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ORIGINAL ARTICLE

Perioperative morbidity, oncological outcomes and predictors of pT3a upstaging for patients undergoing partial nephrectomy for cT1 tumors

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Abstract
Objectives To evaluate perioperative morbidity, oncological outcome and predictors of pT3a upstaging after partial nephrectomy (PN).
Materials and methods Retrospective study of 1042 patients who underwent PN for cT1N0M0 renal cell carcinoma between 2007 and 2015. A total of 113 cT1 patients were upstaged to pT3a, while 929 were staged as pT1. Demographic, perioperative and pathological variables were reviewed. We compared the clinico-pathological characteristics, perioperative morbidity and oncological outcomes between pT3a and pT1 groups. Multivariate regression evaluates variables associated with T3a upstaging. Recurrence-free survival (RFS) and overall survival analyses were performed. Survival curves were compared using log-rank test.
Results The pT3a tumors were high complexity tumors (median RENAL score 8 vs. 7, $p<0.01$), higher hilar (h) location (27.5 vs. 14.8%, $p<0.01$), higher grade (57.5 vs. 38.2%, $p<0.01$), and higher positive surgical margins (18.6 vs. 5.8%, $p<0.01$. Patients with pT3a had a higher estimated blood loss, transfusion rate, ischemia time and overall complications, though there were no differences in median e-GFR decline and major (Grade III-V) complications. Five-year RFS was 78.5% for pT3a group vs. 94.6% for pT1 group (log-rank $p<0.01$). Male gender (OR 2.2, $p<0.01$), and R.E.N.A.L. score (OR 2.3, $p=0.01$) were preoperative predictors of upstaging. We acknowledge limitations in our study, most are inherent problems of retrospective studies.
Conclusion Perioperative morbidity, after partial nephrectomy, is acceptable in cT1/pT3 tumors in comparison to cT1/pT1; however, upstaged patients had a worse oncological outcome. cT1/pT3a tumors are associated with adverse clinico-pathological features. Preoperative risk predictors of upstaging were higher R.E.N.A.L. score and male gender.

Keywords Partial nephrectomy · pT3a · Recurrence · Survival · Upstage

Introduction

The last few years have been marked by a growth in the use of partial nephrectomy (PN) for complex renal masses. This has led to an overall increase in the number of upstaged tumors. When comparing results of upstaged tumors between partial and radical nephrectomy (RN), PN does not appear to compromise the chance for cancer cure in patients upstaged pathologically to pT2 or pT3 renal masses [1–3].

The question of whether upstaged and non-upstaged tumors have different outcomes continues to be discussed in the literature. Few published studies address this question, with a wide range of results. Some investigators found no difference in disease recurrence for upstaged patients [4, 5]; in contrast, others found that pathologically upstaged renal masses are subject to inferior oncological outcomes [2]. This discrepancy is due to different definitions of upstaging, (upstaging from cT1 to pT2-3, from cT1-2 to pT3 or from cT1a to pT3), different definitions of outcomes and lack of robust results.

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Two articles in the literature, compared upstaged to non-upstaged patients after PN in terms of recurrence. These studies had a short median follow-up period of less than 23 months and small number of upstaged patients (41 and 66, respectively), limiting their generalization [2, 6].

Ideally, we would like to evaluate the perioperative morbidity and oncological outcomes of upstaged patients in order to assess the safety of PN in this population and to inform patients regarding outcomes; furthermore, by identifying preoperatively, the patients who are most likely to be upstaged, we can better choose our patients for active surveillance or ablative therapy.

The aim of our series was to evaluate the characteristics, perioperative morbidity, oncological outcome, and risk predictors of pT3a upstaging after partial nephrectomy for cT1 tumors.

Materials and methods

We retrospectively reviewed our institutional review board-approved PN database. Data consisted of consecutive records of patients who underwent PN for clinically localized (cT1N0M0) renal cell carcinoma (RCC) between 2007 and 2015. Overall, 1042 patients (710 cT1a and 332 cT1b) were included in this study. Of this cohort, 113 patients were upstaged to pT3a on final pathology, while 929 patients were staged as pT1.

Patient demographics (age, gender, race, body mass index (BMI), Charlson comorbidity index, clinical tumor characteristics (R.E.N.A.L. nephrometry score: consists of (R) adius (tumor size as maximal diameter), (E) xophytic/endophytic properties of the tumor, (N) earness of tumor deepest portion to the collecting system or sinus, (A) nterior (a)/posterior (p) descriptor and the (L) ocation relative to the polar line, radiological maximum tumor diameter, laterality), and pathological tumor characteristics (maximum tumor diameter, American Joint Cancer Committee staging, margin status, grade, or perirenal fat invasion, lymphovascular invasion (LVI) and tumor necrosis (TN) were assessed. All specimens were analyzed by dedicated urological pathologists. A positive surgical margin (PSM) was defined as extension of tumor to the inked surface of the resected specimen on final pathology.

The complexity of the surgery was defined by the R.E.N.A.L. score. Renal masses with a R.E.N.A.L. range 4–6, 7–9 and 10–12 are deemed low, moderate and high complexity lesions, respectively, as described by Kutikov et al. [7].

Perioperative outcomes studied were operative time, warm ischemia time (WIT), cold ischemia time (CIT), estimated blood loss (EBL), transfusion rate, Clavien-Dindo classification of postoperative complications, reoperation rate, 30-day readmission rate, and 6–12 months postoperative estimated glomerular filtration rate (e-GFR). Postoperative complications were graded as minor (GI-II) and major (GIII-V).

Continuous variables were described as a median and interquartile range. Categorical variables were described as frequency and percentage. We compared demographics and perioperative outcomes of PN between pT3a and pT1 groups. The Mann–Whitney U test was used for continuous variables and the Chi-squared test was used for categorical variables. Multivariate logistic regression analysis was then done to evaluate for variables independently associated with T3a tumor upstaging. Preoperative significant variables on univariate analysis were included in the multivariate analysis.

Follow-up was done according to the surveillance protocol and consisted of medical history, routine blood tests, chest X-ray for low-risk patients or CT-scan for high-risk patients, enhanced abdominopelvic CT-scan or MRI if indicated, whereas brain CT or skeletal MRI if clinically indicated. Overall, 817 patients with a minimum one post-operative imaging follow-up were included in this survival study. We compared the oncological outcomes (disease progression and overall survival) between pT3a and pT1 groups. Recurrence-free survival (RFS) was defined as the time between the date of surgery and the date of proved disease progression. Metastasis consisted of distant lesions or metachronous retroperitoneal lymph nodes localization, whereas local recurrence consisted of lesion in the partial nephrectomy bed or in the renal space. Patients with no evidence of disease on the last follow-up were censored. Overall survival (OS) was defined as the time between the date of surgery and the date of death (all causes). RFS and OS analyses were performed using the Kaplan–Meier method and the log-rank test.

Analysis was performed using SPSS v20 software (IBM SPSS Statistics, Armonk, NY: IBM Corp., USA). All tests used 5% as a significance threshold.

Results

One hundred thirteen patients (10.8%) out of 1042 had an upstaging to pT3a on final pathology report. Table 1 shows the patients' characteristics for pT3a in comparison to pT1. Patients with pT3a were older (median 63 vs. 60 years, $p=0.02$), mostly male (74.4 vs. 60.8%, $p<0.01$), had a higher rate of solitary kidney (9.7 vs. 3.9%, $p<0.01$) with a lower baseline e-GFR (median 75 vs. 83 ml/min/1.73 m^2, $p<0.01$). There were no statistically significant differences between the two groups in terms of race ($p=0.1$), CCI ($p=0.6$), and BMI ($p=0.2$).

Table 1 Characteristics of the 1042 patients in terms of pathological stage

Variable	cT1/pT3a	cT1/pT1	*p*
N (%)	113 (100%)	929 (100%)	
Gender *n* (%)			
Male	83 (74.4)	565 (60.8)	<0.01
Female	30 (25.6)	364 (39.2)	
Age (years)			
Median [IQR]	63 [55–71]	60 [52–68]	0.02
Race *n* (%)			
White	103 (90.7)	799 (86.0)	0.1
Other	10 (9.3)	130 (14.0)	
BMI (kg/m^2) *n* (%)			
[<25]	16 (14.2)	148 (15.9)	0.2
[25–29.9]	32 (28.3)	337 (36.3)	
[30–34.9]	38 (33.6)	241 (25.9)	
[≥35]	27 (23.9)	203 (21.9)	
CCI			
Median [IQR]	1 [0–2]	1 [0–2]	0.6
Solitary kidney *n* (%)			
Yes	11 (9.7)	36 (3.9)	<0.01
No	102 (90.3)	893 (96.1)	
Surgical approach *n* (%)			
Open	47 (41.6)	262 (28.2)	<0.01
Robotic	66 (58.4)	667 (71.8)	
Baseline e-GFR (ml/min)			
Median [IQR]	75 [57–92]	83 [67–97]	<0.01

Continuous variables were described as a median and interquartile range. Categorical variables were described as frequency and percentage

The Mann–Whitney U test was used for continuous variables and the Chi-squared test was used for categorical variables

All tests used 5% as a significant threshold

CC index Charlson Comorbidities Index, *ASA score* American Society of Anesthesiologists score, *BMI* body mass index, *e-GFR* estimated glomerular filtration rate defined by the Modification of Diet in Renal Disease (MDRD)

Table 2 shows tumor characteristics for the two groups. pT3a tumors were bigger (median 4.0 vs. 3.0 cm, $p<0.01$), with more clear cell subtype (75.2 vs. 61.2%, $p=0.02$), had a higher R.E.N.A.L. score (median 8 vs. 7, $p<0.01$), higher tumor grade (57.5 vs. 38.2%, $p<0.01$), higher LVI (15.9 vs. 1.7%, $p<0.01$), higher tumor necrosis (15 vs. 7.5%, $p<0.01$), and higher positive surgical margin (18.6 vs. 5.8%, $p<0.01$).

In pT3 tumors, sinus fat invasion was identified in 74 tumors (60.4%), perinephric fat invasion in 39 tumors (39.6%), and venous invasion in 11 patients (11.5%).

Table 3 shows the perioperative and postoperative outcomes for the cohort. Patients with pT3a had a higher EBL (median, 250 vs. 150 mL, $p<0.01$), higher transfusion rate (16.1 vs. 8.1%, $p<0.01$), higher WIT (median, 23 vs. 20 min, $p<0.01$) higher CIT (median, 35 vs. 29 min, $p<0.01$), and higher overall postoperative complications (37.1 vs. 24.3%, $p<0.01$). There were no differences in urine leak (2.7 vs. 1.9%, $p=0.5$), angioembolization rate (1.8 vs. 2.1%, $p=1$), reoperation (4.4 vs. 2.5%, $p=0.2$), 30-day readmission rates (7 vs. 7.4%, $p=1$), and ▲e-GFR decline (median −10 vs. -9 ml/min/1.73 m^2, $p=0.9$) between the two groups.

Multivariate logistic regression analysis was then performed to determine factors independently associated with tumor upstaging. Preoperatively identified significant variables were included in the multivariate analysis. Tumor size and baseline e-GFR were not introduced in the model in order to avoid collinearity due to their correlation to R.E.N.A.L. score and solitary kidney, respectively, in terms of providing no extra useful information, simply duplicate measurements. Gender, age, solitary kidney rate, surgical approach, R.E.N.A.L. score and hilar (h) location were considered for the multivariate analysis (Fig. 1). Independent predictive variables of upstaging were, male gender (OR 2.2, $p<0.01$), and R.E.N.A.L. score (OR 2.3, $p=0.01$) (Table 4).

Overall, 817 patients with minimum one postoperative imaging follow-up were included in the survival analysis. After a median follow-up of 35 (22–52) months, there were 18 patients (18.8%) in the pT3a group diagnosed with recurrence, including 5 local recurrences (5.3%), and 13 metastases (13.5%). Median time-to-recurrence in this group was 15 (10–29) months, median time-to-local recurrence was 13 (10–18) months, and median time-to-metastasis was 15 (13–29) months. In pT1 group, 29 patients (3.9%) were diagnosed with recurrence, including 12 (1.6%) local recurrences, and 17 metastases (2.3%). Median time-to-recurrence in this group was 20 (13–32) months, median time-to-local recurrence was 14 (11–24) months, and median time-to-metastasis was 27 (16–41) months. The sites of distant metastasis (in order of most to least common) were, lung, peritoneum, bone, retroperitoneal lymph nodes, contralateral adrenal gland, pancreas, brain and non-adjacent colon.

The Kaplan–Meier survival curves for RFS and OS according to pathological T stage are shown in Figs. 2, 3. Two- and five-year RFS probabilities for pT3a and pT1 were 86.4 vs. 78.5% and 97.7 vs. 94.6%, respectively (log-rank $p<0.01$). In our cohort, there were 5 deaths in pT3a group, and 18 in pT1 group. The 2- and 5-year OS probabilities for pT3a and pT1 were 94.7 vs. 89% and 99.2 vs. 95.6%, respectively (log-rank $p=0.02$).

Table 2 Tumor characteristics: cT1/pT3a vs. cT1/pT1

Variable	pT3a	pT1	*p*
N (%)	113 (100%)	929 (100%)	
Preoperative tumor size (cm)			
Median [IQR]	4.2 [3.0–5.2]	3.1 [2.3–4.2]	<0.01
Pathological tumor size (cm)			
Median [IQR]	4.0 [2.8–5.0]	3.0 [2.1–4.0]	<0.01
Clinical stage			
cT1a	45 (39.8)	665 (71.6%)	<0.01
cT1b	68 (60.2)	264 (28.4%)	
Side *n* (%)			
Left	54 (47.8)	475 (51.1)	0.5
Right	59 (52.2)	454 (48.9)	
Tumor histology *n* (%)			
Clear cell	85 (75.2)	569 (61.2)	0.02
Papillary	15 (13.3)	203 (21.9)	
Chromophobe	9 (8.0)	80 (8.6)	
Other	4 (3.5)	77 (8.3)	
R.E.N.A.L. score *n* (%)			
Low [4–6]	22 (19.5)	353 (38.0)	<0.01
Moderate [7–9]	63 (55.8)	453 (48.8)	
High [10–12]	28 (24.8)	123 (13.2)	
RENAL score			
Median [IQR]	8 [7–10]	7 [6–9]	<0.01
Tumor touches the main artery or vein (h): Hilar *n* (%)			
Yes	31(27.5)	137 (14.8)	<0.01
No	82 (72.5)	792 (85.2)	
Type of ischemia			
Cold	34 (30%)	211 (22.7%)	0.1
Warm	79 (70%)	718 (77.3)	
Grade *n* (%)			
Low (I–II)	48 (42.5)	574 (61.8)	<0.01
High (III–IV)	65 (57.5)	355 (38.2)	
pT3a subgroups ***n*** (%)			
Sinus fat	74 (60.4)	NC	
Perinephric fat	39 (39.6)		
Venous invasion	11 (11.5)		
Lymphovascular invasion *n* (%)			
Yes	18 (15.9)	16 (1.7)	<0.01
No	95 (84.1)	913 (98.3)	
Tumor necrosis *n* (%)			
Yes	17 (15.0)	70 (7.5)	<0.01
No	96 (85.0)	859 (92.5)	
Margin status *n* (%)			
Positive	21 (18.6)	54 (5.8)	<0.01
Negative	92 (81.4)	875 (94.2)	

Continuous variables were described as a median and interquartile range. Categorical variables were described as frequency and percentage

The Mann–Whitney U test was used for continuous variables and the Chi-squared test was used for categorical variables

All tests used 5% as a significant threshold

R.E.N.A.L. nephrometry score consists of [R]adius [tumor size as maximal diameter], [E]xophytic/endophytic properties of the tumor, [N]earness of tumor deepest portion to the collecting system or sinus, [A]nterior [a]/posterior [p] descriptor and the [L]ocation relative to the polar line, *NC* not concerned

Discussion

Based on recent literature, the current evidence suggests that localized renal cancer is the best managed by PN rather than by RN, regardless of surgical approach. Currently, PN has become the standard of care for small renal masses (≤4 cm) as well as in larger tumors (≤7 cm). This increasing acceptance for PN in bigger tumors is related in part to the higher incidence of CKD in this population [8, 9]. With adoption of PN, and changes in technologies such as robotic surgery, the last few years have been marked by a growth in the use of PN for complex renal masses [10]. This has led to an overall increase in the number of upstaged tumors.

We decided to examine upstaging from cT1 tumors to pT3a. We excluded the cT2 tumors for two reasons: the therapeutic options in cT1 and cT2 are different, and as shown by Lam et al. [11], tumor size cut-off of 7 cm is a prognostic factor of survival in pathological stage T3a. We did not limit our study only to cT1a tumors (≤4 cm) since Chevinsky et al. [12], and others highlight the increased risk of recurrence in pT3a tumors across all sizes, and specifically in tumors less than 4 cm. We did not exclude any pattern of local invasion (sinus fat, perinephric fat or venous invasion), as several studies [13] found that in patients with pT3a renal cell carcinoma, the location of extrarenal extension was not an important prognostic factor of worse oncological outcome.

In this study, 113 patients (10.8%) were upstaged from cT1 to pT3a. The incidence of pT3a upstaging in this cohort is within previously reported series. The upstaged group was associated with adverse clinical (higher R.E.N.A.L. score, higher hilar tumors) and pathological features (high grade, clear cell subtype and high positive margin rate) confirming previous studies [2, 6, 14, 15].

Perioperative outcomes were reasonable in pT3a group compared to pT1 group with no difference in major complications (grade III–IV), urine leak, angio-embolization, 30-day readmission and reoperation. Although WIT (23 vs. 20 min) and CIT (35 vs. 29 min) were significantly higher in the upstaged group, the median ischemia time in the two groups was lower than the accepted threshold. The decline in e-GFR (▲ e-GFR) was similar in the two groups, though the upstaged group had a higher rate of solitary kidney. This result is consistent with those found in relevant literature in terms of median renal function decline in solitary kidney [14]. It is to be noted that 29 patients (61.2%) with solitary kidney had undergone partial nephrectomy using cold ischemia technique. Solitary kidney was associated with upstaging in bivariate analysis. Potential underestimation of tumor stage has to be kept in mind when dealing with tumor in solitary kidney.

Table 3 Perioperative and postoperative outcomes comparison according to pathological stage

Variable	cT1/pT3a	cT1/pT1	*p*
N (%)	113 (100%)	929 (100%)	
Operative time (min)			
Median [IQR]	182 [150–241]	180 [143–216]	0.1
Warm ischemia time (min)			
Median, [IQR]	23 [19–29]	20 [15–26]	0.01
Cold ischemia time (min)			
Median [IQR]	35 [28–58]	29 [24–43]	0.01
EBL (ml)			
Median [IQR]	250 [100–400]	150 [100–300]	<0.01
Intra-operative complications *n* (%)			
Liver laceration	9 (7.9)	37 (3.9)	0.08
Arterial injury repaired	2 (1.2)	2 (0.3)	
Epigastric artery injury	2 (1.2)	3 (0.4)	
Pleural injury	0 (0)	2 (0.3)	
Serosal tear duodenum	5 (4.6)	25 (3.5)	
Ureteral injury repair UU anastomosis	0 (0)	1 (0.14)	
Pancreatic tail laceration	0 (0)	2 (0.14)	
Mesentery injury	0 (0)	1(0.14)	
Transfusion *n* (%)	18 (16.1)	75 (8.1)	0.01
G III-V postoperative complications *n* (%)	12 (10.6)	60 (6.5)	0.09
Overall postoperative complications *n* (%)	42 (37.1)	226 (24.3)	<0.01
Urine leak	3 (2.7)	18 (1.9)	0.5
Angio-embolization	2 (1.8)	20 (2.1)	1
Surgical reoperation *n* (%)	5 (4.4)	23 (2.5)	0.2
30-day readmission *n* (%)	8 (7)	69 (7.4)	1
Postoperative e-GFR (ml/min)			
Median [IQR]	65 [44–76]	71 [58–87]	0.04
▲ e-GFR (ml/min)			
Median [IQR]	−10 [−15 to −2]	−9 [−17 to −1]	0.9

Urine leak was defined as persistent drain output >48 h after PN with biochemical analysis consistent with urine or radiographic evidence of urine leak

Continuous variables were described as a median and interquartile range. Categorical variables were described as frequency and percentage

The Mann–Whitney *U* test was used for continuous variables and the Chi-squared test was used for categorical variables

All tests used 5% as a significant threshold

▲ *e-GFR* postoperative e-GFR—baseline e-GFR, *e-GFR* estimated glomerular filtration rate defined by the Modification of Diet in Renal Disease (MDRD)

The upstaged group had a higher EBL and transfusion rate; this could be explained by the higher complexity of this tumor as shown by the R.E.N.A.L. score and the hilar (h) location. The rate of urine leak and major complications were low in the two groups. We think that the absence of difference is related to lack of power. Power refers to the probability that the test will find a statistically significant difference when such a difference actually exists.

In our series, preoperative independent risk factors for upstaging were gender and R.E.N.A.L. score [6, 15]. When adding histology (subtypes) and grade (low vs. high) to the multivariate analysis, R.E.N.A.L. score, gender, histology and grade emerge as independent predictors of upstaging (data not shown). This second model had a higher adjusted R^2. Indeed, using this model as preoperative predictors of upstaging requires preoperative tumor biopsy. In a recent study, Halverson et al. [16] retrospectively evaluated 151 small renal masses that underwent both percutaneous renal mass biopsy and subsequent partial or radical nephrectomy. For diagnosing malignancy, there was complete concordance between the histology rendered by core biopsy and that rendered

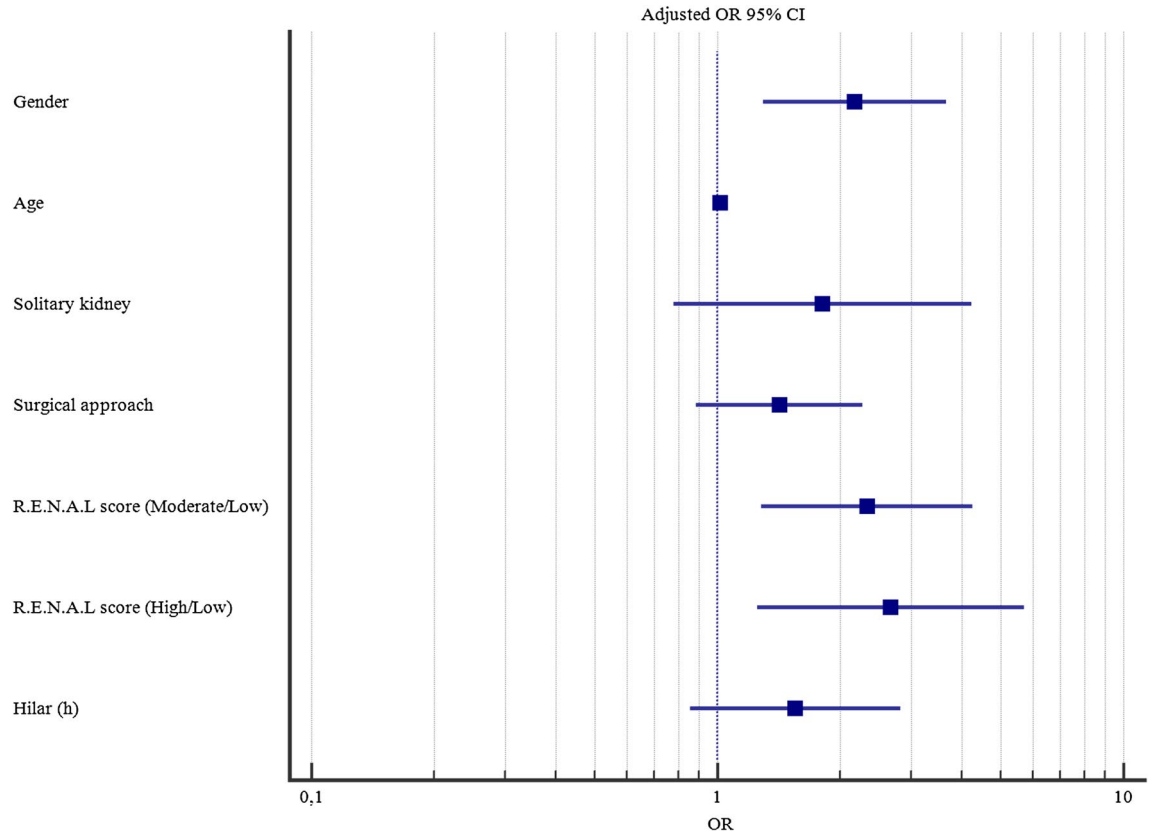


Fig. 1 Forest plot of adjusted preoperative factors predicting up-staging

Table 4 Preoperative factors predicting upstaging to pT3a: multivariate logistic regression

Variable	OR [95% CI]	*p*
Gender		
Female	1	0.003
Male	2.2 [1.2–3.6]	
R.E.N.A.L. score		
Low [4–6]	1	0.01
Moderate [7–9]	2.3 [1.3–4.2]	
High [10–12]	2.7 [1.3–5.7]	

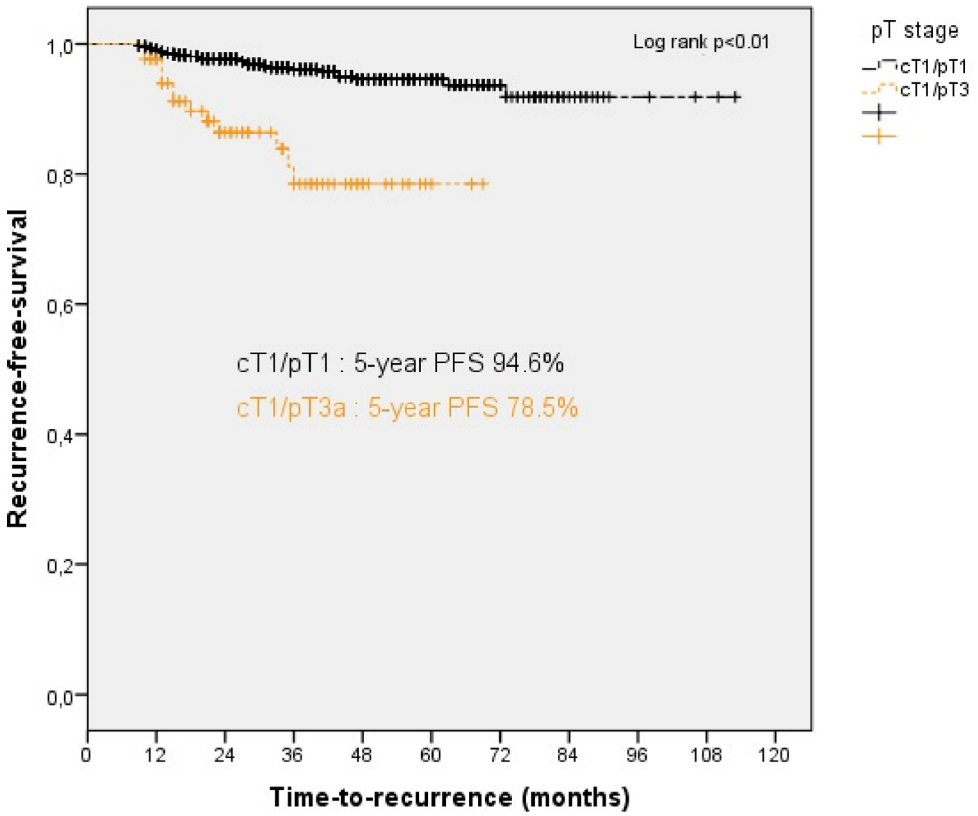
Gender, age, solitary kidney, surgical approach, R.E.N.A.L. score and hilar (h) location were considered for the multivariate analysis. *OR* odds ratio. All tests used 5% as a significant threshold

by surgery. Histologic concordance was 94% and Fuhrman nuclear grade concordance was 65%. Non-diagnostic findings from tumor biopsy were present in 15–22% of large contemporary series. The non-diagnostic findings and the concordance rate for tumor grade and histology subtypes are limiting the utility of renal biopsy, for the time being, in predicting risk stratification. However, until better risk assessment instruments are available, such as genetic profiling or other biomarkers, tumor biopsy could be a reliable tool in high-risk patients (male, moderate/high RENAL score) in improving the risk stratification.

Our results concerning DFS and overall survival are consistent with those of other series [1, 2, 6], showing that upstaged patients had a worse oncological outcome than non-upstaged ones. Our findings also, corroborate those of Nayak et al. [2] who found that oncological outcomes are worse than traditionally thought.

The upstaged cohort was not compared to similar upstaged pT3a tumors treated by radical nephrectomy, so one cannot conclude that partial nephrectomy, and not the aggressive tumor biology, is the responsible factor for this high recurrence rate in this group.

Of all the recurrences, the rate of local recurrence in our study was higher than similar studies with the same follow-up period [17, 18]. This could be explained by a higher diagnostic rate of local recurrence in our series, secondary to a better surveillance protocol with wide usage of abdominal CT-scan, and renal bed biopsy



Kaplan-Meier analysis of Recurrence-free survival. Comparison of the curve by log rank test. All tests used 5% as a significance threshold.

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Number exposed to risk cT1/pT1	706	700	650	554	463	376	305	248	195	149	107	71	50	31	13	5	3
Number exposed to risk cT1/pT3a	111	108	91	71	55	45	35	24	17	11	6	3	0	0	0	0	0

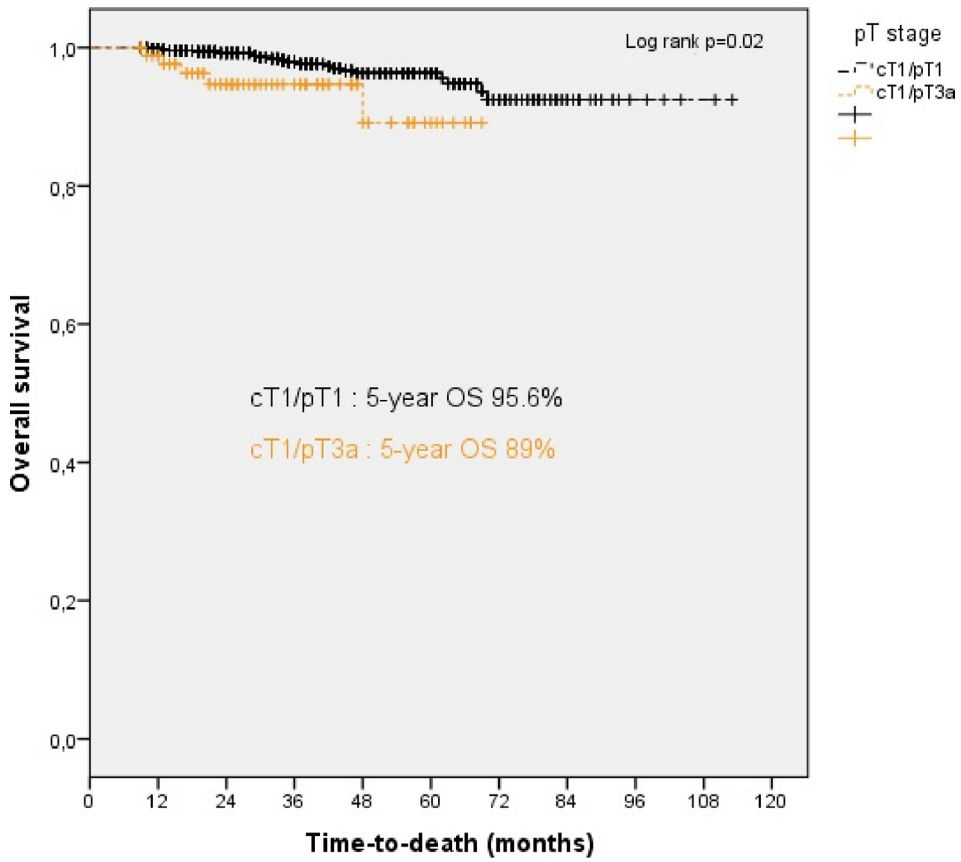
Fig. 2 Recurrence-free-survival cT1/pT1 vs. cT1/pT3a. Kaplan–Meier curves

whenever there were radiological modifications suspicious of local recurrence. Patients' follow-up period in this study was informative, since median time-to-recurrence reported in the literature for the two groups was reached [17].

We acknowledge some limitations in our study; most are inherent problems of retrospective studies, even though data were collected prospectively by chart review, on the basis of a predetermined registration grid.

Conclusion

Perioperative morbidity, after partial nephrectomy, is acceptable in cT1/pT3 in comparison to cT1/pT1 tumors; however, upstaged patients had a worse oncological outcome. cT1/pT3a tumors are associated with adverse clinico-pathological features. Preoperative risk predictors of upstaging were higher R.E.N.A.L. score and male gender. A better preoperative risk stratification is mandatory in order to recognize these tumors.



Kaplan-Meier analysis of overall survival. Comparison of the curve by log rank test. All tests used 5% as a significance threshold.

Time (months)	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84	90	96
Number exposed to risk cT1/pT1	929	871	769	683	591	504	425	348	283	230	179	128	87	58	37	17	8
Number exposed to risk cT1/pT3a	113	107	99	80	64	54	42	30	22	15	8	3	3	0	0	0	0

Fig. 3 Overall survival cT1/pT1 vs. cT1/pT3a. Kaplan–Meier curves

Compliance with ethical standards

All authors made a substantial contribution to the material submitted for publication; all have read and approved the final manuscript and have no direct or indirect commercial financial incentive associated with publishing the article. We certify that the manuscript is not under consideration by another journal or electronic publication and that it has not been previously published

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