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Prognosis, Predictors, and Treatment for pT3a Upstaging in cT1 Renal Cell Carcinoma

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Abstract

Purpose: The significance of upstaging of cT1 to pT3a (cT1pT3a) Renal Cell Carcinomas (RCC) is not clear. The objectives of this study were to assess the impact of this upstaging on Overall Survival (OS), Cancer Specific Survival (CSS), Recurrence-Free (RFS) and Metastases-Free Survival (MFS); to identify predictive factors for cT1pT3a and to evaluate the safety of partial nephrectomy in cT1p3a tumors.

Material and Methods: A retrospective analysis was performed of 429 cases of cT1N0M0 RCC submitted to nephrectomy, partial or radical, between January 2010 and December 2019. Kaplan-Meier method and Log Rank test were applied to evaluate long-term results. Logistic regression was applied to assess predictive factors.

Results: There were 39 cases of upstaging. The OS, CSS, MFS were significantly lower in the cT1pT3a group compared to cT1pT1 group. RFS was lower in cT1pT3a group, but the difference was not significant. The higher the RENAL score and the larger the lesion, the greater the probability of upstaging. cT1 tumors in dialysis patients had lower risk of upstaging. OS, CSS, MFS were significantly higher in cT1pT3a patients submitted to partial nephrectomy regarding those undergoing radical nephrectomy. The RFS was higher, but the difference was not significant.

Conclusion: cT1pT3a RCC had a worse prognosis. It was found that the larger and more complex the nodule, the greater the probability of cT1pT3a. In patients on dialysis the lesions had a lower risk of upstaging. Even in cases with a high probability of upstaging, partial nephrectomy can be offered if technically feasible.

Keywords: Renal cell carcinoma; Clinical T1; Pathological T3a; Oncological outcomes; Predictive factors

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Introduction

Diagnostic imaging has evolved in such a way that the number of incidental Renal Cell Carcinomas (RCCs) has significantly increased. This trend toward earlier detection correlates with better prognosis and has resulted in the increased use of minimally invasive surgical techniques and ablative modalities to decrease the morbidity. Tumors ≤ 7 cm in greatest dimension, limited to the kidney, correspond to cT1 according to 2017 TNM classification [1]. In this scenario, guidelines recommend a wide spectrum of treatment options, ranging from surveillance to timely surgery. T3a tumors extend into the renal vein or its segmental branches or invade the pelvicalyceal system, perirenal and/or renal sinus fat, but not beyond Gerota fascia. While pathological upstaging from cT1 to pT2 depends on size, intrinsic characteristics can directly turn a cT1 into pT3a. From 4% to 9% of all cT1N0M0 may harbor pT3a stage at final pathology. Unfortunately, current imaging modalities have a limited ability for detecting the adverse pathologic features associated with pT3a upstaging. Ideally, such patients should undergo prompt surgical treatment, instead of non-interventional or focal treatments [2]. Partial Nephrectomy (PN) is the preferred treatment for small masses. Moreover, elective PN is being explored also for large and complex renal masses. Concerns about the oncological safety of PN in this upstaging scenario have been raised, even though equivalent outcomes to Radical Nephrectomy (RN) have been reported [3].

The aim of this retrospective analysis was to assess the impact of cT1pT3a upstaging on Overall Survival (OS), Cancer Specific Survival (CSS), Recurrence-Free (RFS) and Metastases-Free Survival (MFS). It was also intended to identify predictive factors for cT1pT3a and to evaluate the safety of

PN in cT1p3a tumors.

Material and Methods

This retrospective study included 429 patients with RCC cT1N0M0 who underwent surgery between January 1st, 2010, and December 31st, 2019, in the Department of Urology and Renal Transplantation at Hospital and University Center of Coimbra. Only primary, single, cT1N0M0 tumors were selected. Only cases whose histological result revealed RCC were analyzed. Cases of nephrectomy which histology reveal benign lesions (oncocytoma; angiomyolipoma; metanephric adenoma; leiomyoma; papillary adenoma; hemangioma) were excluded, as were cases of synchronous tumors, renal graft tumors and recurrences. Clinical stage was determined by preoperative Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).

The population consisted of 303 men (70.6%). Regarding comorbidities, 85 patients had a history of cardiology pathology (19.8%); 260 arterial hypertensions (60.6%); 104 diabetes mellitus (24.2%); 95 obesity (22.1%). It should be noted that 67 patients had Chronic Kidney Disease (CKD) (15.6%) and 12 had End-Stage Renal Disease (ESRD) on renal replacement therapy (hemodialysis/peritoneal dialysis). Forty-eight patients were reported to smoke.

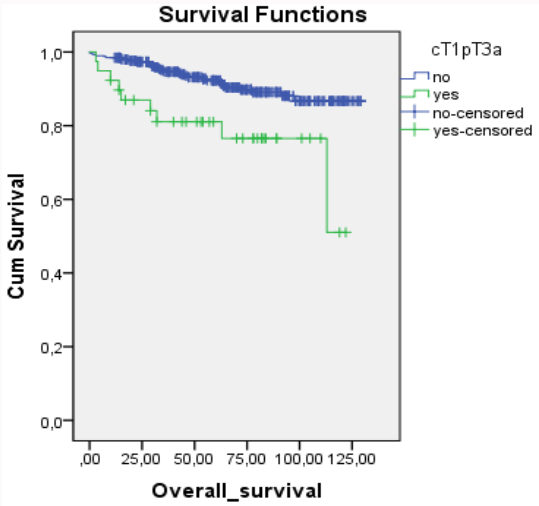
The neoplasm affected the right kidney in 199 cases (46.4%); it was found in the upper pole in 95 cases (22.1%), in the lower pole in 127 cases (29.6%), and it was mesorenal in 168 patients (39.2%). The lesion was in a renal pole, but with mesorenal extension in 38 cases. Only in one case was it not possible to access preoperative abdominal CT, which made it impossible to assess the location of the lesion. The suspicious mass was found in the medial border in 115 cases (26.8%). The lesion was mainly endophytic (>50%) in 90 cases (21%) and mainly exophytic (>50%) in 165 cases (38.5%). Based on imaging, 271 patients had lesions <4 cm, cT1a (63.2%); 158 had tumors ≥ 4 but <7 cm, cT1b (36.8%). The mean RENAL score was 7 (4-12). The RENAL score was calculated by reviewing preoperative CT and/or MRI.

Regarding the nephrectomy performed, 305 (71.1%) patients underwent PN (82 open PN (19.1%) and 223 laparoscopic PN (52%)) and 124 (28.9%) patients underwent RN (19 open and 105 laparoscopic surgery).

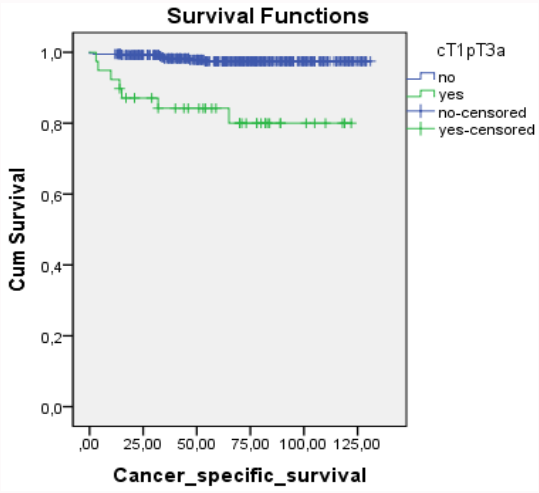
Patients included in the study were divided into pathologic T1 (pT1) and T3a (pT3a) groups. Patient demographics and tumor characteristics were evaluated and compared between the two groups. Kaplan-Meier survival curves and the log rank test were used to investigate OS, CSS, RFS and MFS. Multivariate analyses using logistic regression were used to determine the clinicopathological features associated with pT3a upstaging. To assess the impact of PN in cT1pT3a patients, OS, CSS, RFS, MFS and Glomerular Filtration Rate (GFR) were compared between patients submitted to PN and RN using the Mann-Whitney test. A *p*-value <0.05 was considered statistically significant, and all analyses were performed using SPSS software (version 24 0; IBM SPSS Statistics).

Results

The pathological analysis of the nodule revealed clear cell RCC (ccRCC) in 224 patients (52.2%), papillary RCC (pRCC) in 93 patients (21.7%) and chromophobic RCC (chRCC) in 99 patients (23.1%). The remaining 13 cases were rare variants: 2 MIT family translocation RCC; 5 mucinous tubular and spindle cell carcinoma; 3 multiloculated cystic carcinoma; 1 case of hereditary leiomyomatosis



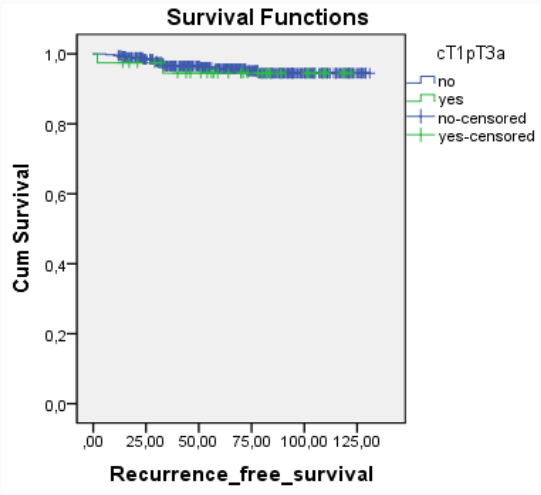
Graph 1: Kaplan-Meier curve comparing the OS between groups (cT1pT3a *vs.* cT1pT1/2).



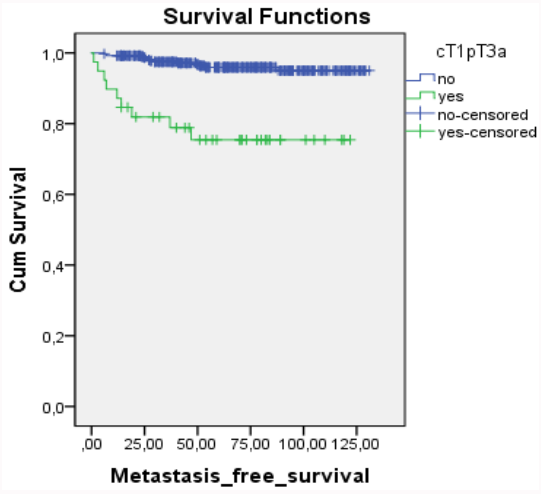
Graph 2: Kaplan-Meier curve comparing the CSS between groups (cT1pT3a *vs.* cT1pT1/2).

and RCC; 1 tubulocystic RCC; 1 non-classifiable RCC. The surgical piece showed areas of sarcomatoid differentiation in 2 cases (0.5%), vascular invasion in 58 patients (13.5%) and tumor necrosis in 64 patients (14.9%). The histological study showed 257 pT1a (59.9%), 125 pT1b (29.1%), 8 pT2 (1.9%) and 39 pT3a (9.1%). Criteria for pT3a upstaging were invasion of the renal vein or its branches in 2 cases, invasion of the perirenal fat in 28 cases, invasion of renal sinus fat in 11 patients, invasion of the pelvicalyceal system in 3 cases. There are cases with 2 criteria for pT3a upstaging. Table 1 compares the cT1pT3a patient group with the control group (cT1pT1/2).

The follow-up of patients until December 2020 (clinical records, imaging exams) was analyzed. During the period under analysis, 42 people died, and in 15 cases it was due to progression of RCC despite ongoing treatment. The median OS was 116.949 months. OS was significantly lower in the upstaged group (96.945 *vs.* 118.575 months, p=0.003). Regarding RCC CSS, the median survival was 126,708 months, being significantly lower in the group with upstaging (102.445 *vs.* 128.474 months, p<0.001). Graph 1 and 2 represent the Kaplan-Meier curves comparing the OS and CSS between



Graph 3: Kaplan-Meier curve comparing the RFS between groups (cT1pT3a *vs.* cT1pT1/2).



Graph 4: Kaplan-Meier curve comparing the MFS between groups (cT1pT3a *vs.* cT1pT1/2).

groups. RFS was defined as the time from surgery to the occurrence of recurrence in the same kidney or at the surgical site. There were 18 cases of local recurrence. RFS was lower in the cT1pT3a group, although the difference was not statistically significant (116.295 *vs.* 125.984 months, p=0.828). 23 patients developed metastases after nephrectomy. MFS was significantly longer in the control group (not cT1pT3a) (126.560 *vs.* 96.373 months, p<0.001). Graph 3 and 4 compare RFS and MFS between the upstaging and the control group, respectively.

Table 2 represents the results of the logistic regression. The higher the RENAL score and the larger the lesion, the greater the probability of upstaging [p=0.013; Exp(B)=1.493 and p=0.006; Exp(B)=1.849, respectively]. On the other hand, cT1 tumors in patients on dialysis had lower risk of upstaging (p=0.039; Exp(B)=0.107).

We evaluated whether performing PN had a negative impact in cases of cT1pT3a to assess the safety of this surgery when the preoperative risk of upstaging is high. Of 39 cases of cT1pT3a 12 had undergone PN. To evaluate the results of PN in cases of cT1pT3a, 2 cases were removed in which remaining kidney nephrectomy was

Table 1: Characteristics of the population analyzed.

	No cT1pT3a	cT1pT3a	Mann-Whitney test p-value
Patient demographic characteristics			
Men	70.51%	71.79%	
Women	29.49%	28.21%	
Arterial hypertension	60.51%	61.54%	
Diabetes mellitus	24.62%	20.51%	
Obesity	22.05%	23.08%	
Tobacco	11.79%	5.13%	
CKD	14.62%	25.64%	
CKD on dialysis	2.56%	5.13%	
Age at surgery	61.7 (23-88)	65.9 (42-86)	0.057
Renal nodule characteristics on imaging examination			
Right kidney	46.67%	43.59%	
Kidney upper pole	22.31%	20.51%	
Kidney lower pole	30%	25.64%	
Mesorenal	39.74%	33.33%	
Upper pole neoplasm with mesorenal extension	4.36%	10.26%	
Lower pole neoplasm with mesorenal extension	3.33%	10.26%	
Medial rim of kidney	25.64%	38.46%	
cT1a	66.67%	28.21%	
cT1b	33.33%	71.79%	
Endophytic (>50%)	20.77%	23.08%	
Exophytic (>50%)	39.49%	28.21%	
Size	3.58 (0.8-7)	5.17 (1.2-7)	p<0.001
RENAL score (mean)	8.4 (4-12)	6.8 (4-11)	p<0.001
PADUA score (mean)	7.8 (6-12)	8.8 (6-11)	p<0.001
Surgery-related variables			
Partial nephrectomy	75.13%	30.77%	
Total nephrectomy	24.87%	69.23%	
Open partial nephrectomy	19.74%	12.82%	
Laparoscopic partial nephrectomy	55.38%	17.95%	
Open radical nephrectomy	3.59%	12.82%	
Laparoscopic radical nephrectomy	21.28%	56.41%	
Surgery time (minutes)	119.8 (40-245)	133.3 (65-270)	p=0.1
Hospitalization time (days)	7 (3-29)	7.6 (4-27)	p=0.298
Histological features of resected nodule			
ccRCC	52.56%	48.72%	
pRCC	22.05%	17.95%	
chRCC	22.31%	30.77%	
Sarcomatoid differentiation	0	5.13%	
Vascular invasion	12.05%	28.21%	
Tumor necrosis	13.33%	30.77%	

necessary during postoperative hospitalization for PN. In cases of cT1pT3a, the RFS was longer in patients submitted to PN compared to RN (24 *vs.* 17.2 months; p=0.087). MFS was significantly longer in cT1pT3a cases treated by PN (27.8 *vs.* 15.8 months; p=0.003). CSS was also higher in cT1pT3a cases submitted to PN (27.1 *vs.* 16 months;

Table 2: Table variables in the equation of the logistic regression.

	Sig.	Exp(B)	95% CI for Exp(B)	
			Lower	Upper
PREDICTIVE FACTOR				
Size	0.006	1.849	1.195	2.859
RENAL score	0.013	1.493	1.090	2.045
CKD in dialysis	0.039	0.107	0.013	0.890
NO PREDICTIVE FACTOR				
CKD	0.059	0.357	0.122	1.041
Endophytic (>50%)	0.079	2.557	0.896	7.298
Tobacco	0.096	3.948	0.784	19.892
Mesorenal	0.147	2.438	0.730	8.139
Right kidney	0.191	1.687	0.770	3.693
Medial rim of kidney	0.210	.595	0.265	1.339
Arterial hypertension	0.213	1.694	0.739	3.882
Exophytic (>50%)	0.219	1.854	0.693	4.963
Upper kidney pole	0.393	1.773	0.476	6.611
Lower kidney pole	0.497	1.577	0.424	5.872
chRCC	0.557	0.463	0.035	6.046
Man	0.610	0.799	0.338	1.890
Obesity	0.761	1.150	0.466	2.836
pRCC	0.799	0.709	0.051	9.940
cT1a	0.913	0.928	0.243	3.548
ccRCC	0.925	1.129	0.090	14.207

p=0.006). The OS was higher in cT1pT3a patients submitted to PN (27.5 *vs.* 15.9 months; p=0.004). Regarding the functional outcome, it was found that patients undergoing PN have significantly higher GFR 1 year after surgery (78.3 *vs.* 53.1 ml/min; p<0.001). Considering only the cases of cT1pT3a (excluding 2 cases requiring nephrectomy of the remaining kidney), patients undergoing PN presenting GFR 1 year after surgery statistically superior to the group undergoing RN (73.6 *vs.* 51.7 ml/min; p=0.021).

Discussion

There are many studies in the literature supporting a negative impact of cT1pT3a upstaging on RFS [4-7], as well as on CSS and OS [3,7-9]. Recurrence tends to occur as metastases, rather than local recurrence, progression not being linked to failed local control [6].

The impact of tumor size on pT3a prognosis is not well established, with some studies suggesting that recurrence is not affected by tumor size [10,11], whereas others found a relation. Chen et al. [12] found a shorter five-year CSS and RFS in pT3aN0M0 RCC tumors >7 cm compared to tumors ≤ 7 cm, while Yoo et al. [13] detected recurrence in 44% and 14.6% of pT3a tumors >7 cm and <7 cm, respectively.

Some studies did not find this negative impact. Roberts et al. [14] concluded that all lesions classified as T1 by preoperative CT behave as pathological T1 irrespective of had perinephric fat invasion on pathological analysis (same RFS, OS). Therefore, it is reasonable to pursue minimally invasive and ablative therapies based only on preoperative CT and pathological T stage does not seem to provide any prognostic value, especially in small peripheral tumors. Ramaswamy et al. [15] also concluded that pathologic upstaging did not result in worsened oncologic outcomes. Of the patients with a cT1 tumor submitted to nephrectomy that had occult pT3a tumor, none developed locally recurrent or metastatic disease.

Regarding variables known in the preoperative period, several authors describe that larger tumors are a risk factor for upstaging, which is in agreement with our results [2,4,6,9,15]. Veccia et al. [3] demonstrated age, tumor size, and RENAL score to be predictors of upstaging. Elderly patients might get surgery later given the propensity for active surveillance in these patients, leading to an increased incidence of upstaging [6,9]. In line with others [3], we found that the larger and more complex the tumors, the greater the risk of cT1pT3a upstaging. Gorin et al. [5] revealed that a high RENAL score, tumor diameter and hilar location were associated with upstaging. Mouracade et al. [16] listed as preoperative risk factors of upstaging higher RENAL score and male gender. The association of gender with upstaging may derive from a higher exposure of men to important risk factors, such as hypertension and smoking. Nevertheless, Ramaswamy et al. [15] found that the RENAL score did not predict pT3a upstaging. Regarding histological variables, not available before surgery, Veccia et al. [3] identified the histological variant of RCC, Fuhrman grade, and positive surgical margin as predictors. Ramaswamy et al. [15] identified ccRCC and positive surgical margins as predictors. Other authors stated that upstaging is associated with a higher Fuhrman grade [6,9]. The ISUP classification is only applicable to ccRCC and pRCC, so it was not evaluated in our study due to missing data (chRCC). The analysis of surgical margins was not considered in our study because of RN cases missing data.

Renal nodules identified in ESRD patients on dialysis were at lower risk for upstaging. The risk of developing RCC in native end-stage kidneys is ten times higher than in general population. RCC associated with ESRD are commonly multicentric and bilateral, found in younger patients (mostly male), and have a lower T stage and ISUP grade, and fewer lymph nodes and/or distant metastases than RCC in non-ESRD cases [17]. ESRD patients tend to have more medical checkups, including ultrasonography, CT and MRI. This facilitates the detection of RCC at an early stage, resulting in a relatively favorable outcome and pathological status [18]. In these cases, the kidney does not have function and it is easy to agree to perform a nephrectomy and rarely opt for surveillance, which may explain the diagnosis of CCR at an earlier stage.

PN is associated with improved OS in localized RCC, being strongly indicated in cT1a tumors and favored over RN in cT1b tumors whenever feasible. Many studies had suggested that a reduced GFR associated with RN may lead to a higher incidence of CKD and cardiovascular mortality, while showing similar oncological outcome. Thus, PN has become the standard treatment for small renal tumors [1]. Tumor size, complexity, and hilar location could guide the surgeon to perform PN or RN. Nevertheless, the decision is also driven by surgeon expertise. There are controversies regarding the oncological safety of PN in cT1pT3a patients. Chung et al. [19] found that patients with cT1pT3a treated with PN have a significantly improved OS compared with RN. Ziegelmueller et al. [20] concluded that performing PN in patients with pT3a tumors <7 cm leads to prolonged survival rates compared to performing RN. Other authors concluded that cT1pT3a submitted to PN had similar oncological results compared to performing RN [6,21-23], while achieving better functional results [24,25]. Consequently, PN can suppress the progression of tumor and reduce the risk of postoperative CKD. However, other authors found that among cT1pT3a patients,

those undergoing PN appear to have inferior RFS relative to those undergoing RN [26].

Conclusion

cT1 RCC upstaged in pT3a have a worse prognosis and the larger and more complex the renal nodule, the greater the probability of cT1pT3a. On the other hand, in patients with CKD on dialysis, the lesions that were identified had a lower risk of upstaging. Predictive factors may greatly aid in the preoperative counseling of patients regarding the risk of pT3a RCC. However, even in cases with a high probability of corresponding to cT1pT3a, PN can be offered if technically feasible.

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