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Outcomes and predictors of benign histology in patients undergoing robotic partial or radical nephrectomy for renal masses: a multicenter study

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Introduction Theaim of this study was to assess preoperative factors associated with benign histology in patients undergoing surgical removal of a renal mass and to analyze outcomes of robotic partial nephrectomy (PN) and radical nephrectomy (RN) for these masses.

Material and methods Overall, 2,944 cases (543 benign and 2,401 malignant) who underwent robotic PN and RN between 2003–2018 at 10 institutions worldwide were included. The assessment of the predictors of benign histology was made at the final surgical pathology report. Descriptive statistics, Mann-Whitney U, Pearson's χ^2, and logistic regression analysis were used.

Results Patients in the benign group were mostly female (61 vs. 33%; p <0.001), with lower body mass index (BMI) (26.0 vs. 27.1 kg/m^2; p <0.001). The benign group presented smaller tumor size (2.8 vs. 3.5 cm; p <0.001), R.E.N.A.L. score (6.0 vs. 7.0; p <0.001). There was a lower rate of hilar (11 vs.18%; p = 0.001), cT≥3 (1 vs. 4.5%; p <0.001) tumors in the benign group. There was a statistically significant higher rate of PN in the benign group (97 vs. 86%; p <0.001) as well as a statistically significant lower 30-day re-admission rate (2 vs. 5%; p = 0.081). Multivariable analysis showed male gender (OR: 0.52; p <0.001), BMI (OR: 0.95; p <0.001), and cT3a (OR: 0.22; p = 0.005) to be inversely associated to benign histology.

Conclusions In 18% of cases, a benign histologic type was found. Only 3% of these tumors were treated with RN. Female gender, lower BMI, and higher T staging showed to be independent predictors of benign histology.

Key Words: benign renal masses ‹› malignant renal masses ‹› renal cell carcinoma ‹› predictors

INTRODUCTION

Renal cell carcinoma (RCC) represents the sixth and the tenth most common malignancy in males and females, respectively [1]. The last two decades saw an overall increase in incidence of RCC in the US population, whereas mortality significantly decreased [2]. The incidence increase could be due to higher exposure to predisposing factors such as hypertension, diabetes, smoking etc., as well as to the earlier incidental diagnosis of renal masses [3, 4]. The latter translated into the recommendation of partial nephrectomy (PN), active surveillance (AS), and ablation therapies as possible strategies for small renal masses (SRM) management [5, 6].
Renal biopsy, biological markers and radiologic tools have been assessed to characterize SRM [7]. Predictors of benign histology have been investigated but evidence remains sparse [8]. This can have important clinical implications such as the risk of overtreatment [9]. Some authors raised concerns about the dissemination of robotic surgery favoring overtreatment of SRM [10]. Others argued that robotic surgery favored the decrease of radical nephrectomy (RN) [11], which in many centers is still used for SRM [12]. On the other hand, the role of renal biopsy, which could help determine histology, remains underused [13].
The aim of this study was to assess the factors associated to benign histology of renal masses after robotic surgery in a large retrospective multi-institutional international study and to analyze the outcomes of robotic PN and RN for these masses.

MATERIAL AND METHODS

After Institutional Review Board approval and data use agreement, clinical information of 3,479 patients who underwent robotic PN and RN for renal masses between 2003 and 2018 were collected within a retrospective multi-institutional dataset. Overall, 2,944 cases (543 benign and 2,401 malignant), performed at 10 large-volume tertiary institutions presented complete data regarding benign or malignant histology. None of the patients included underwent preoperative renal biopsy. Exclusion criteria included genetic syndromes such as Von-Hippel Lindau disease, Bigg-Hogg-Dubé disease, tuberous sclerosis, bilateral renal tumors, and previous surgery for malignant renal tumor.

Variables definition

The following variables were considered:
- Baseline features: age, gender (male), body mass index (BMI), race (Caucasian), American Society of Anesthesiologists (ASA) Score ≥3, diabetes, hypertension, chronic kidney disease (CKD) ≥III, pre-operative hemoglobin (Hb) and estimated glomerular filtration rate (eGFR) according to MDRD formula, and solitary kidney status;
- Clinical tumor staging: tumor size, R.E.N.A.L. Score, R.E.N.A.L. Score complexity (low, intermediate, high), T stage (any), N stage (any), and M stage (any);
- Surgical outcomes: retroperitoneal approach rate, operative time (OT), estimated blood loss (EBL), intraoperative transfusions and complications, post-operative overall and major complications (Clavien-Dindo ≥3), length of stay (LoS), re-admission rate within 30-days, eGFR at discharge;
- Pathological outcomes: tumor size, T staging (T ≥3), N staging, and positive surgical margins (PSM).

End-point

The main outcome of the present study was the assessment of the predictors of benign histology at final surgical pathology report.

Statistical analysis

Statistical analysis was performed according to guidelines for reporting statistics in urology clinical studies [14]. It consisted of two steps.
First, the Shapiro-Wilk test was used to establish data distribution. Continuous and binomial variables were reported as median and interquartile range (IQR) or frequencies and proportion, respectively. Mann-Whitney U and Pearson's χ^2 tests were deemed as appropriate for the comparison among the two groups.
Second, univariate and multivariate logistic regression analyses were used to evaluate the odds ratio (OR) and confidence intervals (CI) of the predictors of benign histology. According to previous evidence, the model included age, gender (female vs. male), BMI, pre-operative eGFR, R.E.N.A.L. Score (continuous), tumor hilar location, and cT staging in five categories (1a, 1b, 2a, 2b, and 3a) as covariates.

All tests were two-sided and statistical significance was set at p <0.05. Stata® 15.0 (StataCorp 2017. Stata Statistical Software: release 15. StataCorp LLC, College Station, TX, USA) was used to perform statistical analysis according to the following syntax: *swilk, ranksum, tabulate chi2, logistic.*

RESULTS

Overall, 18% of patients were found to have benign histology at final pathology report, and 3% of them underwent RN.

At baseline, there were more female patients in the benign group (61 vs. 33%; p <0.001), and this group presented a lower BMI [26.0 (23.6–29.1) vs. 27.1 (24.5–30.5) kg/m^2; p <0.001], lower rate of ASA ≥3 (32 vs. 39%; p = 0.013), lower rate of diabetes (11 vs. 17%; p = 0.008), lower rate of hypertension (37 vs. 44%; p = 0.004) and better eGFR [83.6 (68.0–97.1) vs. 81.0 (64.4–96.0) ml/min/1.73 m^2; p = 0.048]. Moreover, the benign histology group also presented smaller tumor size [2.8 (2.0–4.3) vs. 3.5 (2.3–7.0) cm; p <0.001], lower R.E.N.A.L. score [6.0 (5.0–8.0) vs 7.0 (6.0–9.0); p <0.001], and lower rate of hilar (11 vs. 18%; p = 0.001), and cT ≥3 stage (1 vs. 4.5%; p <0.001) (Table 1).

Pathology confirmed a smaller tumor size in the benign group [2.8 (1.9–4.2) vs. 3.5 (2.2–6.0) cm; p <0.001].

Multivariable analysis showed male gender (OR: 0.52; 95%CI: 0.41–0.67; p <0.001), BMI (OR: 0.95; 95%CI: 0.93–.98; p<0.001), and cT3a (OR: 0.22; 95%CI: 0.07, 0.63; p = 0.005) to be inversely associated with benign histology (Table 2).

Table 1. *Baseline features and outcomes*

Variables	Benign	Malignant	p value
Number of patients	543 (18%)	2,401 (82%)	
Baseline features			
Age (years)	61.0 (52.0–70.0)	61.6 (52.0–69.8)	0.745
Gender (male)	266/543 (49%)	607/2,392 (67%)	<0.001
BMI (kg/m^2)	26.0 (23.6–29.1)	27.1 (24.5–30.5)	<0.001
ASA ≥3	154/488 (32%)	802/2,074 (39%)	0.013
Diabetes	53/462 (11%)	365/2,116 (17%)	0.008
Hypertension	169/461 (37%)	929/2,117 (44%)	0.004
CKD ≥III	28/452 (6%)	178/2,072 (9%)	0.092
Pre–operative Hb (g/dl)	13.8 (12.8–14.9)	14.1 (12.9–15.1)	0.046
Pre–operative eGFR (ml/min/1.73m^2)	83.6 (68.0–97.1)	81.0 (64.4–96.0)	0.048
Solitary kidney	13/475 (3%)	73/1,994(4%)	0.324
Clinical tumor staging			
Tumor size (cm)	2.8 (2.0–4.3)	3.5 (2.3–7.0)	<0.001
R.E.N.A.L. (continuous)	6.0 (5.0–8.0)	7.0 (6.0–9.0)	<0.001
R.E.N.A.L. (complexity)			<0.001
Low (4–6)	242/457 (53%)	772/2,041 (38%)	
Intermediate (7–9)	174/457 (38%)	864/2,041 (42%)	
High (10–12)	41/457 (9%)	405/2,041 (20%)	
Tumor hilar location	46/403 (11%)	299/1,669 (18%)	0.001
cT			<0.001
1a	393/538 (73%)	1,377/2,371 (58%)	
1b	80/538 (15%)	408/2,371 (17%)	
2a	49/538 (9%)	379/2,371 (16%)	
2b	10/538 (2%)	107/2,371 (4.5%)	
3a	6/538 (1%)	95/2,371 (4%)	
3b	–	2/2,311 (0.2%)	
4	–	3/2,311 (0.3%)	
Surgical outcomes			
PN	529/543 (97%)	2,048/2,392 (86%)	<0.001
Pathological outcomes			
Tumor size (cm)	2.8 (1.9–4.2)	3.5 (2.2–6.0)	<0.001
PSM	18/473 (4%)	103/2,346 (4%)	0.567

ASA – American Society of Anesthesiologists Score; BMI – body mass index; CKD – chronic kidney disease; Hb – hemoglobin; eGFR – estimated glomerular filtration rate; PN – partial nephrectomy; RN – radical nephrectomy; PSM – positive surgical margins

DISCUSSION

The incidence of benign renal tumors among renal masses is around 15–30% [9, 15], and composite models and nomograms showed to be inconclusive tools to predict the rate of benign histology [16]. In our analysis, we found 18% of tumors to be benign which is within the range established in the literature. Among these, most were diagnosed in female patients. In a retrospective study including 135 cases, Mauermann et al. described a higher "female-to-male ratio" for benign renal masses compared to RCC (1.18:1 vs. 0.57:1; p <0.001) [17]. Moreover, the authors described angiomyolipoma to be the most frequent benign variant among females. Equally, in our analysis angiomyolipoma was more frequent in females (78% vs. 22%) and was the most common benign tumor among them: 43% (Table 3). On the other hand, Kim et al. found the prevalence of benign renal masses to be higher among males in a national dataset [15]. Given these, in our analysis, male gender showed to be significantly not associated with benign histology (OR: 0.52; p <0.001).

We evaluated BMI as a predictor of benign histology as well, and we found each point of BMI decrease to be associated with benign histology. Epidemiological data largely demonstrated the association of RCC with high BMI, despite the 'obesity paradox'. Indeed, these patients seem to present higher incidence of RCC, but less aggressive disease with better oncological outcomes [18]. Kava et al. retrospectively

Table 2. *Logistic regression predictors benign tumor*

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	p value	OR	95%CI	p value
Age	0.99	0.99, 1.00	0.514	1.00	0.98, 1.00	0.968
Gender						
Female	Ref			Ref		
Male	0.47	0.39, 0.56	<0.001	0.52	0.41, 0.67	<0.001
BMI	0.96	0.94, 0.98	<0.001	0.95	0.93, 0.98	0.001
Pre-operative eGFR	1.00	0.99, 1.00	0.099	0.95	0.88, 1.03	0.722
R.E.N.A.L. Score	0.83	0.79, 0.87	<0.001	0.95	0.88, 1.03	0.256
Tumor hilar location	0.59	0.42, 0.82	<0.001	0.80	0.53, 1.20	0.282
cT						
1a	Ref			Ref		
1b	0.68	0.52, 0.89	0.005	0.79	0.55, 1.14	0.214
2a	0.45	0.32, 0.62	<0.001	0.77	0.48, 1.22	0.276
2b	0.32	0.17, 0.63	0.001	0.60	0.24, 1.49	0.272
3a	0.22	0.09, 0.50	<0.001	0.22	0.07, 0.63	0.005

BMI – body mass index; eGFR – estimated glomerular filtration rate; OR – odds ratio; CI – confidence interval

evaluated a cohort of 316 consecutive patients who underwent PN and achieved our same result [19]. Nevertheless, in our study the negative association between BMI increase and benign histology might be consequence of a selection bias, given the lower rate of diabetics and hypertensive patients in the benign group.

Regarding tumor characteristics, the benign group presented less aggressive disease with smaller size, lower R.E.N.A.L. score, lower rate of hilar location, and lower clinical TNM staging. Nevertheless, only cT3a staging showed to present a negative association to benign histology (OR: 0.22; p = 0.005). This could represent a clue for the surgeon during decision making, even though there are several pitfalls which limit radiological evaluation of renal masses [20]. The role of the above-mentioned covariates to predict histology is still controversial. Indeed, Kutikov et al. developed a nomogram which suggested the potential role of R.E.N.A.L. score to predict malignant histology [21]. Again, in a single center study on 334 patients with renal tumor, the association of tumor size and the variable N 3 (nearness) with tumor histology and higher Fuhrman grade was demonstrated [22]. On the contrary, Antonelli et al. in a validation study of Kutikov's nomogram failed to demonstrate the predictive role of the R.E.N.A.L. nomogram [23]. In all these studies tumor size was an independent predictor of histology, but we did not consider it as a covariate because this is already included in the R.E.N.A.L. score. It is worth noting that in this study hilar tumor location was not a predictor of tumor benign histology. This data corroborates the findings made by Bauman which described lateral tumor location as an independent predictor of benign tumor [8].

Table 3. *Benign histology subtypes*

Benign histology	Female (247)	Male (142)	Overall (389)
Adenoma	5/5 (100%)	–	5/389 (1%)
Angiomyolipoma	107/136 (78%)	29/136 (22%)	136/389 (35%)
Cystic nephroma	2/2 (100%)	–	2/389 (0.5%)
Oncocytoma	98/200 (49%)	102/200 (51%)	200/389 (51%)
Others	35/46 (76%)	11/46 (24%)	46/389 (12%)

Moreover, a recently published study suggested no difference in the incidence of benign renal tumors between non-hilar and hilar location (17.4 vs. 12.9%) suggesting no compelling rationale to perform RN for hilar tumors [24]. Nevertheless, in our cohort, RN was still mostly performed for hilar tumors (57 vs. 12%; p <0.001) compared to PN (data not shown). Overall, PN was performed for 97% and 86% of benign and malignant tumors, respectively.

Given these, we noticed that 3% of RN still present a benign histology at final pathology report. Recently, Nguyen et al. evaluated treatment trend and costs of benign renal masses within the National Inpatient Sample database. The authors identified 7,099 benign tumors and RN still represented 44.4% of treatments [25]. In a multicenter retrospective analysis by Ljungberg et al., including 506 consecutive patients diagnosed to have a benign renal tumor, RN was performed in 24% of cases [26]. The lower incidence of RN in our study might be due to the nature of the institutions involved, where PN represents the preferred treatment for renal masses, even in case of large and complex tumors [27, 28]. Moreover, this report relied only on robotic procedures, but laparoscopic RN is still preferred to robotic RN

in many centers worldwide. Nevertheless, our findings underline once again the burden of an accurate pre-operative diagnosis of benign renal tumor to avoid surgical treatment, especially RN. Evidence demonstrated a paradigm shift in benign renal masses treatment and renal biopsy use [13], but further efforts are needed to predict renal neoplasm histology and to avoid overtreatment. Indeed, a retrospective analysis within a cohort of 542 patients who underwent routine renal tumor biopsy before either PN or RN demonstrated that tumor biopsy reduced the surgery for benign neoplasms [29]. Unfortunately, renal mass biopsy was not routinely performed within the institution involved in this study and we could not account for renal biopsy in this study. In addition, in the era of cost containment, surgical management of benign renal tumors represent a significant economic effort [25]. Given these, the surgical management of benign renal masses is still controversial and the decision to proceed to surgery should be individualized and based on the assessment of competing risks of mortality. Nevertheless, the non-interventional management is debated as well. Indeed, AS is poorly enquired for benign renal neoplasms, and currently data regarding long long-term AS of non-angiomyolipoma has short term follow-up and average tumor size of 2 cm or less [30].

However, our results could aid the surgeon to better understand which patient might benefit more from a renal biopsy before, avoiding unnecessary surgical treatments.

Herein we presented one of the largest 'real-life' data analysis relying to the predictors of benign histology in patients with renal masses who underwent robotic surgery. The multicenter design and the large sample size represent the strength points; nevertheless, several limitations need to be acknowledged. Given the retrospective nature, a high risk of selection, blinding, and attrition bias should be considered. All data come from tertiary, large volume centers with robotic equipment and surgeons experienced in renal cancer management, making the results not applicable to every institution in reality. In addition, none of the centers involved performed renal biopsy, routinely. In our analysis, we could not account for detailed radiological data such as Hounsfield Units, which could be useful to identify benign renal masses characteristics [31], or the use of CT rather than MRI [32]. Lastly, despite the large sample size, the number of benign tumors is limited, thus we claim for future large, prospective, multicenter studies to give stronger evidences regarding this topic.

CONCLUSIONS

In a large contemporary multicenter series of patients undergoing surgical removal of renal tumor, in 18% a benign histologic type was found on final pathology. Notably, only 3% of these tumors were treated with RN, which is a lower compared to previous literature. Female gender, lower BMI, and higher T staging showed to be independent predictors of benign histology. Based on our data, decision for surgery on benign masses may safely prioritize minimally invasive PN, and should be driven by a patient specific and individualized assessment of competing causes of morbidity and mortality.

Incorporating better diagnostic tools in the future might help facilitate improved characterization of the biological potential of renal tumors and to avoid overtreatment.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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