Outcomes of Robot-assisted Partial Nephrectomy for Clinical T2 Renal Tumors: A Multicenter Analysis (ROSULA Collaborative Group)

OUTCOMES OF ROBOT-ASSISTED PARTIAL NEPHRECTOMY FOR CLINICAL T2 RENAL TUMORS: A MULTICENTER ANALYSIS (ROSULA* COLLABORATIVE GROUP)

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*RObotic SUrgery for LArge renal mass (ROSULA) project

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ABSTRACT

Background: While partial nephrectomy (PN) represents the standard surgical management for cT1 renal masses, its role for cT2 tumors is controversial. Robotic assisted PN is being increasingly implemented worldwide.

Objective: To analyze perioperative, functional, oncological outcomes of robot-assisted PN (RAPN) for cT2 tumors.

Design, setting, and participants: Retrospective analysis of a large multicenter multi-national dataset of patients with non-metastatic cT2 masses treated with robotic surgery (ROSULA: RObotic SUrgery for LArge renal mass).

Intervention: Robotic assisted PN (RAPN).

Outcome measurements and statistical analysis: Patients' demographics, lesion characteristics, perioperative variables, renal functional data, pathology and oncological data were analyzed. Univariable and multivariable regression analyses assessed the relationships with the risk of intra-/post-operative complications, recurrence and survival.

Results and limitations: 298 patients were analyzed. Median tumor size was 7.6 cm (7-8.5). Median RENAL score was 9 (8-10). Median ischemia time was 25 min (20-32). Median estimated blood loss was 150 ml (100-300). Sixteen patients had intraoperative complications (5.4%), whereas 66 (22.1%) had postoperative complications (5.0% were Clavien grade ≥3). Multivariable analysis revealed that lower RENAL score (OR 0.46, p=0.021) and confirmed pathological pT2 stage (OR 0.51, p=0.001) were protective against postoperative complications. 243 lesions (81.6%) were malignant. Twenty patients (8.2%) had positive surgical margins. Ten deaths and 25 recurrences/metastases occurred at a median follow-up of 12 months (5-35). At univariable analysis, higher pT stage was predictive of likelihood of recurrences/metastases (p=0.05). ANOVA test showed significant deterioration of renal function at discharge, while remaining stable over time at 1-yr follow-up. Main limitation of this study is the retrospective design.

Conclusions: RAPN in setting of select cT2 renal masses can be safely performed with acceptable outcomes. Further studies are warranted to corroborate our findings and to better define the role of robotic nephron-sparing for this challenging indication.

Patient summary: This report shows that robotic surgery can be used for safe removal of a large renal tumor in a minimally invasive fashion, maximizing preservation of renal function, and without compromising cancer control.

1. Introduction

Current guidelines recommend partial nephrectomy (PN) as the standard surgical treatment for clinical T1a renal tumors, whenever technically feasible [1, 2], given better renal functional preservation compared to radical nephrectomy (RN) [3]. However, for larger localized renal tumors, RN is still regarded as the reference standard, despite emerging data suggesting a potential role for a nephron-sparing approach in selected cases [4]. For T1b renal masses, PN was shown to provide to be not inferior to RN in terms of cancer control [5-7]. Recent reports, mainly limited to open surgery series, suggest that even in patients with larger masses (> 7 cm, clinical T2), PN does not compromise cancer-specific mortality [8–10].

With the diffusion of robotic daVinci surgery, experience with robot-assisted PN (RAPN) has exponentially grown over the last decade, and this has led to broaden the utilization of the procedure to more complex tumors. However, RAPN for clinical T2 renal masses represents a challenging intervention, and very few case series have been reported to date [11-16].

The aim of the present study was to analyze the perioperative, functional and oncological outcomes of RAPN for cT2 tumors in a large multi-institutional dataset (RObotic SUrgery for LArge renal mass – ROSULA project).

2. Materials and Methods

2.1. Study design

The ROSULA is a multi-center multi-national project including 22 robotic centers worldwide. A dataset of patients consecutively underwent robotic surgery either by radical or nephron sparing approach for ≥ cT2 renal masses was created. Institutional Review Board

approval or exempt was obtained at each Center. The purpose-built ROSULA database was queried for patients with non-metastatic cT2 renal masses who had undergone RAPN at 19 of participating institutions during the study period (July 2007 – Sep 2017) (**Suppl. Figure 1**).

The following parameters were collected:

a. patients' baseline characteristics (age, gender, race, body mass index [BMI], ASA score, presence of diabetes mellitus, hypertension or preoperative chronic kidney disease [CKD] stage ≥ III, solitary kidney status, preoperative hemoglobin, serum creatinine and estimated Glomerular Filtration Rate, as calculated by the MDRD formula [17];
b. tumor characteristics (side, clinical size, clinical stage according to TNM [18], cystic features, RENAL nephrometry score (tumor complexity was graded as low, moderate and high, RENAL score 4–6, 6–9 and 10–12, respectively [19]);
c. perioperative variables (transperitoneal vs retroperitoneal approach, operative time, warm ischemia time, percentage of clamp-less and cold ischemia technique procedures, estimated blood loss [EBL], intra-operative complications [including transfusions], conversions, and postoperative complications [graded according to the Clavien-Dindo system [20] – complications ≥ grade III were considered as major], length of hospital stay and hemoglobin at discharge;
d. pathology data (pathologic tumor size, pathologic stage according to TNM, tumor histology according to the 2004 World Health Organization criteria

[21], tumor grade according to Fuhrman [22], margin status, presence of sarcomatoid differentiation, presence of tumor thrombus).

e. Functional data, including serum creatinine and eGFR at discharge and at 1, 6 and 12 postoperative months. Postoperative "early" (at discharge) acute renal injury (AKI) was defined according to the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) criteria [23].

f. Oncological data, including tumor recurrence, tumor metastasis, cancer-specific mortality.

2.2. Study objectives

Primary study endpoint was the assessment of surgical (perioperative) outcomes. In this regard, as a surrogate of surgical quality, a "trifecta" outcome was used, which included negative surgical margins, no perioperative complications, and WIT $\leq$ 25 minutes [24]. Secondary endpoints were the short term (1 year) functional and oncological outcomes.

2.3. Statistical analysis

Means + standard deviations (SD) were used to report variables with a normal distribution; medians and interquartile ranges (IQR) in case of variables with a non-normal distribution instead. Frequencies and proportions were used to report categorical variables. The means of continuous and categorical variables were compared by using the student T- and the Chi-square tests, respectively. ANOVA test was used to compare more than two groups.

Univariable and multivariable forward stepwise logistic regression analyses assessed the relationships of variables of interest with the risk of: (a) intraoperative complications, (b) overall postoperative complications, and (c) postoperative renal dysfunction as defined according to the RIFLE criteria.

Univariable analyses were used to test the effect of variables of interest on the probability of recurrences or metastases. Due to the small number of cancer-related deaths, the analysis was avoided for this outcome. Significance level was set at p-value < 0.05. Statistical analysis was performed using Statistic 8.0 Software (Tulsa, Oklahoma, US).

3. Results

Two-hundred ninety-eight patients who underwent RAPN for cT2 renal mass were included in the analysis. In **supplementary Table 1**, number of cases per Institution is provided. A trend towards a higher number of cases was observed during the study period (**Figure 1**). Patients' baseline characteristics are reported in **Table 1**. Median clinical tumor size was 7.6 (IQR: 7-8.5) cm. Median RENAL score was 9 (IQR: 8-10).

3.1. Surgical outcomes

Only 8.4% of the procedures were performed by retroperitoneal approach. Mean operative time was 163 $\pm$ 75 minutes. Twenty-two (7.4%) procedures were performed by clamp-less approach. Median ischemia time was 25 (IQR: 20-32) minutes, with 5% of procedures performed by cold ischemia technique. Median estimated blood loss (EBL) was 150 ml (100-300). Sixteen patients had intraoperative complications (5.4%). Fifteen patients received intraoperative blood transfusions (5%), and one conversion to RN occurred (0.3%), which was due to sticky fat possibly compromising the oncological efficacy in soft large

mass with high risk of rupture. The detailed list of perioperative data and complications is reported in **Table 2**. Sixty-two patients (20.8%) had postoperative complications. Among these, fifteen had a major (Clavien grade $\geq$3) complication (5%).

Median length of hospitalization was 4 days (3-5). At discharge, hemoglobin was significantly reduced with respect to baseline (13.8$\pm$1.7 vs 10.4$\pm$3.0; p<0.001).

At univariable analysis, EBL and BMI were predictors of intraoperative complications (p < 0.001 and = 0.001, respectively). Clinical tumor size (< 0.001) and pT stage 3 vs 2 (p = 0.003) were predictors of postoperative complications. Multivariable logistic regression demonstrated that simple RENAL score (4-6) and non-pathological upstaging (pT2) were independently associated with a decreased risk of development of complications (OR 0.46, p=0.021 and OR 0.51, p=0.001, respectively).

3.2. Renal functional outcomes

ANOVA test showed significant deterioration of renal function at discharge (median decrease 17.5%, p-values < 0.001), while at 1-yr follow-up both SCr and eGFR were comparable to their discharge value (p = 0.798 and 0.159, respectively) (**Supplementary Figure 2**). Out of 180 patients who had complete eGFR data preoperatively and at discharge, sixty-two patients (34.4%) experienced postoperative AKI (**Table 2**). On multivariate analysis, preoperative eGFR < 60 ml/min/1.73^{m2}, increasing clinical tumor size (every 1 cm), and preoperative diabetes mellitus were independent predictors of postoperative AKI (OR = 2.61, 1.98 and 5.13, p < 0.001, = 0.009 and 0.018, respectively - **Table 3**).

3.3. Oncological outcomes

Pathology data are detailed in **Table 4**. Median size at final pathology was 7.4 cm (IQR 6.4-8.2). Most of the lesions were malignant (n=243; 81.6%). Among malignant

lesions, 58 % were Fuhrman grade 1-2 (or without grading), and 42% Fuhrman grade 3-4. In 9 cases a sarcomatoid differentiation was found. Twenty patients (8.2%) had positive surgical margins. Forty-two patients (17.2%) were down-staged to pT1a-b, whereas 93 (38.3%) were upstaged to pT3-4 at final pathology. Among the 63 patients who underwent lymph-nodes dissection, only one patient had nodal involvement (pN1).

Twenty-five recurrences or progression to metastasis (actuarial progression rate: 10.3%) were observed and 2 deaths (0.7%) related to metastatic renal cancer occurred after a median follow-up of 12 months.

At univariable Cox regression, pT3a pathological upstaging was the only significant predictor of recurrence/metastasis (p = 0.05, **Figure 2A**); tumor thrombus, higher Fuhrman grade (3-4) and sarcomatoid differentiation showed a trend towards significance (**Figure 2B** and **Figure 3A, B**, respectively).

3.4. Trifecta

A "trifecta" outcome was achieved in 120 (49.4%) patients among the 243 patients who had malignant lesions.

4. Discussion

To the best of our knowledge, this represents the largest series of RAPN for cT2 renal masses to date. The present analysis relies on a robust sample from various Institutions worldwide with an established robotic program, and it allows to draw some interesting conclusions about this "extreme" indication for a robotic nephron-sparing approach. Overall, we found RAPN for cT2 renal masses to be safely feasible, with acceptable perioperative and functional outcomes.

In a recent systematic review, Mir et al found only 4 studies comparing PN to the "gold standard" RN in the subset of patients with cT2 tumors. In their analysis, PN was found to have significantly higher blood losses and likelihood of complication rates. Nonetheless, these PN in these comparative analyses were performed with open and laparoscopic, as opposed to robotic approach. [4].

Studies on robotic nephron-sparing surgery for larger masses remain quite sparse and limited [11-14]. Malkoc et al. recently reported a single center study comparing a series of 54 robotic to 56 open partial nephrectomies for >7 cm renal tumors [15]. RAPN was found to be superior to the open approach, but median ischemia time was above 30 minutes in both the approaches. The incidence of overall complications was 18.5 % and 28.6 %, in favor of robotic, with a major complications rate of 3.7 % and 12.5 %, respectively. Complications rate of RAPN for highly complex renal masses were reported to be almost the same in a recent prospective series by Porpiglia et al., with 23.8% and 4.8 of overall and major complications, respectively [25].

Of note, the results from our multicenter study confirmed that even in case of cT2 renal tumors, the robotic approach allows for acceptable ischemia time (median 25 min) [26], and complication rates (21% overall, 5% major complications). If data on complications are slightly higher than what previously reported for RAPN [11-16], they appear to be consistently lower to series reporting complications for T2 open PN [6, 15]. Our findings that increasing tumor complexity and tumor size are predictive of postoperative complications are consistent with recent reports from large national and institutional databases. [27, 28]. Our reported Trifecta rate of 49.4% is lower than reports from series with small renal masses. Nonetheless, given that predictors for Trifecta include increasing tumor complexity or size,

our findings are not surprising. Interestingly, our findings are similar to those of Abdel Raheem and co-workers published who reported a Trifecta rate of 37.5% when examining Trifecta rates in patients undergoing PN for complex renal masses [29].

Regarding the functional data, one-third of the patients experienced postoperative AKI, as assessed by RIFLE criteria [23]. Similar rates were reported in a large sample of PN procedures by Rajan et al [30]. AKI was found to correlate by baseline patient's factors like eGFR and diabetes, as also reported by others [31]. More interestingly, tumor size was also a predictor of postoperative AKI, which can be explained by larger excision of renal parenchyma. In this respect, Zhang et al reported that parenchymal mass reduction and ischemia both contribute to acute changes after PN, and while postoperative AKI is associated with suboptimal recovery, even patients with grade 2/3 AKI up to 90% of recovery can be expected [32]. In our analysis, while eGFR was found overall to be significantly reduced at 1 month postoperatively more than 15%, it remained stable over time, which is in line with previous findings [33].

Notably, a significant proportion of patients experienced up-staging to pT3a after PN. Up-staged pT3a patients had worsened recurrence/metastasis free survival across all clinical tumor stages after PN. In a recent single institution analysis, Mouracade and colleagues evaluated on more than 1000 patients with cT1 staged renal masses the perioperative morbidity, oncological outcome and predictors of pT3a upstaging after partial nephrectomy [34]. They found that male gender and R.E.N.A.L. score were preoperative predictors of upstaging. In our multicenter cohort, we had 70% of male patients and a median RENAL score of 9. In our study, while we noted several factors trending towards significance as

predictors for recurrence or metastases, none reached statistical significance. This is most likely a limitation due to the short follow up of our cohort.

While the adoption of a nephron sparing approach for higher risk masses might be concerning from an oncological standpoint, population-based studies suggest that even in patients with adverse pathologic features, PN does not seem to compromise cancer-specific mortality, and therefore the decision to perform a PN should mostly rely on the technical feasibility [35]. In our series, the high pT3 staged tumors (33%) might be one explanation for the 8% rate of positive surgical margins. Indeed, 10 patients (50%) who had positive surgical margins were upstaged to pT3. Moreover, if one considers the open surgery literature specifically regarding the larger masses, this rate compares favorably. Indeed, in a recent review the range of positive surgical margins for these cases was found to be 0 to 31% [36]. In support of our data, in the Mouracade study pT3a tumors had 18.6% of positive surgical margins rate [34]. Using the US National Cancer Database, Fero et al. reported an overall increased rate of positive margins at 7.3%, driven by increasing use of minimally invasive approaches, and not by higher clinical stage [37].

Moreover, in a multicenter retrospective survey, Bensalah and co-authors analyzed 111 patients with PSM, concluding that PSM status more likely occurs when surgery is imperative, as could be the case of more complex renal lesions. In that study, PSM status did not influence cancer-specific survival but it was associated with increased risk of recurrence [38]. More recently, Khalifeh and colleagues found an 18-fold higher risk for recurrence in case of PSM, after adjusting for multiple tumors, tumor size, tumor growth pattern and pathological stage [39].

Concerning the oncological outcomes, our analysis showed an actuarial rate of 8.6% of recurrences or metastases, with 2 cancer-related deaths (0.7% actuarial cancer-specific mortality) occurred after a median follow-up of 12 months. Such findings could be read as satisfactory too. Indeed, even if there is still limited retrospective evidence about the oncological efficacy of PN for renal tumors larger than 7 cm, the available literature data reported in a recent review with follow-up range of 13.1 to 70 months showed 5-year progression-free survival and 5-year overall survival ranging from 71 to 92.5% and from 66 to 94.5%, respectively [36].

Our study is not devoid of limitations. First and foremost, the retrospective design accounts for some inherent biases, including patient selection and differences in surgical technique. It was beyond the scope of the present analysis to compare RAPN to the reference standard RN, and therefore a control arm was not considered. Also, the available follow-up of this cohort was limited (median 12 months), and it did not allow evaluating long term outcomes. One might argue that would be interesting to know how many cT2 renal masses were seen at these institutions during the time-period of the study to gauge the level of selection bias and to determine if most patients with cT2 masses offered robotic PN and how patients were ultimately selected for a robotic vs open partial approach. Unfortunately, we do not have this detailed information. The choice of one approach (robotic) versus the other (open) was at discretion of each surgeon. Having said that, the aim of the study was not to determine “practice patterns” of management of these large renal masses at participating institutions, but rather to report their experience with the robotic PN for this “extreme” indication. Concerning the evaluation of renal function, we concur that while the use of eGFR is a practical viable option, ideally a nuclear renal scan should be adopted [17].

However, this was not available for this study. Last, no centralized radiologic or pathologic review was performed for the here reported cases.

Notwithstanding these limitations, this series represents the largest describing the outcomes of mostly elective RAPN for large (clinical stage T2) renal masses in a "real-life" scenario. On the other hand, these study findings may not be generalizable to the entire urologic community, and they are reserved for experienced robotic surgeons/centers of excellence. Even though cT1a and certainly cT1b tumors may be challenging for most, and PN remains overall underused for these "standard" indications. Future definition of maximum tumor threshold and more accurate preoperative staging are mandatory to optimize the outcomes. Moreover, image-guidance technology could aid in expanding the role of RAPN for these challenging indications [40].

Conclusions

RAPN in case of large renal masses can be safely performed with acceptable outcomes. Further studies are warranted to corroborate our findings and to better define the role of RAPN for this challenging indication. For the time being, the decision to proceed with robotic nephron sparing surgery should be weighted based on the technical feasibility and patient's individualized competing risk of morbidity and cancer related events.

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Figures' Legend

Figure 1. Chart showing the number of robot assisted partial nephrectomy (RAPN) during the study period.

Figure 2. Cumulative Proportion of Recurrence or metastasis (Kaplan-Meier curves) after stratification by A) pT stages according to TNM and B) presence of tumor thrombus (TT).

Figure 3. Cumulative Proportion of Recurrence or metastasis (Kaplan-Meier curves) after stratification by A) Fuhrman grade and B) presence of sarcomatoid pattern (sarc.).

Supplementary Figure 1. Study flow chart.

Supplementary Figure 2. Box and Whisker Plots showing Median, Inter-Quartile range (25-75%) and Minimum and Maximum values of the distribution (Min-Max) of A) Serum Creatinine (SCr) and B) estimated Glomerular Filtration Rate (eGFR). Overall ANOVA test showed a significant difference in SCr and eGFR (preoperative vs. postoperative, $p < 0.001$). Conversely, no differences were found among the postoperative values of both SCr and eGFR ($p = 0.798$ and 0.159, respectively).