse events.[2,3] Renal hilar clamping is frequently utilized during RPN to minimize blood loss and improve visualization during tumor excision and renorrhaphy. WIT and the degree of renal parenchymal preservation can impact long-term renal function,[4,5] especially among patients with pre-existing chronic kidney disease (CKD).[6] Among patients with a solitary kidney treated with PN, longer WIT is associated with short- and long-term renal functional consequences, suggesting that ischemia is a relevant metric.[4]

Patient, surgeon, and tumor variables including anatomic complexity can affect the duration of WIT during NSS. As metrics for measuring anatomic complexity have been adopted to accurately adjust for case mix between providers and published series,[7] it has become increasingly apparent that comparison of likewise tumors is necessary to meaningfully compare outcomes following NSS. Standardized tools such as NS have proven useful to objectively quantify anatomic features of renal tumors, and may provide clinically useful information in helping select surgical approach for partial nephrectomy.[8–10] Given the deleterious effects of renal ischemia, use of efforts to minimize WIT should be entertained when planning a surgical approach, especially during imperative situations such as a tumor in a solitary kidney. Our objective was to assess the association between tumor complexity, quantified by NS, and prolonged WIT in patients undergoing RPN for clinically localized renal masses.

## Material and Methods

Following institutional review board approval, our prospectively maintained kidney tumor database was queried to identify all patients undergoing RPN for clinical stage I–III renal tumors from 2007–2012 with available nephrometry score data. Surgery was offered to patients with absolute, relative and elective NSS indications when considered technically feasible at the surgeon's discretion. Clinical variables evaluated included patient (age, gender, Eastern Cooperative Oncology Group [ECOG] performance status, body mass index [BMI], renal function) tumor (NS, hilar designation, solitary kidney, largest tumor size, laterality), and operative (year of surgery, estimated blood loss [EBL], WIT, collecting system entry [CSE]) characteristics. Clinical co-morbidity severity was determined using the weighted Charlson comorbidity index (CCI).(9) Tumor anatomic characteristics were assessed using the R.E.N.A.L.-Nephrometry scoring system,[7] and patients were stratified into low (NS 4–6), intermediate (NS 7–9), and high (NS 10–12) anatomic complexity groups. As part of our prospectively maintained kidney cancer database, NS is calculated

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and recorded for each renal mass at surgery and verified by 2 physicians familiar with the R.E.N.A.L. nephrometry scoring system. Tumor staging was designated according to the TNM classification based on the 2010 American Joint Committee on Cancer/International Union against Cancer classification system.

All surgeries were performed by one of five full-time urologic oncologists. All masses were approached laparoscopically with robotic assistance employing a three-arm technique with port location tailored to the location of the renal tumor and hilum. Intraoperative ultrasound was performed to rule out multifocal disease and delineate resection margins. Hilar control was performed in all cases (cases done off-clamp were excluded from analysis) and tumors were excised sharply with frozen section analysis to determine margin status. Collecting system defects were repaired when encountered. Renorrhaphy was performed with or without bolsters of oxidized cellulose and retroperitoneal drain and urinary catheter were placed in all patients.

WIT was examined as a categorical (<30 or ≥30 minutes) and continuous variable. Patients with WIT ≥30 minutes were compared to those with WIT <30 minutes using the individual components of nephrometry (size, endo/exophycity, nearness to sinus/urothelium, anterior/posterior, location relative to polar line, and hilar structures) total NS, NS complexity group, age, gender, race, largest tumor size, ECOG PS, EBL, BMI, CSE, and CCI. Patient and tumor characteristics were compared using Fisher's Exact and Wilcoxon Rank-Sum tests. The associations between WIT ≥30 minutes and covariates were assessed using multinomial logistic regression models using WIT<30 minutes as the reference group. Covariates meeting a $P$ <0.10 level of significance were included for model development, and our final model was adjusted for age, gender, race, BMI, surgeon, EBL, CSE, NS complexity group, individual NS components, and CCI. All analyses were performed using Stata, version 10 (StataCorp, College Station, TX), all hypothesis tests were 2-sided, and the criterion for statistical significance was $P$ <0.05.

## Results

A total of 375 patients (mean/median age 58/59±11 years, 64.8% males, 85.6% white, and mean CCI 1.0±1.3) with clinical stage I (93.6%), II (1.3%), or III (5.1%) renal tumors (mean/median tumor size 3.1/2.8 ±1.5 cm, mean NS sum 6.8±1.8) met the final inclusion criteria. As objectified by NS, 44%, 49.6%, and 6.4% of patients had low-, medium-, and high-complexity lesions, respectively. Mean/median operative time and EBL were 189/185±66 minutes and 128/60±146 mL, respectively. Mean WIT was 25±14 minutes (median 24 min; range 18–65 min), and 37.9% of patients had a WIT ≥30 minutes (Table 1).

Comparing patients by high and low tumor anatomic complexity, significant differences in tumor diameter (4.3±2.0 vs. 2.5±0.9 cm; p<0.001, hilar tumor location (29.2% vs. 4.2%; p<0.001), collecting system entry (40.0% vs. 7.9%; p<0.001), EBL (267±247 vs. 90±94 mL; <0.001), operative time (215±54 vs. 177±76 min; p=0.004), and WIT ≥30 minutes (62.5% vs. 25.5%; p<0.001) were observed, while no differences were observed between patient age, gender, race, tumor location, CCI, renal function, surgery year, and BMI. Significant differences in mean/median warm ischemia time were observed when comparing low

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(19.4/20±12.1 min), intermediate (28.6/27±12.8 min) and high (36.1/33±13.7 min) NS complexity groups ($p<0.001$). Whether considered as a categorical or continuous variable, higher anatomic tumor complexity remained associated with increased WIT.

After adjustment for age, gender, race, BMI, CCI, surgeon, EBL, CSE, tumor location, CKD stage, surgery year, and NS complexity group, intermediate (OR 1.9 [CI 0.9–3.9]) and high (OR 7.6 [CI 1.7–33.9]) NS complexity, CSE (OR 3.3 [CI 1.4–7.7]), and surgeon (OR 3.1 [CI 0.8–12.8]) were associated with WIT ≥30 minutes. When considered as a continuous variable, NS (OR 1.4 [CI 1.1–1.7]; $p=0.001$) was associated with WIT ≥ 30 minutes. Tumor location, EBL, BMI, and renal function were not associated with prolonged WIT (Table 2). A sensitivity analysis restricting covariates to surgical factors alone did not significantly impact our findings (data not presented).

## Discussion

Herein we present the largest series to date examining the effect of renal tumor anatomic complexity on WIT among patients treated with RPN. Intermediate and high tumor anatomic complexity as measured by NS and CSE were associated with a WIT greater than 30 minutes. Individual components of NS, including anterior/posterior and hilar tumor locations were not associated with prolonged WIT. Higher renal mass complexity increases the difficulty of surgical resection,[11,12] and expectedly led to an increased risk of prolonged WIT. The current data provide further evidence that standardized reporting of tumor anatomic complexity affords meaningful outcome comparisons and identifies modifiable targets to improve outcomes.

The determinants of renal function following RPN remain a highly controversial topic with substantial clinical relevance.[13] Ischemia time[4,14,15] as well as the quantity[5,16,17] and quality[5,13] of parenchymal preservation have independently been shown to impact renal functional recovery after RPN. Renal parenchymal preservation is increasingly identified as the primary predictor of unilateral renal function after PN, [12,13,16–18] however warm ischemic interval is a surrogate for surgical complexity and it directly correlates with parenchymal volume loss.[5,13,15–17] While studies of volume loss have been criticized for their subjective determination of residual renal volume[13,16] and use of mathematical modeling,[12,17] the use of computed tomography volumetric analysis using free-hand scripting has revealed similar results.[5] While most preserved nephrons will recover from ischemic insult, the caveat is that WIT still plays a role if not maintained within reasonable limits or associated with hypothermia.[5,13,18]

Renal pedicle clamping is often necessary during PN, especially for hilar tumors or those with deep parenchymal invasion.[4] Renal ischemia aids in hemostasis and visualization during tumor excision, and allows precise surgical closure of the collecting system and reapproximation of the parenchymal defect.[4] Given the increased risks of irreversible renal parenchymal injury associated with prolonged WIT, an ischemic duration of 30 minutes has historically served as the “safe” cutoff point.[19] However the optimal WIT cutoff (20, 25, or 30 minutes)[5,14] for predicting adverse renal consequences is debatable, and each increasing minute of warm ischemia invites additional risk of renal consequences, especially among

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those with a solitary kidney or significant baseline renal dysfunction.[4] Warm ischemia is associated with a reduction in medullary blood flow causing hypoxic injury to tubular structures,[20] and the degree of damage appears proportional to the warm ischemia time; as warm ischemia is prolonged, the distal tubular cells, which are normally protected by the persistence of adenosine triphosphate, produce cytokines responsible for apoptosis[19] which exacerbate the inflammatory response and stimulate further injury.[20] Indeed the maximal safe duration of WIT has been challenged, and hilar clamping times of up to 90 minutes have been shown to be safe in porcine models.[21] Clinically, WIT's of 40–55 minutes have also been shown to be safe and effective.[22]

Prolonged WIT, if indiscriminately applied, would likely lead to adverse outcomes. Therefore, while parenchymal preservation may have the greatest effect on renal function after PN, ischemia time remains a modifiable peri-operative factor of particular importance among patients with underlying renal disease.[18] In a recent examination of perioperative and functional outcomes of off-clamp RPN in a large multi-institutional cohort using propensity score analysis to account for potential confounders, off-clamp RPN was associated with shorter operative times and a smaller decrease in renal function.[23] While various off-clamp approaches and techniques to eliminate or minimize global renal ischemia have been described,[23] most practitioners performing RPN rely on warm ischemia.[23] Advances in RPN have reduced WIT's even in the most complex cases,[24] but in 2010, the relative annual increase in the utilization of RPN was 45.4%,[25] and with RPN becoming the minimally invasive approach of choice and increasingly being applied to larger and more complex tumors,[26] WIT will remain an important consideration. Evaluation of change in calculated GFR revealed no significant association with WIT. This result likely reflects the function of the healthy contralateral kidney and is not surprising. Therefore given the absence of pre-operative functional renal studies, the aim of the current analysis was not to evaluate the effect of WIT on renal functional outcomes, but rather to objectively identify those patients at increased risk for prolonged WIT. We demonstrate that higher tumor complexity is associated with prolonged WIT, and among patients at high-risk for renal dysfunction, this information may be considered to select patients for hypothermic or zero-ischemia approaches.[27]

Although intuitive that a more complex procedure may increase WIT, historically the clinical usefulness of such data is limited by the lack of standardized quantification of tumor anatomic complexity, and it is essential to control for anatomic complexity to account for differences in clinical outcomes. Not surprisingly, CSE was also associated with prolonged WIT, which can be explained by the extra time required to repair collecting system defects. Opening of the collecting system and blood loss can be seen as indirect signs of tumor complexity and technical difficulties encountered during surgery that can influence postoperative outcomes.[28] Other smaller series have reported similar results. Among 141 patients undergoing laparoscopic PN, a significant difference in WIT between patients with high and low complexity tumors (31 vs 16 minutes, respectively) was observed.[11] In a slightly larger series of patients undergoing RPN, total NS, tumor size, endophyticity, and nearness to the collecting system were associated with WIT.[29] Analysis of NS components within the current cohort revealed no association between tumor location (anterior/posterior/hilar) and WIT. Much of the dissection for complex hilar lesions can be performed prior to

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clamping the renal vessels, minimizing the need for excessive ischemia. Conversely, Mufarrij *et al.*[30] observed no significant association between NS complexity groups and WIT. However, their cohort was homogeneous and consisted mainly of tumors <4 cm in diameter, reducing the overall complexity of resected lesions.[30]

While NS should not be the only variable considered when assessing pre-operative risk, herein we demonstrate its ability to serve as an objective surrogate for expected surgical difficulty and WIT, thereby providing an increased estimation of peri-operative tumor specific risks. This information can be utilized for pre-operative planning, clinical decision making and patient counseling. Although tumor complexity as stratified by NS was associated with WIT, this provides evidence that components of the NS may indeed be more important than the overall score. The principle limitations to our study include a retrospective methodology, inherent selection biases based on surgeon and patient preferences, and inclusion of five different surgeons. To minimize surgeon bias, surgeon was included as a covariate in the regression model and did not significantly impact the main study findings.

Our findings represent a contemporary tertiary care surgical experience that should not be considered generalizable to community practice. Interobserver variance in NS assignment and the lack of internal validation of complexity grouping could bias our results. Further, our selection of a 30 minute warm ischemic interval was based largely on historical data, and varying alternative cut-offs have been utilized by others. Finally, while tumor complexity can be easily objectified, numerous unmeasured subjective factors contribute to WIT. The most difficult to assess objectively is a surgeon's urgency to remove the hilar clamp, which is highly subjective and dependent upon surgeon experience, tolerance of bleeding and risk of urinary leak, reconstructive technique, and his/her perception of risk for a given patient, and correlation of a dynamic variable such as WIT with a single objective variable (NS) can never capture the complete clinical picture accounting for surgeon variability.

## Conclusions

In our large institutional cohort, quantification of anatomic complexity using the NS is associated with WIT greater than 30 minutes in patients undergoing RPN for localized renal tumors. This provides further evidence that standardized reporting of tumor anatomic complexity affords meaningful outcome comparisons and assists in clinical decision making and patient counseling.

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**Table 1**

Demographic and clinical parameters for patients undergoing RPN stratified by nephrometry score complexity

| | Low Complexity | Intermediate Complexity | High Complexity | Overall Cohort | p-value |
|---|---|---|---|---|---|
| **N (%)**<br>**Mean ± SD** | **165 (44)** | **186 (49.6)** | **24 (6.4)** | **375** | - |
| **Age (yrs)** | 58.5±11.4 | 57.7±11.8 | 56.8±11.3 | 58.0±11.6 | 0.700 |
| **Gender** | 165 (66.7) | 186 (60.8) | 24 (83.3) | 375 | 0.074 |
| **Female** | 55 (33.3) | 73 (39.3) | 4 (16.7) | 132 (35.2) | |
| **Male** | 110 (66.7) | 113 (60.8) | 20 (83.3) | 243 (64.8) | |
| **Race** | | | | | 0.672 |
| **White** | 140 (84.8) | 159 (85.5) | 22 (91.7) | 321 (85.6) | |
| **Non-white** | 25 (15.2) | 27 (14.5) | 2 (8.3) | 54 (14.4) | |
| **CKD Stage** | | | | | 0.926 |
| **I** | 71 (43) | 76 (40.9) | 12 (50) | 159 (42.4) | |
| **II** | 68 (41.2) | 85 (45.7) | 10 (41.7) | 163 (43.5) | |
| **≥ III** | 17 (10.3) | 16 (8.6) | 1 (4.2) | 34 (9.1) | |
| **Unknown** | 9 (5.5) | 9 (4.8) | 1 (4.2) | 19 (5.1) | |
| **GFR, % change** | 4.8±1.8% | 1.1±1.7% | 1.1±1.9% | 3.1±1.8% | 0.185 |
| **BMI** | 30 ± 7.9 | 30.7 ± 7.2 | 30.4 ± 7.0 | 30.2 ± 7.5 | 0.730 |
| **CCI** | 0.9±1.4 | 1.0±1.3 | 0.9±1.1 | 1.0±1.3 | 0.822 |
| **Tumor Size (cm)** | 2.5±0.93 | 3.4±1.6 | 4.3±2.0 | 3.1±1.5 | **<0.001** |
| **Operative Time (min)** | 177±76 | 197±54 | 215±54 | 189±66 | **0.004** |
| **EBL (mL)** | 90±94 | 145±154 | 267±247 | 128±146 | **<0.001** |
| **Nephrometry Score: “Hilar”** | 7 (4.2) | 36 (19.4) | 7 (29.2) | 50 (13.3) | **<0.001** |
| **Nephrometry Score: “anterior”** | 90 (54.6) | 92 (49.5) | 11 (45.8) | 193 (51.5) | 0.541 |

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| | Low Complexity | Intermediate Complexity | High Complexity | Overall Cohort | p-value |
|---|---|---|---|---|---|
| **Nephrometry Score: "posterior"** | 60 (36.4) | 73 (39.3) | 11 (45.8) | 144 (38.4) | 0.636 |
| **Collecting System Entry** | 12 (7.9) | 44 (26.0) | 8 (40.0) | 64 (18.8) | **<0.001** |
| **WIT (min)** | 19.4±12.1 | 28.6±12.8 | 36.1±13.6 | 25.0±13.6 | **<0.001** |
| **WIT ≥30 min** | 42 (25.5) | 85 (45.7) | 15 (62.5) | 142 (37.9) | **<0.001** |

BMI, body mass index; CCI, Charlson comorbidity index; EBL, estimated blood loss; GFR, glomerular filtration rate (ml/min/1.73 $m^2$); NS, tumor nephrometry score; SD, standard deviation; WIT, warm ischemia time. Data presented as n (%) excluding patients with missing data, unless otherwise noted.

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## Table 2

Multivariable logistic regression analysis demonstrating associations between patient characteristics and warm ischemia time ≥30 minutes.

| Variable | HR | 95% CI | *p*-value |
|---|---|---|---|
| **Nephrometry Score Complexity** | | | |
| **Intermediate** | 1.9 | 0.9–3.9 | **0.031** |
| **High** | 7.62 | 1.7–33.9 | **0.008** |
| **Nephrometry Score** | 1.4 | 1.1–1.7 | **0.001** |
| **Tumor Location** | | | |
| **Anterior** | 1.18 | 0.57–2.4 | 0.658 |
| **Posterior** | 1.8 | 0.68–6.8 | 0.191 |
| **Nephrometry Score** | | | 0.064 |
| **Hilar** | 2.23 | 0.0.73–6.8 | |
| **CCI** | 1.23 | 0.95–1.6 | 0.114 |
| **EBL** | 1.0 | 0.998–1.02 | 0.895 |
| **Age** | 0.98 | 0.94–1.00 | 0.105 |
| **Gender** | | | 0.074 |
| **Male** | 2.02 | 0.94–4.4 | |
| **Race** | 1.31 | 1.02–10.7 | **0.046** |
| **BMI (kg/m$^2$)** | 0.97 | 0.91–1.02 | 0.239 |
| **Collecting System Entry** | 3.28 | 1.4–7.7 | **0.006** |
| **CKD Stage** | | | |
| **I** | 1.21 | 0.63–2.31 | 0.570 |
| **II** | 1.17 | 0.33–4.08 | 0.811 |
| **≥III** | 1.68 | 0.42–6.68 | 0.463 |
| **Surgery Year** | 0.861 | 0.67–1.10 | 0.237 |
| **Surgeon** | 3.12 | 0.76–12.76 | **<0.001** |
| **GFR, % change** | 1.02 | 0.995–1.04 | 0.1421 |

BMI, body mass index; CCI, Charlson comorbidity index; EBL, estimated blood loss; GFR, glomerular filtration rate (ml/min/1.73 m$^2$).