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Upstaging to pT3a disease in patients undergoing robotic partial nephrectomy for cT1 kidney cancer: Outcomes and predictors from a multi-institutional dataset

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ABSTRACT

Objectives: Surgically treated clinical T1 (cT1) kidney cancer has in general a good prognosis, but there is a risk of upstaging that can potentially jeopardize the oncological outcomes after partial nephrectomy (PN). Aim of this study is to analyze the outcomes of robot-assisted PN (RAPN) for cT1 kidney cancer upstaged to pT3a, and to identify predictors of upstaging.

Material and methods: The study cohort included 1,640 cT1 patients who underwent RAPN between 2005 and 2018 at 10 academic institutions. Multivariate logistic regression model was used to assess the predictors of upstaging. Kaplan-Meier curves and multivariable Cox regression analyses were used to evaluate recurrence-free survival and overall survival.

Results: Overall, 74 (4%) were upstaged cases (cT1/pT3a). Upstaged patients presented larger renal tumors (3.1 vs. 2.4 cm; $P = 0.001$), and higher R.E.N.A.L. score (8.0 vs. 6.0; $P = 0.004$). cT1/pT3a group had higher rate of intraoperative complications (5 vs. 1% $P = 0.032$), higher pathological tumor size (3.2 vs. 2.5 cm; $P < 0.001$), higher rate of Fuhrman grade ≥3 (32 vs. 17%; $P = 0.002$), and higher number of sarcomatoid differentiation (4 vs. 1%; $P = 0.008$). Chronic kidney disease (CKD) stage ≥3 (OR: 2.54; $P < 0.014$), and clinical tumor size (OR: 1.07; $P < 0.001$) were independent predictors of upstaging. cT1/pT3a group had worse 2-year (94% vs. 99%) recurrence-free survival ($P < 0.001$).

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Conclusions: Upstaging to pT3a in patients with cT1 renal mass undergoing RAPN represents an uncommon event, involving less than 5% of cases. Pathologic upstaging might translate into worse oncological outcomes, and therefore strict follow-up protocols should be applied in these cases.

Keywords: Robotic partial nephrectomy; Upstaging; Outcomes; Predictors

1. Introduction

The exponential increase in early detection of kidney cancer has dramatically changed its management over the past 2 decades, and partial nephrectomy (PN) has replaced radical nephrectomy as standard surgical treatment for T1 disease [1,2]. A paradigm shift towards PN was also observed in the management of T1b and T2 renal masses [3−5]. Robotic-assisted PN (RAPN) is rapidly emerging as preferred surgical approach for PN, given its potential benefits [6]. Other less invasive treatment options, such as active surveillance and kidney ablation, can be adopted for selected cases.

While surgically treated clinical T1 (cT1) kidney cancer has in general a good prognosis, there is a risk of upstaging that can potentially jeopardize the oncological outcomes of patients undergoing PN [7]. It is commonly accepted to consider "upstaged" those cT1 tumors which result as pT3a at final pathology. This because the upstaging to pT2 or pT3b could be consequence of the radiologist misjudgment of the tumor dimension or of the presence of venous thrombus [8].

Which could be the predictors as well as the impact of the upstaging on the prognosis remains unclear. The aim of the current study was to provide further evidence regarding the predictors, and the prognostic value of the upstaging to pT3a relying on one of the largest cohorts of cT1 patients who underwent RAPN at 10 high volume centers.

2. Materials and Methods

2.1. Study population

This is a retrospective international study including data of RAPN performed at 10 academic Institutions (6 European and 4 USA). Institutional review board approval and data sharing was obtained at each center involved. Data of 1,641 patients who underwent RAPN between 2005 and 2018 were collected. Among these, 74 (4%) were upstaged cases (cT1/pT3a), and they were retrospectively compared to 1,566 patients whose preoperative staging was confirmed at pathological final report (cT1/pT1).

2.2. Variable definition

Baseline (age at the surgery, gender, body mass index [BMI], American Society of Anesthesiologists [ASA] Score ≥3, diabetes, hypertension, chronic kidney disease [CKD] stage ≥3, preoperative Hb, estimated glomerular filtration rate [eGFR], and solitary kidney status), clinical staging (tumor size, R.E.N.A.L. Score [continuous and categorical], exophytic properties, and hilar location), surgical outcomes (operative time, estimated blood loss, hilar management [artery clamp, artery and vein clamp, zero ischemia], ischemia time, intraoperative transfusions, intraoperative complications, overall, and major complications [according to Clavien-Dindo classification ≥3], length of stay, readmission rate within 30 days, Hb at discharge, and eGFR and Δ eGFR at discharge), pathological outcomes (tumor size, benign histology, histology, Fuhrman grade ≥3, sarcomatoid differentiation, positive surgical margins, recurrence and death rate) were assessed.

Follow-up consisted of a postoperative baseline visit at 3 months after surgery. Subsequently, the minimum follow-up consisted of at least 1 annual visit. All patients included in this study underwent CT scan/MRI or abdomen ultrasound plus chest X-ray at 6 months after surgery and then annually.

2.3. End-point

The outcomes of our study were represented by the upstaging (defined as pT3a disease at final histopathology), recurrence-free survival (RFS) (defined as positive imaging during follow-up) and overall survival (OS).

2.4. Statistical analysis

Statistical analyses, as well as reporting and interpretation of the results, were conducted according to established guidelines [9] and consisted of 4 steps. First, Shapiro-Wilk test was used to evaluate data distribution. Medians and interquartile ranges or frequencies and proportions were reported for continuous or categorical variables, respectively. The comparison between the 2 groups (cT1/pT3a vs. cT1/pT1) was assessed through Mann-Whitney *U* test for continuous data, and Pearson's chi-sqaure test for dichotomous. Second, logistic regression model was used to identify the predictors of upstaging. Third, 2- year RFS and OS were estimated using Kaplan-Meier method between the 2 groups of interest. Log-rank test was used to assess univariable differences. Fourth, Cox regression analysis was performed to assess the predictors of disease recurrence and overall mortality. All statistical tests were performed with Stata 15.0 (StataCorp 2017. Stata Statistical Software: release 15. StataCorp LLC, College Station, TX), and statistical significance was set at $P \leq 0.05$.

3. Results

Overall, 74 (4%) patients were upstaged at final histopathology (cT1/pT3a). At baseline cT1/pT3a group presented higher rate of CKD stage ≥3 (20 vs. 7%; $P = 0.001$), larger renal tumors (median size 4.3 vs. 2.7 cm; $P < 0.001$), and higher R.E.N.A.L. score (median 8 vs. 6; $P = 0.004$; Table 1) relative to cT1/pT1 group.

No statistically significant difference was observed in terms of operative time, and estimated blood loss, whereas cT1/pT3a group had longer median ischemia time (20 vs. 16 minutes; $P = 0.011$). cT1/pT3a group had higher rate of intraoperative complications 5 vs. 1%; $P = 0.032$ (Table 2). We found worse median eGFR at discharge in the upstaged group (65 vs. 76.7 ml/min; $P < 0.001$), as well as higher Δ eGFR (10 vs. 6.4 ml/min; $P = 0.033$) (Table 1).

In terms of pathological outcomes, cT1/pT3a group had higher pathological median tumor size (3.2 vs. 2.5 cm; $P < 0.001$), higher rate of Fuhrman grade ≥3 (32 vs. 17%; $P = 0.002$), and sarcomatoid differentiation (4 vs. 1%; $P = 0.008$). An absolute higher recurrence rate was found in the upstaged group (7 vs. 2%; $P = 0.003$) (Table 1 and Supplementary Table 1).

At multivariable logistic regression analysis, CKD stage ≥3 (odds ratio [OR]: 2.5; 95% confidence interval [CI]: 1.21, 5.34; $P = 0.014$) and clinical tumor size (OR: 1.07; 95%CI: 1.05, 1.10; $P < 0.001$) were independent predictors of upstaging (Table 3).

Overall, the rate of recurrence and overall mortality was 2 and 3.2%, respectively. The median follow-up in patients who survived was 32 months.

Survival analysis demonstrated worse 2-year (94% [95%CI: 76, 98%] vs. 99% [95%CI: 98, 99]) RFS in the cT1/pT3a group (log-rank $P < 0.001$). No statistically significant difference was noticed between upstaged and non-upstaged group in terms of OS at 2 years (97% [95%CI: 79, 99] vs. 98% [95%CI: 97, 99]): log-rank $P = 0.472$ (Fig. 1). At Cox multivariable analysis, Fuhrman grade ≥3 (hazard ratio [HR]: 5.49; 95%CI: 2.07, 14.56; $P = 0.001$), and upstaging (HR: 6.69; 95%CI: 1.49, 32.74; $P = 0.013$) were independent predictors of disease recurrence. ASA ≥ 3 was the only predictor of overall mortality (HR: 3.15; 95%CI: 1.05, 9.42; $P = 0.040$) (Table 4).

4. Discussion

This is a comparative analysis between non-upstaged (cT1/pT1) and upstaged (cT1/pT3a) patients after RAPN. Our results showed that only 4% of cT1 renal masses were upstaged to pT3a. We underlined some differences among the two groups which could be useful to identify preoperatively those patients who might conceal a pT3a tumor, who could require a different surgical and follow-up management.

The correlation between parenchymal renal tumor and CKD is wellestablished as neoplastic masses substitute functional with nonfunctional parenchyma. In addition, renal masses could compress excretory system and compromise urine outflow. Radiological studies assessed microvessel and lymphatic vessel density, and perfusion values in neoplastic kidneys and found them as lower as the pT staging was higher, even if the results did not achieve the conventional levels of statistical significance [8]. Notably, Dey et al. assessed the predictors of preoperative proteinuria and CKD and found clinical staging to be associated to preoperative kidney function [10]. Despite in our analysis renal masses were all cT1, we found a higher rate of CKD in the upstaged group with a difference of 11% between the two groups. This finding confirms the aforementioned results suggesting presence of CKD as a clue of pT3a tumor at final histology.

The risk of upstaging was found to be associated to clinical tumor dimension and nephrometry score as well. Tumor size and higher R.E.N.A.L. score were already accounted as predictors of tumor malignancy and grading [11]. Moreover, a recent analysis regarding the proliferative activity of T1 renal masses demonstrated a direct proportionality between malignant cells proliferative activity and nephrometry score. Indeed, neoplasms with higher R.E.N.A.L. score had higher Ki67 expression, a well-known marker of cell proliferation [12]. Our data do not deviate from available evidence and corroborate the correlation of tumor dimension and nephrometry score with upstaging, as supposed by other authors [13]. Noteworthy, clinical tumor dimension in our analysis reached the independent predictor of upstaging (OR: 1.07; 95%CI: 1.05, 1.10; $P < 0.001$). Gorin et al. evaluated the predictors of upstaging in a large multicenter cohort of RAPN cases. They also found upstaged tumors to be 4% of their entire sample and built a multivariate model including gender, R.E.N.A.L. complexity, clinical tumor dimension, and hilar location. Their analysis demonstrated the association between tumor dimension, and hilar location with upstaging [14]. On the contrary, we failed to find hilar location to be an independent predictor of upstaging, as also reported Correa et al. [15]. This discrepancy could be explained by the fact that in the study by Gorin et al. [14] there was a higher rate of hilar located tumors (i.e., 46%). Of note, Correa et al. [15] reported approximately the same percentage of hilar tumors compared to our series.

Despite the more complex tumor features within the cT1/pT3a group, these did not influence the surgical outcomes. The only one difference was recognized in terms of ischemia time and intraoperative complications which were higher in the upstaged group. Once again, this data corroborate the higher complexity of upstaged lesions, which might imply a challenging tumor resection with higher risk of intraoperative complications and longer ischemia time. To the best of our knowledge, only another study assessed the risk of intraoperative complications in upstaged renal masses and the authors found a higher risk in the cT1/pT3a groups, but it did not achieve the conventional level of significance $P = 0.08$ [16]. Regarding ischemia time, despite the longer time in the cT1/pT3a group, both groups had an ischemia time under 25 minutes and the difference was of

Table 1
Baseline features and outcomes

Variables	cT1/pT1	cT1/pT3a	*P* value
Number of patients	1,566 (96%)	74 (4%)	
Baseline features			
Age (y)	61.0 (52.0-69.7)	63.4 (55.0-70.0)	0.118
Gender (male)	1,036/1,566 (66%)	54/74 (73%)	0.225
BMI (kg/m^2)	26.9 (24.3-30.0)	27.2 (25.0-31.0)	0.323
ASA score ≥ 3	507/1,406 (36%)	30/65 (46%)	0.247
Diabetes	185/1,299 (14%)	13/56 (23%)	0.174
Hypertension	542/1,303 (42%)	28/56 (50%)	0.212
CKD stage ≥ 3	96/1,298 (7%)	14/69 (20%)	**0.001**
Solitary kidney	50/1,347 (4%)	5/66 (7%)	0.113
Preop Hb (g/dl)	14.3 (13.2-15.1)	14.3 (13.8-15.3)	0.341
Preop eGFR (ml/min/1.73 m^2)	84.0 (68.3-98.9)	79.6 (59.7-95.3)	0.120
Clinical tumor staging			
Tumor size (cm)	2.4 (1.9-3.1)	3.1 (2.3-3.5)	**0.001**
R.E.N.A.L. (continuous)	6.0 (5.0-8.0)	8.0 (6.0-9.0)	**0.004**
R.E.N.A.L. (complexity)			0.232
Low (4−6)	690/1,316 (52%)	17/49 (38%)	
Intermediate (7−9)	523/1,316 (40%)	27/49 (55%)	
High (10−12)	103/1,316 (8%)	5/49 (12%)	
Exophytic properties			0.433
>50%	609/1,211 (50%)	18/44 (41%)	
<50%	460/1,211 (38%)	19/44 (43%)	
Entirely endophytic	142/1,211 (12%)	7/44 (16%)	
Hilar location	122/1,166 (10%)	10/54 (18%)	0.062
Surgical outcomes			
OT (min)	159.0 (120.0-210.0)	165.0 (133.0-205.0)	0.566
EBL (ml)	100.0 (50.0-200.0)	100.0 (50.0-250.0)	0.758
Renal hilum management			0.648
Artery clamp	940/1,313 (72%)	42/55 (76%)	
Artery and vein clamp	171/1,313 (13%)	7/55 (13%)	
Zero ischemia	202/1,313 (15%)	6/55 (11%)	
Ischemia time (min)	16.0 (11.0-23.0)	20.0 (14.5-27.0)	**0.011**
Intraoperative transfusions	21/1,452 (1%)	2/59 (3%)	0.480
Intraoperative complications	23/1,545 (1%)	3/59 (5%)	**0.032**
Overall complications	206/1,555 (13%)	11/74 (15%)	0.689
Major complications[a]	21/154 (14%)	-	0.476
Length of stay (d)	4.0 (3.0-5.0)	4.0 (3.0-6.0)	0.164
Readmission 30 days	35/879 (4%)	1/56 (2%)	0.408
Hb at discharge (g/dl)	12.1 (10.9-13.2)	12.2 (10.6-13.6)	0.506
eGFR at discharge (ml/min/1.73 m^2)	76.7 (60.3-93.6)	65.0 (49.0-77.3)	**<0.001**
Δ eGFR at discharge (ml/min/1.73 m^2)	6.4 (-2.7-18.0)	10.0 (2.3-23.5)	**0.033**
Pathological outcomes			
Tumor size (cm)	2.5 (1.8-3.0)	3.2 (2.5-4.2)	**<0.001**
Histology			0.610
Benign	8/1,552 (0.5)	-	
ccRCC	1,110/1,552 (71%)	51/74 (69%)	
pRCC	259/1,552 (17%)	11/74 (15%)	
chRCC	123/1,552 (8%)	10/74 (13%)	
Other	52/1,552 (3.5%)	2/74 (3%)	
Fuhrman grade ≥ 3	197/1,121 (17%)	10/30 (32%)	**0.002**
Sarcomatoid differentiation	9/1,351 (1%)	2/49 (4%)	**0.008**
PSM	56/1,549 (4%)	2/73 (3%)	0.694
Recurrence	29/1,566 (2%)	5/72 (7%)	**0.003**
Deaths	47/1,471 (3%)	2/71 (2%)	0.859

ASA = American Society of Anesthesiologists; BMI = body mass index; ccRCC = clear cell renal cell carcinoma; chRCC = chromophobe renal cell carcinoma; CKD = chronic kidney disease; EBL = estimated blood loss; eGFR = estimated glomerular filtration rate; OT = operative time; pRCC = papillary renal cell carcinoma; PSM = positive surgical margins.

Bold values mean statistically significant.

[a] Clavien ≥ 3.

Table 2
Intraoperative complications description

Intraoperative complications	cT1/pT1	cT1/pT3a
Bleeding	3	1
Tumor effraction	1	1
Ureteral lesion	2	1
Vessel lesion	3	-
Bowel lesion	1	-
Pleural lesion	1	-
Unknown	12	-

only 4 minutes, which does not entail any clinical difference. A challenging tumor resection might translate into longer ischemia time, lower healthy parenchyma preservation, and more difficult reconstructive phase which could influence postoperative kidney function [17]. In fact, upstaging group presented lower postoperative eGFR, and higher eGFR variation above all. Notably, this difference was not noticed preoperatively.

Pathological outcomes demonstrated worse results in the upstaged group with higher tumor size, higher rate of Fuhrman ≥3, and sarcomatoid differentiation. Literature evidence regarding pathological outcomes are controversial. Russel et al. found no difference between upstaged and non-upstaged group in terms of Fuhrman grade and sarcomatoid differentiation [18], whereas Lee et al. confirmed our findings [19]. This difference could be due to the different methods adopted to power the study, and the different design of the analysis. Notwithstanding these controversial findings, it is likely that upstaged patients present worse histological features. Indeed, our survival outcomes showed worse RFS in the upstaged group, but also upstaging, and Fuhrman grade to be predictors of recurrence. Shah et al. performed a multicenter retrospective review of 1,240 patients who underwent PN for small renal masses. In this analysis the authors aimed to evaluate the predictors of survival outcomes. The regression analysis demonstrated pT2−pT3a, clear cell histology, and Fuhrman grade to be independent predictors of recurrence [20]. Recently, a single center study described survival outcomes differences between non-upstaged and upstaged renal tumors. Moreover, the authors performed a subanalysis stratifying the groups according to histology, and they found upstaged ones to present worse overall, and histology stratified RFS [21]. On the other hand, pathological upstaging seems not to worsen oncological outcomes in those patients undergoing radical nephrectomy [22]. In our analysis we assessed whether or not there was a difference in recurrence site between the non-upstaged and the upstaged group, and we found no statistically significant difference between local and distant recurrence: $P = 0.275$ (data not shown).

Table 3
Logistic regression of predictors of tumor upstaging

Variables	Univariate analysis			Multivariate analysis		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Age	1.01	0.99, 1.04	0.051	1.01	0.99, 1.04	0.116
Gender (male)	1.38	0.81, 2.33	0.227	1.52	0.77, 2.98	0.223
BMI	1.02	0.98, 1.07	0.239	1.04	0.99, 1.10	0.062
CKD stage ≥ 3	3.18	1.71, 5.93	**<0.001**	2.54	1.21, 5.34	**0.014**
Hilar tumor location	1.94	0.95, 3.96	0.067	1.07	0.48, 2.37	0.861
Clinical tumor size	1.06	1.04, 1.08	**<0.001**	1.07	1.05, 1.10	**<0.001**

CI = confidence interval; OR = odds ratio.
Bold values mean statistically significant.

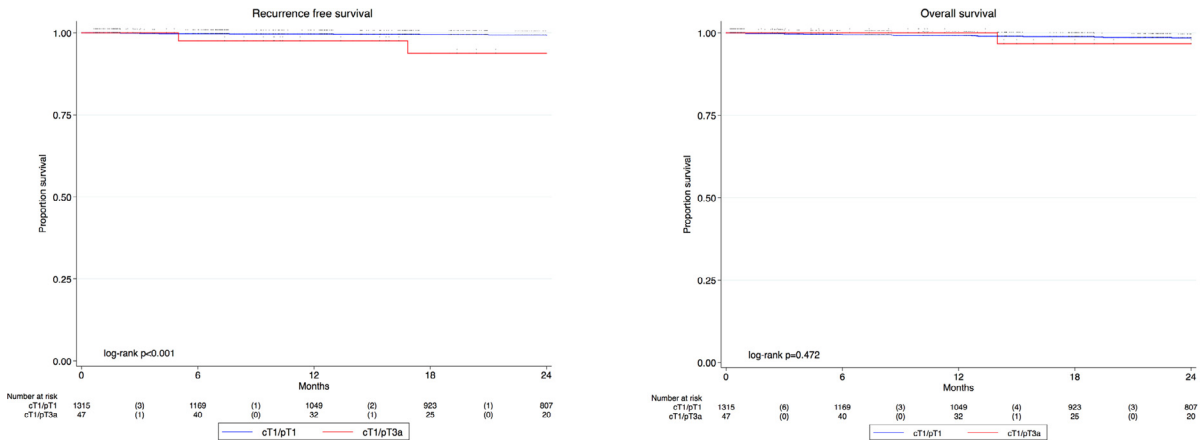

Fig. 1. Kaplan-Meier curves of RFS and OS.

Table 4
Multivariate Cox regression analysis of disease recurrence and overall mortaliy

Variables	Disease recurrence			Overall mortality		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age	0.98	0.95, 1.02	0.406	0.98	0.94, 1.01	0.303
BMI	0.80	0.69, 0.93	0.003	0.92	0.82, 1.03	0.188
ASA score ≥ 3	1.38	0.50, 3.82	0.533	3.15	1.05, 9.42	**0.040**
Clinical tumor size	1.01	0.98, 1.05	0.258	1.00	0.97, 1.04	0.598
Fuhrman grade ≥ 3	5.49	2.07, 14.56	**0.001**	0.99	0.29, 3.33	0.998
cT1/pT3a	6.69	1.49, 32.74	**0.013**	4.48	0.79, 25.35	0.090

CI = confidence interval; HR = hazard ratio.
Bold values mean statistically significant.

The aforementioned findings might induce to reconsider the management of cT1 renal masses. Indeed, the risk of upstaging, and recurrence make reasonable to address this kind of patients to a strict and longer follow-up. Notably, several studies described the risk of metachronous renal cell carcinoma at long distance, which might require a life-long follow-up [23]. Given these facts, the risk of upstaging arouses some concerns regarding the dimensional-based management of renal masses. Indeed, our results demonstrate that a more accurate characterization of renal tumors is due during the decision making. In addition, the decision whether or not to perform PN in patients at risk of upstaging should consider the protective role of renal function on all-cause and cancer-specific survival as well [24]. Probably the advent of the "omics" will add new means to tailor the best treatment for each patient [25].

Our study is characterized by intrinsic limitations which should be disclosed. The retrospective nature of the analysis makes it subject to selection, detection, and attrition bias. Thus, our results should be interpreted with caution. Our data come from high-volume centers, so they might not be generalized to different hospital settings. The nature of the dataset did not allow to perform a cancer-specific survival analysis regarding mortality, so we were not able to draw any conclusion about cancer-specific outcomes. Moreover, we did not stratify upstaged patients according to vasculature invasion, invasion into the pelvic-calyceal system, perirenal fat invasion, or sinus fat invasion. Finally, studies with longer follow-up are needed to confirm our findings.

5. Conclusions

Upstaging to pT3a in patients with cT1 renal mass undergoing RAPN represents an uncommon event, involving less than 5% of cases. One should be aware that pathologic upstaging might translate into worse oncological outcomes, and therefore strict follow-up protocols should be applied in these cases. Preoperative identification of these cases remains challenging, and it needs further investigation.

Conflict of interest

The authors declare that they have no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urolonc.2019.12.024.

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