

Insignificance of Perirenal Fat Invasion in Small Renal Masses

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Abstract

Objective: To evaluate oncologic outcomes in clinical T1a tumors which remain pathologic T1a compared to tumors which were upstaged to pathologic T3a due to perirenal fat invasion.

Methods: A retrospective database was created of all patients with solitary clinical T1a renal masses who underwent surgical intervention for renal cell carcinoma from 2000 to 2012 at a single institution. Patients with pathologic T1a renal cell carcinoma were compared to those upstaged to T3a for differences in overall mortality and disease-free survival using Kaplan-Meier and Cox Proportional Hazards models.

Results: Of the 218 patients with cT1a, 24 (11%) were upstaged to pathologic T3a. Kaplan-Meier survival estimates revealed there to be no statistical differences in overall mortality. Multivariate regression analysis revealed that only age, histology, and Charlson index score were predictors of overall survival. Hazard ratios for ≥ 65 years of age, clear cell histology, and Charlson index score per point were 2.2 times (95% CI:1.38-3.57, $p < .001$), 1.68 times (95% CI:1.03-2.77, $p = .04$), and 1.38 (95% CI:1.22-1.56, $p < .0001$), respectively. Upstaging a cT1a renal mass to pT3a due to perirenal fat invasion was not a significant predictor of overall survival.

Conclusion: Clinically diagnosed T1a tumors which are upstaged to pathologic T3a secondary to perirenal fat invasion have similar oncologic outcomes when compared to clinically diagnosed T1a tumors which remain pathologic T1a. Patients with clinical T1a tumors which are upstaged to pathologic T3a due to perirenal fat invasion should be counseled that other health status considerations have a greater effect on overall survival than upstaging.

Abbreviations: RCC: Renal Cell Carcinoma; BMI: Body Mass Index, CXR: Chest X-Ray

Introduction

The incidence of renal cell carcinoma (RCC) has increased over the last several decades, believed to be largely driven by increased detection of incidental small renal masses. Increased utilization of cross sectional imaging has led to an increased detection of incidental

small renal masses defined as tumors 4 cm or less in diameter. This increased detection is believed to be the primary cause of an increasing incidence of renal cell carcinoma (RCC) [1]. The primary treatment modality for these small renal masses is surgical excision typically with partial nephrectomy. This treatment modality provides a definitive diagnosis and appropriate TNM staging. Current TNM staging for RCC defines T1a as a tumor 4 cm or less in the greatest dimension but limited to the kidney [2]. Due to this strict definition, a small percentage of these

small renal masses are actually upstaged because of extra-renal involvement. Upstaging to pathologic T3a (pT3a) can occur for the following three reasons regardless of tumor size: sinus fat invasion, renal vein or segment branch invasion, and perinephric fat invasion. However, pT3a does not encompass a homogenous group in the terms of cancer-specific and overall survival [3-8]. In addition to not representing a homogenous group, tumor size has been previously shown to be significant prognostic predictor in the setting of pT3a disease [3,9]. The lack of homogeneity has created controversy pertaining to the prognostic implications of perirenal fat invasion in pT3a tumors [5-7]. The objective of the present study is to report the incidence of pT3a upstaging in a contemporary cohort of patients with clinical T1a renal tumors and to compare oncologic outcomes.

Materials and Methods

A retrospective database was created reviewing patients who had undergone surgical intervention for renal cell carcinoma at our institution from 2000 to 2012. The type of surgery (partial nephrectomy or radical nephrectomy) was based upon the surgeon and patient preference after careful consideration of the tumor size, location, radiographic appearance, patient's overall health, and surgeon comfort. Patients with nodal or metastatic disease, a history of RCC, bilateral tumors, and non-RCC tumor found on final pathologic analysis were excluded from this study. The records of 468 patients were identified of which 218 had undergone surgery for a solitary cT1a tumor.

The follow-up period in months was defined from the date of surgery to the last follow-up visit. The National Comprehensive Cancer Network guidelines at the time of diagnosis were used to establish post-operative surveillance schedule [10]. Clinical staging was performed using either computed tomography or magnetic resonance imaging. The images were reviewed by primary investigators and compared to the original radiologic reports provided by the radiologists to determine the disease status and evidence of recurrence. The patients' pathologic reports were also reviewed and

pathologic staging was performed according to the 2010 American Joint Committee on Cancer Tumor Necrosis and Metastasis, 7th edition based upon the description by the original pathologist [11]. The cohort was then divided into two groups based upon T staging (pT1a and pT3a). All analysis was based upon clinical records.

Comparison of baseline demographics and clinical factors, such as age, gender, body mass index (BMI), tobacco use, and Charlson comorbidity index score prior to diagnosis, was performed between the 2 cohorts. The other variables analyzed included tumor size, RCC subtype, and grade. On multivariate Cox Proportional Hazards Model (MVA), analysis was controlled for age, 2 cohorts, histology type, and Charlson comorbidity index score.

Statistical analysis was done in SAS 9.3. Categorical variables were compared using Chi-square or Fisher's exact test where appropriate and continuous variables using the student's t-test. All survival analysis was performed on overall survival since only one recurrence was observed within the cohort. Kaplan-Meier analysis was used for determination of univariate survival effect of the variables using the log-rank test. The Cox Proportional Hazards model was used as the univariate and multivariate regression model to determine the effects of variables on survival, variables with a $p \leq .1$ were considered for the multivariate model. Statistical significance was achieved at $P < 0.05$.

Results

Of the cohort of 218 patients who had undergone surgical excision for cT1a RCC, 24 (11%) patients were upstaged to pT3a due to perirenal fat invasion and the remaining 194 (89%) remained pT1a. The median follow up period for this group was 55 months. Table 1 shows the comparison between the upstaged and the non-upstaged patients. The two groups were significantly different in the age of the patient, tobacco use, grade, and Charlson comorbidity index score.

Variable	All (n = 218)	pT3a (n = 24)	pT1a (n = 194)	P value
Male	121 (55.5%)	15 (62.5%)	106 (54.6%)	0.46
Age	62.1 ± 12.8	70.4 ± 10.8	61.0 ± 12.7	0.0007
BMI	30.6 ± 7.6	29.5 ± 8.0	30.8 ± 7.5	0.44
Tobacco	44 (24.31%)	1(5%)	43(26.7%)	0.049
Charlson Score				
0	82 (37.6%)	1 (4.2%)	81 (41.8%)	0.0003
1	61 (28.0%)	9 (37.5%)	52 (26.8%)	

2	37 (17.0%)	8 (33.3%)	29 (15.0%)	
3	13 (6.0%)	-	13 (6.7%)	
4	15 (6.9%)	5 (20.8%)	10 (5.2%)	
5	4 (1.8%)	1 (4.2%)	3 (1.6%)	
6	3 (1.4%)	-	3 (1.6%)	
7	3 (1.4%)	-	3 (1.6%)	
Partial Nephrectomy	125 (57.3%)	12 (50%)	113 (58.3%)	0.44
Tumor Size	27.9 ± 11.1	28.3 ± 10.9	27.9 ± 11.1	0.88
Histology				
Clear Cell	163 (75.1%)	16 (66.7%)	147 (76.2%)	0.31
Chromophobe	12 (5.5%)	3 (12.5%)	9 (4.7%)	
Papillary	35 (16.1%)	4 (16.7%)	31 (16.1%)	
Other	7 (3.2%)	1 (4.2%)	6 (3.1%)	
Fuhrman Grade				
NA	9 (4.1%)	3 (12.5%)	6 (3.1%)	
1	28 (13.4%)	0(0%)	28 (14.9%)	< .0001
2	146 (69.9%)	11 (52.4%)	135 (71.8%)	
3	29 (13.9%)	6 (28.6%)	23 (12.2%)	
4	6 (2.9%)	4 (19.1%)	2 (1.1%)	

Table 1: Demographics.

The average age of the study population was 62.1±12.84 years; however, statistical differences were discovered between the two groups with the mean age of 70.4 in the upstaged pT3a group and 61.0 in the pT1a group. Higher

grade tumors were statistically found in the pT3a group with 19% being Fuhrman grade 4. The pathologic characteristics data is summarized in Table 1. The univariate and multivariate comparison is found in Table 2.

Variable	Univariate			Multivariate		
	HR	95% CI	P Value	HR	95% CI	P Value
Gender (F vs M)	0.95	0.60-1.49	0.82	-	-	-
Age(≥65 vs < 65)	2.15	1.35-3.40	0.001	2.22	1.38-3.57	0.001
BMI (≥30 vs < 30 kg/m ²)	0.81	0.51-1.27	0.36	-	-	-
Charlson comorbidity index	1.32	1.17-1.47	<.0001	1.38	1.22-1.56	<.0001
Type of Surgery (partial vs complete Nephrectomy)	0.95	0.60-1.52	0.84	-	-	-
Fuhrman Grade (1-4)	1.23	0.84-1.78	0.28	-	-	-
Histology (clear cell vs other types)	1.62	0.99-2.64	0.051	1.68	1.03-2.77	0.04
Upstaging (T3a vs T1a)	1.82	0.96-3.46	0.07	1.33	0.69-2.56	0.39

Table 2: Univariate and multivariate analysis of prognostic factors for overall survival of patients with small renal masses. Univariate and multivariate analysis (Univariate variables with p < .1 were used in the multivariate model.)

Kaplan-Meier survival estimates revealed no statistical differences in overall mortality between the two groups. Univariate survival analysis revealed several factors including age, Charlson index score, and histology. Multivariate regression analysis revealed that age, histology, and Charlson index score were predictors of overall survival. Those ≥ 65 years of age were 2.2 times (95% CI: 1.38-3.57) more likely to be deceased, p < .001, those with a clear cell histology were 1.68 times (95% CI:

1.03-2.77) more likely to be deceased (p = .04) and for each increase in the Charlson index patients were 1.38 times (95% CI: 1.22-1.56) more likely to be deceased (p < .0001). In multivariate regression analysis, upstaging a cT1a renal mass to pT3a due to perirenal fat invasion was not a significant predictor of overall survival.

Only one of the 218 patients developed a recurrence and this patient was from the pT1a group. No patient with

in this cohort died secondary to RCC. The all-cause mortalities totaled 77 (35.3%) for the study population. All mortalities in this cohort have occurred secondary to non-renal cell carcinoma related causes.

Discussion

The incidence, clinical characteristics, and outcomes of clinical T1a RCC which are upstaged to T3a on final pathologic staging have not been widely reported. In the cohort of this study, 24 (11%) patients had their lesion upstaged to pT3a due to perirenal fat involvement. Ramaswamy et al. reported an upstaging incidence of 13.3% in their analysis of cT1 masses [12]. However, Gorin et al. reported a 3.9% rate of upstaging to pT3a in their cohort of patient who received a robotic-assisted partial nephrectomy for cT1 tumors [13]. The incidence of pT3a upstaging within our cohort appears to be within previously reported ranges.

Pathologic T3a represents a nonhomogeneous group consisting of sinus fat invasion, perirenal fat invasion, muscular venous branch invasion and renal vein invasion. Chevinsky et al. [7] recently report the incidence of each type of pT3a as the following: sinus fat invasion 42%, perirenal fat invasion 33%, muscular venous branch invasion 29% and renal vein invasion 20% [7]. In our cohort all of the tumors which were upgraded based upon perirenal fat invasion. An explanation for these discordant results might be that our cohort only included patients who were clinical T1a.

Gilbert et al. reported that perirenal fat invasion was not a predictor of worse disease free survival in comparison to pT1-T2 [7,14]. However, Gorin et al. [13] previously reported a lower recurrence-free survival in patients with pT3a when compared to pT1 and pT2 tumors (91.8% and 99.2%, respectively; $p=.003$) with the median follow-up of 17.3 months [13]. Their cohort differed from ours in that they included tumors up to 10 cm in size. It is important to note that our cohort only consisted of tumors smaller than 4cm. Other analyses have shown perirenal fat invasion to be predictive but associated with size [7,15]. Chevinsky et al. [7] reported the risk of recurrence was dependent on the size of the tumor in the presence of perinephric fat invasion.

In addition sinus fat invasion, muscular venous branch invasion, and renal vein invasion were independent predictors of higher risk of disease recurrence on multivariable controlling for tumor size [7]. In present study we demonstrated no increased risk of recurrence which appears to be consistent with the dependent

relationship between size and presence of perinephric fat invasion in predicting risk of recurrence. However, Chevinsky et al. [7] found an increased risk of recurrence in pT3a when compared to pT1a. Their analysis included all subtypes of pT3a which could explain the increase risk of recurrence since our analysis found no increased risk of recurrence when upstaging was attributed to perirenal fat invasion. These findings emphasize the importance of accurate pathological staging in particular the subtype of pT3a.

TMN included tumor size in staging because it is an important prognostic factor of 5-year survival [16]. The size of the tumor in the setting of pT3a RCC secondary to fat invasion has been previously shown to be an important factor for predicting outcomes [9]. Increasing tumor size and hilar location were also found to be independently associated with upstaging to T3a [17]. However, there exists a lack of literature exploring the significance of pT3a RCC in the setting of tumors less than 4 cm in size. This cohort revealed that the natural history of pT3a RCC secondary to perirenal fat invasion and smaller than 4 cm appears to behave like pT1a renal masses, particularly with recurrence and overall survival. In the setting of small renal masses, pT3a upstaging due to perirenal fat invasion might not be a poor prognostic indicator. In spite of this, it would be premature to assume that pT3a due to perirenal fat invasion is an insignificant finding and further investigation is warranted in a multi-institutional manner prior to revising the TNM classifications or current follow up protocol guidelines.

Current National Comprehensive Cancer Network guidelines change dramatically when a cT1a lesion is upgraded to a T3a. Stage pT1a guidelines recommend history and physical examination and comprehensive metabolic panel every 6 months for 2 years then annually for up to five years. In addition to this, recommendations include a chest x-ray (CXR) and abdominal imaging with CT, MRI, or ultrasound within 3-12 months of surgery and then consider repeating annually for 3 years based on individual risk factors. However, pT3a RCC has a more intense surveillance regimen with history and physical exam every 3-6 months for 3 years, comprehensive metabolic panel every 6 months for 2 years then annually for 5 years, and abdominal CT or MRI as well as a chest CT within 3-6 months of surgery then every 3-6 months for at least 3 years then annually up to 5years [16]. The intense follow up protocol for T3a RCC comes with increased costs both financial and emotional. If a small renal mass T3a lesion behaves like a T1a lesion then patients can be spared from these increased surveillance

and may be followed based on the T1a follow up guidelines. Current guidelines should be continued to be followed, however consideration to modify them in the future may be necessary in the era of cost effective medicine.

No evidence of compromised clinical or oncologic outcomes was found in patients with lesions upstaged to pT3a due to perirenal fat involvement. No patients in the upstaged group experienced disease recurrence during the study's follow-up period. These findings support the notion that immediate adjunctive systemic therapy is not necessary in patients with pathologic T3a upstaging. The low recurrence rate is most likely explained by the natural history of small renal masses. Despite low recurrence rate, it is important to note that patient's with RCC should follow a strict surveillance protocol.

Several limitations do exist in this study. One of which is the cohort is small and from a single institution. Small sample size limits the ability to discern differences between the groups that might otherwise have been apparent in a larger cohort. The retrospective nature of the study revealed a lack of consistency in recording tobacco usage. Also due to the retrospective nature of the study, it lacked a central pathologic review. Pathologic findings reported in this study were based upon originally reported findings at the time of surgery and then extrapolated to current TNM staging which could introduce error. Despite this limitation, the study explores the possibility that the upstaging of small renal masses to pT3a due to perirenal fat invasion may be an insignificant finding.

Conclusion

In this study only age >65 years and Charlson index score were noted as negative overall survival predictors. Clinically diagnosed T1a tumors which are upstaged to pathologic T3a secondary to perirenal fat invasion have similar oncologic outcomes when compared to clinically diagnosed T1a tumors which remain pathologic T1a. Patients with clinical T1a tumors which are upstaged to pathologic T3a due to perirenal fat invasion should be counseled that the other patient health status considerations have a greater effect on overall survival than upstaging.

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