Published in final edited form as:

J Urol. 2014 September ; 192(3): 659–664. doi:10.1016/j.juro.2014.03.038.

Growth Kinetics and Short Term Outcomes of cT1b and cT2 Renal Masses Under Active Surveillance

Reza Mehrazin, Marc C. Smaldone, Alexander Kutikov, Tianyu Li, Jeffrey J. Tomaszewski, Daniel J. Canter, Rosalia Viterbo, Richard E. Greenberg, David Y. T. Chen, and Robert G. Uzzo

Division of Urologic Oncology, Department of Surgical Oncology, Fox Chase Cancer Center-Temple University Health System, Philadelphia, PA 19111

Abstract

Objectives—Compared to T1a lesions, the natural history of untreated renal masses is >4cm is poorly understood. We sought to assess the growth kinetics and outcomes of cT1b/T2 cortical renal tumors managed with an initial period of active surveillance (AS), and compared these patients to those who underwent definitive delayed intervention.

Methods—Our institutional, prospectively maintained, renal tumor database was reviewed to identify enhancing solid & cystic masses managed expectantly. Clinically localized tumors >4.0 cm (T1b) that were radiographically followed for >6 months were included for analysis. Tumor size at presentation, annual linear tumor growth rate (LGR), Charlson comorbidity index (CCI), length of follow-up (FU), and clinical outcomes were compared between those who remained on AS or those who underwent delayed surgical intervention.

Results—72 tumors >4cm in diameter (in 68 patients) were identified. 45 patients (66%) were managed solely with AS, while 23 (34%) progressed to intervention. For all lesions, the median tumor size at presentation was 4.9 cm, and the mean LGR was 0.44 cm/year. 14.7% of masses demonstrated no growth over time. Comparing patients managed exclusively with AS and those progressing to definitive intervention, no differences were noted in median tumor size at presentation (4.9 vs. 4.6 cm, $p=0.79$) or median CCI (3 vs. 2, $p=0.6$), while significant differences were seen with respect to median age at presentation (77 vs. 60 years, $p=0.0002$) and mean LGR (0.37 vs. 0.73 cm/year, $p=0.02$). Following adjustment, younger patients (OR 0.91 [CI 0.86-0.97]) and tumors with faster LGR (OR 9.1 [CI 1.7-47.8]) were more likely to undergo delayed surgical intervention. With a median FU of 32 months (mean, 38.9 ± 24.0 ; range 6–105), 9 patients died (13%) from other cause and no patient progressed to metastatic disease.

Conclusions—Localized cT1b or larger renal masses show comparable growth rates to small tumors managed expectantly with low rates of progression to metastatic disease at short term follow up. An initial period of AS to determine tumor growth kinetics is a reasonable option in select patients with significant competing risks and limited life expectancy.

Corresponding author: Reza Mehrazin, MD Division of Urologic Oncology Department of Surgical Oncology Fox Chase Cancer Center 333 Cottman Avenue Philadelphia, PA 19111 Tel: (215) 728-4305 Fax: (888) 410-0855 reza.mehrazin@fccc.edu.

The authors would like to thank Debra Kister and Michelle Collins for their management of the Fox Chase Kidney Cancer Keystone Database.

Keywords

renal cell carcinoma; active surveillance; expectant management; delayed intervention; growth kinetics; kidney cancer

Introduction

In 2013, approximately 65,150 new cases of kidney cancer and renal pelvis are estimated to be diagnosed in the United States ¹. This continuous rise in the incidence of kidney cancer, particularly small tumors less than 4 cm in diameter, has largely been attributed to the increased use of cross-sectional abdominal imaging ². As the proportion of incidentally diagnosed small renal masses (SRMs) has risen, a corresponding increase in the median patient age at diagnosis has also been observed, with the most dramatic rise demonstrated in patients greater than 70 years of age ³.

Although surgical excision remains the standard of care for localized renal tumors, there is growing understanding and recognition that competing risks from medical comorbidities in elderly or unfit patients may outweigh the potential benefits of surgical intervention^{4, 5}. Over-diagnosis of clinically insignificant disease, coupled with additional morbidity due to potentially unnecessary treatments, are two critical harms associated with early or incidental cancer detection ⁶. Over the past decade, data appraising the natural history, progression, and outcomes of untreated clinically localized small renal masses (SRM)^{5, 7-11} has emerged. Although level I evidence supporting active surveillance (AS) of solid malignancies are absent, institutional studies and pooled analyses provide robust contemporary data that an initial short term period of observation to determine tumor growth kinetics may be safe for small enhancing tumors in select candidates.

While the evidence for active surveillance (AS) accumulates, the natural history of tumors greater 4 cm (cT1b/T2) managed expectantly remains poorly characterized. Our aim is to report our institutional experience and describe the growth kinetics of enhancing renal lesions >4cm managed with an initial period of AS.

Materials and Methods

Patient Selection

Our institutional, prospectively maintained, renal tumor database was reviewed to identify enhancing solid and cystic masses managed expectantly from 2000 to 2012. Clinical stage T1a masses (<4cm), transitional cell carcinomas, or patients with suspected metastatic disease were excluded from analysis. We assumed that those patients who developed metastasis within the first 6 months of AS had micrometastatic or undocumented systemic disease at presentation, and these patients were also excluded. Based on standard radiographic staging, localized tumors >4.0 cm (T1b) that were radiographically followed for more than 6 months were included for analysis.

Surveillance Protocol

Patients were stratified by absolute, relative, and elective indications for AS as previously described⁸. Patients were imaged at 3-6 month intervals following initial diagnosis, and the restaging interval was increased to every 6-12 months once stable growth kinetics were established¹². In addition to abdominal imaging, all patients had imaging of the thorax per recommended guidelines¹³. Size comparisons were performed by the treating uro-oncologist, using a consistent radiographic characteristic (maximum tumor diameter) across studies while paying close attention to the cross-sectional cut from which the data was obtained⁸. Tumor growth rate was defined as net change in linear diameter per year. Indications for delayed intervention included patient preference, change in tumor growth kinetics, change or improvement of comorbidity status, or development of tumor related symptoms. Intervention was categorized as radical (open or laparoscopic approach) or nephron sparing surgery (NSS) (open, laparoscopic, or robotic assisted laparoscopic approach). Ablative techniques were not routinely recommended as a treatment option for cT1b/T2 renal masses.

Covariates and Clinical Outcomes

Covariates examined included patient age, gender, Charlson comorbidity index (CCI), indication for AS, tumor size at presentation, duration of AS (months), radiographic tumor characteristics (solid versus cystic), presence of multifocal renal tumors, linear tumor growth rate, surgical pathology, type and reason for intervention, RENAL Nephrometry Score¹⁴, and progression to metastatic disease.

Statistical Analyses

Univariate analysis (UVA), Chi-square, and Wilcoxon rank sum tests were used to assess the associations between categorical and continuous variables and receipt of delayed intervention, respectively. Nominal *p* values of 0.05 were used as the criterion for statistical significance. In the multivariate analyses (MVA), logistic regression was used to look for independent predictors to delayed intervention controlling for age, Charlson score, race, sex, and initial tumor size. Descriptive statistics and analyses were conducted via SAS 9.2 (SAS Institute Inc., Cary, NC).

Results

Of 461 patients managed with AS in our institutional cohort, 68 patients (72 tumors) were identified with cT1b/T2 renal tumors managed expectantly for at least 6 months (Table 1). 60 masses (83%) were solid lesions while 12 (17%) were Bosniak III or IV cystic lesions. 2 patients (3%) had a solitary kidney, 11 patients (16%) had bilateral renal tumors, and 6 (9.5%) had multifocal unilateral lesions. The median age was 70 years (mean, 68.9 ±12.2; range, 40-94), 66% were male, and the median CCI was 3 (mean, 3.25±2.5; range, 0-11). Median initial tumor size at presentation was 4.9 cm (mean, 5.3±1.6; range 4.0-13.7) and the median Nephrometry Score sum was 9 (mean 8.7±1.6, range 5-11). With a median follow up of 32 months (mean 38.9± 25.7, 6-119), the median linear growth rate was 0.34 (mean, 0.44±0.45; range 0-1.48) cm/year and 14.7% demonstrated no growth over time.

45 patients (66%) were managed solely with AS, while 23 patients (34%) progressed to definitive intervention. Indications for progressing to definitive intervention were interval tumor growth (61%), patient choice (26%), medical clearance (4%), and development of tumor related symptoms (4%). Pre-surveillance biopsy was performed in 21 patients (31%). Pathology results from needle core biopsy revealed clear cell RCC (67%), oncocytoma (29%), and chromophobe RCC (4%). Of patients progressing to definitive intervention, 65% underwent nephron sparing surgery and 52% were treated with a minimally invasive approach (6 laparoscopic radical nephrectomy (RN), 6 laparoscopic/robotic partial nephrectomy (PN)). 1 patient (4%) underwent simultaneous RN at the time of esophagectomy for esophageal carcinoma. Malignant renal cell carcinoma was confirmed in 70%, while cortical cyst (22%), oncocytoma (4%), and lipid poor angiomyolipoma (4%) were documented in patients with benign lesions (characteristics summarized in Table 2). 9 (13%) patients died from other causes and no patient progressed to metastatic disease following AS with or without delayed intervention.

Compared to those who received delayed surgical intervention, patients who remained on AS were older (median: 77 vs. 60 years, $p=0.0002$) and showed slower mean annual LGR (0.37 vs. 0.73 cm/year, $p=0.02$). No significant difference was observed with respect to median tumor size at presentation, median CCI, or RENAL Nephrometry Score between groups. Median length of follow-up for patients who remained under AS and those who progressed to intervention was 34 and 24 months, respectively (Table 1). Following adjustment, on MVA, patient age (OR 0.91 [CI 0.86-0.97]) and LGR (OR 9.1 [CI 1.7-47.8]) demonstrated significant associations with receipt of delayed intervention (Table 3).

Discussion

In comparison to other urologic malignancies such as prostate cancer^{15, 16}, the natural history of untreated enhancing renal masses remains poorly characterized. Early institutional series have reported that growth kinetics of SRMs under an initial period of observation appear slow, and that with intermediate term follow-up metastasis is a rare (2%) event^{7-9, 17-20}. As a result, experts have begun to re-evaluate the role of aggressive intervention in elderly patients with significant co-morbidity in which the risks from surgery may outweigh any survival benefit. However, to date there has been a paucity of published data^{21, 22} examining the growth kinetics and clinical outcomes of larger (T1b/cT2) renal tumors managed with AS.

In 2010, Mues and colleagues reported the outcomes of 36 patients with 42 cT1b or cT2 tumors managed with AS with a median growth rate of 0.57cm/year. With a mean follow-up of 36 months, only three patients progressed to definitive intervention and two (5.6%) developed metastases²². In this, the largest contemporary experience of AS for T1b/T2 tumors to date, we similarly observed comparable growth kinetics, a low metastatic rate, and acceptable clinical outcomes to what has been described in the literature for smaller tumors.

Pooled and meta-analytic data suggest that most small tumors grow slowly with mean linear growth rates ranging from 0.28 to 0.31 cm/year^{7, 18}. In our series, although there was considerable variation (0-1.48 cm/year), we noted a comparable mean linear growth rate of

0.44 cm/year despite larger size at the time of diagnosis. Furthermore, prior accounts document a large proportion of patients in which no net (or negative) tumor growth is demonstrated over time, as high as 25-35%²³. In this series, the percentage of tumors with “zero growth” was lower at 15%, perhaps reflecting the biologic tendency of these tumors to have already grown. Moreover, others have shown that larger tumors show overall significantly slower tumor volume change compare to smaller masses over time⁸. This observation, Gompertzian growth kinetics, suggests that initially tumor's growth rate is exponential and then it decreases with increase in size²⁴. Of 72 lesions greater than 4cm at presentation in our series, 14.7% demonstrated no measurable evidence of growth on serial imaging. While this proportion is less than what is reported in the majority of AS series, it does support the notion that some localized lesions can grow quite large without acquiring metastatic potential²⁵. As no lesion without evidence of sequential tumor growth has metastasized while on AS to date⁷, these lesions may represent the ideal candidates for prolonged AS, with lesions demonstrating more rapid kinetics progressing to either renal mass biopsy for risk stratification²⁶ or definitive intervention²⁷.

There are currently no standardized surveillance imaging protocols or universal criteria for intervention for renal masses managed expectantly. Similar to what we have reported previously⁸, rationale for intervention in this series was predominantly rapid growth kinetics or patient preference, and approximately one third of patients ultimately were managed surgically with a mean delay to treatment of 31 months. When comparing patient and tumor characteristics between lesions managed with AS only and those which were not, patients undergoing definitive intervention were significantly younger in age, and had tumors demonstrating more rapid growth kinetics, which is consistent with prior reports^{7, 8}. As previously reported^{28, 29}, a positive growth rate was not synonymous with malignancy. Among lesions progressing to intervention, pathologic evaluation of two masses, which showed no growth over 42 and 16 months of AS, revealed high grade clear cell RCC and type II papillary RCC, respectively. Conversely, five lesions demonstrating worrisome growth (ranging from 0.19-0.92 cm/year) were found to be benign following excision. Encouragingly, the majority of patients in our series who progressed to intervention were managed with nephron sparing and/or minimally invasive techniques despite delays to therapy as long as five years. Most of the patients in our cohort had significant competing risks with limited life expectancy, and pre-surveillance biopsy was pursued only for those patients (31%) when the physician and the patient were certain that the result of biopsy will influence the management.

While our cohort of large renal tumors managed expectantly is small, no patient metastasized with a median follow up of 32 months. However, as previously documented, associations between tumor size and metastatic potential have been reported^{19, 20}, and pooled data analyses have reported a low but not negligible risk of disease progression while under observation⁷. Until results from a multicenter phase II trial³⁰ and large institutional series mature, clinicians will continue to rely on the use of radiographic growth kinetics and selective use of renal mass biopsy to better delineate which lesions are appropriate for observation or require immediate intervention.

Although limited by selection biases, small sample size, and poor generalizability, our early findings suggest that in select patients with significant competing risks who are poor operative candidates, tumor size >4cm should not be used as exclusion criteria for an initial period of AS. However, while unlikely forthcoming, prospective trials comparing AS to conventional surgical treatments with defined selection criteria and standardized imaging protocols are sorely needed prior to broad implementation of AS in general clinical practice. Until level one evidence is available to guide practice, or at minimum long-term institutional survival data, AS should remain an alternative to surgical excision in acceptable operative candidates.

Conclusions

Localized cT1b/T2 renal masses managed expectantly show comparable growth rates to smaller tumors and limited metastatic potential with short-term follow up. An initial period of AS to determine tumor growth kinetics for tumors greater than 4cm is a reasonable option in select patients with significant competing risks and limited life expectancy.

Acknowledgments

This publication was supported in part by grant number P30 CA006927 from the National Cancer Institute. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health. Additional funds were provided by Fox Chase Cancer via institutional support of the Kidney Cancer Keystone Program.

References

1. Siegel R ND, Jemal A. Cancer Statistics 2013. *CA Cancer J Clin.* Jan; 2013 63(1):11–30. [PubMed: 23335087]
2. Hollingsworth JM, Miller DC, Daignault S, et al. Rising incidence of small renal masses: a need to reassess treatment effect. *J Natl Cancer Inst.* 2006; 98:1331. [PubMed: 16985252]
3. Jayson M, Sanders H. Increased incidence of serendipitously discovered renal cell carcinoma. *Urology.* 1998; 51:203. [PubMed: 9495698]
4. Kutikov A, Egleston BL, Wong YN, et al. Evaluating overall survival and competing risks of death in patients with localized renal cell carcinoma using a comprehensive nomogram. *J Clin Oncol.* 2010; 28:311. [PubMed: 19933918]
5. Volpe A, Cadeddu JA, Cestari A, et al. Contemporary management of small renal masses. *Eur Urol.* 2011; 60:501. [PubMed: 21664040]
6. Welch HG, Black WC. Overdiagnosis in cancer. *J Natl Cancer Inst.* 2010; 102:605. [PubMed: 20413742]
7. Smaldone MC, Kutikov A, Egleston BL, et al. Small renal masses progressing to metastases under active surveillance: a systematic review and pooled analysis. *Cancer.* 2012; 118:997. [PubMed: 21766302]
8. Crispen PL, Viterbo R, Boorjian SA, et al. Natural history, growth kinetics, and outcomes of untreated clinically localized renal tumors under active surveillance. *Cancer.* 2009; 115:2844. [PubMed: 19402168]
9. Crispen PL, Uzzo RG. The natural history of untreated renal masses. *BJU Int.* 2007; 99:1203. [PubMed: 17441911]
10. Abouassaly R, Lane BR, Novick AC. Active surveillance of renal masses in elderly patients. *J Urol.* 2008; 180:505. [PubMed: 18550113]
11. Wehle MJ, Thiel DD, Petrou SP, et al. Conservative management of incidental contrast-enhancing renal masses as safe alternative to invasive therapy. *Urology.* 2004; 64:49. [PubMed: 15245934]

12. Campbell SC, Novick AC, Beldegrun A, et al. Guideline for management of the clinical T1 renal mass. *J Urol*. 2009; 182:1271. [PubMed: 19683266]
13. CCN clinical practice guidelines in oncology. Kidney cancer. National Comprehensive Cancer Network Web. :2014.
14. Kutikov A, Uzzo RG. The R.E.N.A.L. nephrometry score: a comprehensive standardized system for quantitating renal tumor size, location and depth. *J Urol*. 2009; 182:844. [PubMed: 19616235]
15. Klotz L, Zhang L, Lam A, et al. Clinical results of long-term follow-up of a large, active surveillance cohort with localized prostate cancer. *J Clin Oncol*. 2010; 28:126. [PubMed: 19917860]
16. Wilt TJ, Brawer MK, Barry MJ, et al. The Prostate cancer Intervention Versus Observation Trial:VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT): design and baseline results of a randomized controlled trial comparing radical prostatectomy to watchful waiting for men with clinically localized prostate cancer. *Contemp Clin Trials*. 2009; 30:81. [PubMed: 18783735]
17. Bosniak MA, Birnbaum BA, Krinsky GA, et al. Small renal parenchymal neoplasms: further observations on growth. *Radiology*. 1995; 197:589. [PubMed: 7480724]
18. Chawla SN, Crispen PL, Hanlon AL, et al. The natural history of observed enhancing renal masses: meta-analysis and review of the world literature. *J Urol*. 2006; 175:425. [PubMed: 16406965]
19. Kunkle DA, Crispen PL, Li T, et al. Tumor size predicts synchronous metastatic renal cell carcinoma: implications for surveillance of small renal masses. *J Urol*. 2007; 177:1692. [PubMed: 17437785]
20. Thompson RH, Hill JR, Babayev Y, et al. Metastatic renal cell carcinoma risk according to tumor size. *J Urol*. 2009; 182:41. [PubMed: 19450840]
21. Lamb GW, Bromwich EJ, Vasey P, et al. Management of renal masses in patients medically unsuitable for nephrectomy--natural history, complications, and outcome. *Urology*. 2004; 64:909. [PubMed: 15533476]
22. Mues AC, Haramis G, Badani K, et al. Active surveillance for larger (cT1bN0M0 and cT2N0M0) renal cortical neoplasms. *Urology*. 2010; 76:620. [PubMed: 20599256]
23. Kunkle DA, Crispen PL, Chen DY, et al. Enhancing renal masses with zero net growth during active surveillance. *J Urol*. 2007; 177:849. [PubMed: 17296355]
24. Norton L. A Gompertzian model of human breast cancer growth. *Cancer Res*. 1988; 48:7067. [PubMed: 3191483]
25. Rothman J, Eggleston B, Wong YN, et al. Histopathological characteristics of localized renal cell carcinoma correlate with tumor size: a SEER analysis. *J Urol*. 2009; 181:29. [PubMed: 19012902]
26. Mason RJ, Abdoell M, Trottier G, et al. Growth kinetics of renal masses: analysis of a prospective cohort of patients undergoing active surveillance. *Eur Urol*. 2011; 59:863. [PubMed: 21353376]
27. Smaldone MC, Corcoran AT, Uzzo RG. Active surveillance of small renal masses. *Nat Rev Urol*. 2013; 10:266. [PubMed: 23567498]
28. Kawaguchi S, Fernandes KA, Finelli A, et al. Most renal oncocytomas appear to grow: observations of tumor kinetics with active surveillance. *J Urol*. 2011; 186:1218. [PubMed: 21849182]
29. Siu W, Hafez KS, Johnston WK 3rd, et al. Growth rates of renal cell carcinoma and oncocytoma under surveillance are similar. *Urol Oncol*. 2007; 25:115. [PubMed: 17349525]
30. Jewett MA, Mattar K, Basiuk J, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. *Eur Urol*. 2011; 60:39. [PubMed: 21477920]

Diagram 1.
Patients with T1b/T2 Masses Under Active Surveillance

Table 1**Patient Demographic Information & Tumor Characteristics**

	Overall (%)	AS (%)	Surgical Intervention (%)	p- value
No. Patients	68	45 (66)	23 (34)	
No. Tumors	72	49 (68)	23 (32)	0.95
Sex (male/female)	44/24	29/16	15/8	0.95
Median Age (range)	70 (40-94)	77 (45-94)	60 (40-87)	0.0002
Median CCI (range)	3 (0-11)	3 (0-11)	2 (0-10)	0.60
Median tumor size on presentation (cm) (range)	4.9 (4.0-13.7)	4.9 (4.0-9.7)	4.6 (4.0-13.7)	0.79
Median tumor size at last fu/surgery (cm) (range)	6.0 (4.0-15.0)	6.1 (4.0-9.7)	6.2 (4.0-15.0)	0.91
Median Nephrometry Score	9	9	9	1
No. Solitary Kidney	2 (3)	2 (4)	0	1.0
No. Bilateral Renal Tumors	11 (16%)	6 (13)	5 (22)	0.27
Median No. Images During AS (mean, range)	4 (4.6±2.4, 2-11)	4 (5.1±2.7, 2-11)	4 (3.7±1.6, 2-9)	0.03
Median Months of follow-up (mean, range)	32 (38.9±25.7, 6-105)	34 (43±25,12-105)	24 (31±20, 6-60)	0.1
Mean Linear Growth Rate:				0.02
Monthly (cm/month)	0.04	0.03	0.06	
Annually (cm/year)	0.44	0.37	0.73	
Tumor Type (%):				0.17
Solid	60 (83)	43 (88)	17 (74)	
Bosniak III or IV cyst	12 (17)	6 (12)	6 (26)	
No. Performed Biopsy:	21 (31)	18 (40)	3 (13)	0.09
Clear Cell	14 (67)	12 (67)	2 (67)	
Oncocytoma	6 (29)	5 (28)	1 (33)	
Chromophobe	1 (4)	1 (5)	0	
Clinical Stage:				0.45
cT1b	65 (90)	43 (88)	22 (96)	
cT2a	5 (7)	5 (10)	0	
cT2b	2 (3)	1 (2)	1 (4)	
Indication for AS:				0.41
Elective	17 (25)	9 (20)	8 (35)	
Relative	21 (31)	16 (36)	5 (22)	
Absolute	30 (44)	20 (44)	10 (43)	

Table 2

Pathologic Assessment in 23 patients who had delayed intervention

Pathology	No. (%)
Benign	7 (30)
Cortical Cyst	5 (71)
Oncocytoma	1 (14)
Angiomyolipoma	1 (14)
Malignant	16 (70)
Clear Cell	10 (63)
Papillary	4 (24)
Sarcomatoid	2 (13)
Stage	
T0	5 (24)
T1b	11 (52)
T2b	1 (5)
T3a	4 (19)
Nuclear grade	
1	2 (9)
2	6 (26)
3	5 (22)
4	3 (13)
Unknown	7 (30)
Type of Surgery	
OPNx	9 (39)
ONx	2 (9)
LPNx	5 (22)
RALPNx	1 (4)
LNx	6 (26)

OPNx: open partial nephrectomy; ONx: Open nephrectomy; LPNx: Laparoscopic Partial Nephrectomy; RALPNx: Robotic-Assisted Laparoscopic Partial Nephrectomy; LNx: Laparoscopic Radical Nephrectomy.

Table 3

Factors Associated with Termination of AS on MVA

	HR (95% CI)	p Value
CCI	0.75 (0.51-1.1)	0.125
Number of Images	0.64 (0.38-1.1)	0.082
Tumor Complexity (NS)	0.71 (0.42-1.2)	0.187
Tumor Growth Rate	9.08 (1.72-47.8)	0.009
Age at Presentation	0.91 (0.86-0.97)	0.005