Natural History of Small Renal Masses

Lei Zhang, Xue-Song Li, Li-Qun Zhou
Department of Urology, Peking University First Hospital, Beijing 100034, China

Objective: To review the natural history and growth kinetics of small renal masses (SRMs).

Data Sources: The literature concerning natural history and growth kinetics of SRMs was collected from PubMed published from 1990 to 2014.

Study Selection: We included all the relevant articles on the active surveillance (AS) or delayed treatment for SRMs in English, with no limitation of study design.

Results: SRMs under AS have a slow growth potential in general. The mean linear growth rate is 0.33 cm/year, the mean volumetric growth rate is 9.48 cm$^3$/year. The rate of metastasis during AS is below 2%. Some factors are associated with the growth rate of SRMs, including tumor grade, histological subtype, initial tumor size, age, radiographic characteristics, and molecular markers. No definite predictor of growth rate of SRMs is defined at present. SRMs with high tumor grade and the subtype of clear cell renal cell carcinoma may have aggressive growth potential.

Conclusions: AS is a reasonable choice for elderly patients with SRMs, who are at high risk from surgery. Progression during observation is the biggest concern while performing AS. There is no definite predictor of progression for SRMs under AS. Percutaneous renal biopsy providing immunohistological and genic biomarkers may improve the understanding of natural history of SRMs.

Key words: Active Surveillance; Growth Kinetics; Natural History; Small Renal Masses

Introduction

During the last 20 years, the incidence of renal tumors has been increasing.\[1\] The increase in diagnosis has been partly attributed to the use of modern imaging procedures, such as ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI) in the past 30 years.\[2,3\] The largest increase is seen in tumors <4 cm, which are now referred to as small renal masses (SRMs), the median age of patients has also increased to 70–90 years old.\[1\] Although the detection of early stage renal tumors has been increasing, and the absolute number of surgical treatments of these tumors has also been rising, the mortality rate of renal tumors remains unchanged. This suggests that the surgical treatment of early stage renal tumors does not decrease cancer-specific mortality, which raises the concerns of over-diagnosing and over-treating in early stage renal tumors.

Incidentally found small renal masses (SRMs), especially for older people, have been arousing attention in urologic practice. Not all SRMs are renal cell carcinoma (RCC), with approximate 20%–30%\[4,5\] confirmed with benign pathology and 20%–30% presenting aggressive malignant potential.\[6,7\] In the absence of effective systemic therapy, radical nephrectomy has been historically the standard treatment of SRMs. Considering the risk of chronic kidney disease resulting from radical nephrectomy\[8,9\] and further cardiovascular disease,\[10–12\] partial nephrectomy has been gradually accepted and become the standard treatment of SRMs based on the equivalent oncologic outcome compared with radical nephrectomy.\[13\] However, most of the SRMs are diagnosed in patients 70–90 years old,\[1\] and for these patients there is an increased surgical risk as a medical comorbidity being a major concern of treatment. Almost one-third of patients who are 70 years old with renal tumors died from unrelated comorbidities within 5 years postoperatively.\[14\] In addition, RCC has an indolent nature in general, once even known as the “internist’s tumors.” Hence, elderly patients with medical comorbidities or limited life-expectancy may not obtain a benefit from surgical treatment. In a retrospective analysis of 537 patients over 75 years old, active treatment that included radical nephrectomy and kidney sparing surgery did not yield a survival benefit compared with active surveillance (AS).\[15\] AS, with serial assessment, has been suggested for SRMs in patients with severe medical comorbidities and limited life-expectancy.

Access this article online

Quick Response Code: 
Website: www.cmj.org
DOI: 10.4103/0366-6999.156139

Address for correspondence: Dr. Xue-Song Li, Department of Urology, Peking University First Hospital, Beijing 100034, China E-Mail: pineneedle@sina.com
Approximately, 20% SRMs present aggressive malignant behavior,\textsuperscript{[6,7]} which is the greatest concern when a patient is considering AS instead of immediate surgery. Observation of SRMs growth during AS give the unique opportunity of learning about the natural history of SRMs, which is also useful in selecting patients with indolent SRMs growth potential. Historically, most SRMs were treated by surgical treatment soon after diagnosis, which led to a small body of knowledge about natural history of SRMs. In the last decade, a number of retrospective reports, prospective studies, and meta-analysis on AS of SRMs introduced a further understanding of the natural history of SRMs.\textsuperscript{[16–37]} In this review, we will discuss the natural history and growth kinetics of SRMs trying to characterize the SRMs with aggressive growth potential based on the existing data.

**Growth Kinetics of Small Renal Masses Under Active Surveillance**

At present, data from a number of published studies on patients with SRMs treated by delayed treatment or managed purposely with AS,\textsuperscript{[16–37]} has led to a relatively mature understanding of the natural history of SRMs. Consistent with previous statement that 20%–30% of SRMs are benign and 60% present indolent growth behavior,\textsuperscript{[6–7]} these studies revealed an encouraging result that SRMs under AS had generally slow growth kinetics and a low rate of metastasis (1.6%) \textsuperscript{[Table 1].} However, there are some considerations that should be noticed in these studies. Most of these studies are retrospective with limited strength, and there is only one prospective study with rigorous criteria and a clear definition of tumor progression. Lack of pathological diagnosis is a drawback to the understanding on the natural history of RCC that are more clinically significant. The growth rate was reflected by the mean growth rate during a period of AS, not recorded over time. Our previous study demonstrated that these tumors account for 23%–33% of SRMs under AS exhibited zero growth in diameter. Previous studies demonstrated that these tumors account for 23%–33% of SRMs under AS exhibited zero growth in diameter.\textsuperscript{[16–37]} After a mean follow-up of 33.5 ± 22.6 months during AS, the mean LGR was 0.31 ± 0.38 cm/year. The only multicenter, prospective, phase II clinical trial on AS of SRMs included 178 patients with 209 SRMs, providing a mean LGR of 0.13 cm/year.\textsuperscript{[44]} The Schwartz equation has been used to calculate the VDT of SRMs;\textsuperscript{[42,43]} VDT = (T − T\textsubscript{0}) × log2/log (V/V\textsubscript{0}). T indicates the date of the final imaging procedure, T\textsubscript{0} is defined as the date of initial imaging procedure, V is the volume at final imaging evaluation, V\textsubscript{0} is the volume at initial imaging evaluation. Previous studies reported various mean VDT of SRMs ranging from 460 to 603 days.\textsuperscript{[16,29,41,44–46]} In a prospective study, Jewett et al.\textsuperscript{[34]} had defined a VDT of <1 year as an indication of progression. Of these studies, some radiology articles accurately evaluated the VDT using an area measuring tool and summation-of-areas technique.\textsuperscript{[29,44,45]} The remaining studies employed mathematical formula to calculate the volume.\textsuperscript{[16,41,46]} We believe that the disparity of VDT between studies might be attributed to the different calculation methods for volume. Although the summation-of-area method is more precise, it is more difficult to calculate in clinical practice.

Linear growth rate may not fully reflect the change of tumor volume. Alternatively, the volumetric growth rate (VGR) or volume doubling time (VDT) is more precise to reflect the growth of SRMs.\textsuperscript{[44]} However, they are more inconveniences for use in clinical practice. The VGR can be calculated depending on a number of available dimensions and formula; 0.5326 × yz, 0.5326 × y ((x + y)/2), or 0.5326x\textsuperscript{3}.\textsuperscript{[19]} A pooled-analysis in 2012 including 259 patients and 284 SRMs demonstrated that the mean VGR was 6.3 ± 27.4 cm\textsuperscript{3}/year during a mean AS of 33.5 months,\textsuperscript{[46]} although 88% of the lesions that had pathologic data available were malignant (n = 117). Consistent with this result, our pooled-analysis revealed a similar mean VGR of 9.48 cm\textsuperscript{3}/year \textsuperscript{[Table 1].} Crispen et al.\textsuperscript{[31]} reported a mean VGR of 17.0 ± 71.6 cm\textsuperscript{3}/year in a retrospective study involving 172 renal tumors in 154 patients under AS. The difference of VGR may be attributed to different calculation method of volume.

The Schwartz equation has been used to calculate the VDT of SRMs;\textsuperscript{[42,43]} VDT = (T − T\textsubscript{0}) × log2/log (V/V\textsubscript{0}). T indicates the date of the final imaging procedure, T\textsubscript{0} is defined as the date of initial imaging procedure, V is the volume at final imaging evaluation, V\textsubscript{0} is the volume at initial imaging evaluation. Previous studies reported various mean VDT of SRMs ranging from 460 to 603 days.\textsuperscript{[16,29,41,44–46]} In a prospective study, Jewett et al.\textsuperscript{[34]} had defined a VDT of <1 year as an indication of progression. Of these studies, some radiology articles accurately evaluated the VDT using an area measuring tool and summation-of-areas technique.\textsuperscript{[29,44,45]} The remaining studies employed mathematical formula to calculate the volume.\textsuperscript{[16,41,46]} We believe that the disparity of VDT between studies might be attributed to the different calculation methods for volume. Although the summation-of-area method is more precise, it is more difficult to calculate in clinical practice.

Consistent with the indolent natural of SRMs, a portion of SRMs under AS exhibited zero growth in diameter. Previous studies demonstrated that these tumors account for 23%–33% of SRMs.\textsuperscript{[34,40,47]} Kunkle et al.\textsuperscript{[47]} did not find a difference in initial tumors size, patient age, radiographic characteristics, and malignancy rate between the SRMs without growth and those with growth. Other studies also found a comparable malignancy rate between these two groups.\textsuperscript{[17,26]} However, Smaldone et al.\textsuperscript{[31]} revealed that no SRMs with zero growth had developed metastasis during AS.\textsuperscript{[49]} Undoubtedly, SRMs with zero growth were more likely to be treated with prolonged AS after imaging examination, while delayed surgical treatment was performed for rapidly growing SRMs.
Prognostic Factors for Small Renal Masses

Growth

Histological type and grade

Histological type and grade are important prognostic factors, but their role in the growth of SRMs is unclear. A previous study demonstrated that the renal oncocytoma was not significantly different from RCC in their growth rate.[26] Although oncocytomas are benign, they have been shown to have a fast growth rate.[48] Oda et al. found that there was no correlation between growth rate and tumor grade of RCC.[49] Kato et al.[21] found that RCC with Fuhrman Grade III grew faster than those with Fuhrman Grades I–II. Our study involving 32 SRMs confirmed to be RCC after delayed surgery of at least 12 months found that the growth rate of Fuhrman Grade I tumors was 0.36 cm/year, slower than that of Fuhrman Grade II (0.88 cm/year) and Grade III tumors (1.04 cm/year).[35] Past studies[33,46] reported a faster growth potential of clear cell RCC compared with papillary renal carcinomas. Smaldone et al.[48] also confirmed that lesions with progression to metastasis during AS were predominantly clear cell RCC.

Initial size of small renal masses

Initial tumor size (defined as the maximal diameter) was the most common baseline characteristics used to predict the growth rate of SRMs. However, the correlation between initial tumor size and growth rate is unclear. Some articles demonstrated no correlation between initial size and the growth rate of SRMs,[23,50] while other studies reported that SRMs with larger initial size grew more rapidly.[11,51] In addition, Crispen et al. demonstrated that smaller renal tumors have greater VGR than larger renal tumors,[31] which was suggestive of Gompertzian growth kinetics, the growth rate of tumors is exponential initially and decreases with the increase of tumor size.

Initial tumor size is also believed to be correlated with the malignancy and grade of SRMs. Frank et al.[53] reported that the possibility of benign disease for SRMs < 1 cm, 1–1.9 cm, 2–2.9 cm, and 3–3.9 cm were 46.3%, 22.4%, 22%, and 19.9%, respectively. They calculated that a 1 cm increase in SRMs size led to a 17% increase in the possibility of malignancy. The invasiveness of SRMs also increased along with an increase in lesion size. Remzi et al.[7] reported that as the size of SRMs increased, the possibility of perirenal fat invasion was also increased: for SRMs < 2 cm, 2.1–3.0 cm, and 3.1–4.0 cm, the possibility of perirenal fat invasion was 4.2%, 14.9%, and 35.7%, respectively. Distant metastasis was found with 2.4% of the SRMs < 3 cm and 8.4% of the SRMs 3.1–4.0 cm. Kunkle et al.[31] found that a 1 cm increase in SRMs size brought a 22% increase in the possibility of distant metastasis. In addition, high Fuhrman grade (G3 and G4) accounted for 5.0%–6.5% of the SRMs 3–4 cm.

Age

Some previous studies discovered no correlation between patient age and the growth rate of SRMs.[50,51] Kouba et al.[25]...
found that the SRMs in patients <60 years old grew faster than those in patients ≥60 years old. Zhang et al. demonstrated age at diagnosis was negatively correlated with the growth rate of SRMs. In another study, the age of patients who need delayed intervention after AS was older than that of patients who stayed in AS. Because young patients have a long life expectancy, less comorbidity, and lower surgical risk comparing with old patients, for young patients with more aggressive SRMs growth during AS, it is more appropriate to consider surgical treatment. In addition, previous research studied 862 SRMs and made a preoperative prognostic nomogram based on a logistic regression analysis involving age, gender, tumor size, symptom, smoking history, etc., the results revealed that SRMs were more likely to be benign in elderly men and young women.

**Radiographic characteristics**
A few of articles tried to find some radiographic features to predict the growth of SRMs. Birnbaum et al. reported a significant correlation between slow growth and homogeneity on CT. Dodelzon et al. found that the SRMs with homogeneity on T2-weighted images of MRI had a significantly slower growth rate than the SRMs without this feature. And they also found a nearly significant slow growth rate among the SRMs with homogeneity on postcontrast images (P = 0.065) and hypointensity on T2-weighted images (P = 0.074).

**Immunohistochemical biomarkers**
Kato et al. found that the positive rate of TUNEL was significantly correlated to the growth rate of SRM, while the positive rate of Ki-67 was not. Oda et al. demonstrated that neither Ki-67 nor TUNEL was associated with the growth rate of incidentally found RCC, but the ratio of Ki-67/TUNEL was strongly correlated with the growth rate. Fujimoto et al. found low expression of the argyrophilic nucleolar organizer regions and proliferating cell nuclear antigen activity was significantly correlated with the VDT of RCC. To date, there is no good molecular predictor of metastasis that helps choose the optimal treatment.

**Progression and Metastasis During Active Surveillance**
Based on our pooled analysis, SRMs generally present with indolent growth; however, a portion of them exhibited disease progression including tumor growth, upstaging, and even metastasis. The possibility of the progression of SRMs is of great concern when doctors considered AS for patients who were unfit for surgery. As yet, there is no definite criterion of progression for SRMs under AS. In a prospective, clinical phase II trial, Jewett et al. defined tumor progression of SRM as tumor growth over 4 cm, VDT < 1 year, and detection of metastatic lesions. A cohort of 178 patients with 209 SRMs was enrolled in that study, of them, 25 SRMs (25/178, 12%) developed local progression, and two patients (2/178, 1.1%) developed metastasis.

Consistent with this result, our pooled analysis reveals a parallel rate of metastasis of 1.6% [Table 1].

A pooled analysis on SRMs progressing to metastasis under AS identified 18 patients (2.0%) who developed metastasis during AS in 18 series that included 880 patients with 936 SRMs. The comparison was made in that study between patients who developed metastasis and patients who did not. Compared with patients without metastasis, patients with metastasis were older (75 vs. 67 years old, P = 0.03), had a greater tumor initial size (4.1 cm vs. 2.3 cm, P < 0.001), a greater tumor initial volume (66 cm³ vs. 12 cm³, P < 0.0001), a faster LGR (0.8 cm/year vs. 0.3 cm/year), and a faster VGR (27 cm³/year vs. 6 cm³/year). They also confirmed the trend toward clear cell RCC and high-grade lesions developing metastasis during AS, and all the lesions were >3 cm when metastatic progression was detected. As for the growth rate of metastatic lesions, Fujimoto et al. demonstrated a relatively shorter VDT (89.4 ± 43.0 days vs. 468.0 ± 84.6 days) in metastatic lesions compared with primary lesions. Although a series of exciting results were obtained, there is no effective method to distinguish the SRMs which would develop progression of metastasis during AS from those SRMs with an indolent growth nature.

**Selection Bias of Natural History of Small Renal Masses**
Although previous studies on the natural history of SRMs revealed a generally indolent growth potential, it should be noted that selection bias may exist in these studies. Most of the SRMs are excised by immediate surgeries, while those SRMs preserved for AS usually have nontypical characteristics in images, and they have relatively slow growth kinetics. Among the patients choosing AS for renal tumors, a significant portion of them suffer from medical disease and they chose AS because of their poor physical condition; the natural history of renal tumors in these patients could be biased by their death from medical disease. All these possible biases should be noticed when discussing the natural history of SRMs.

**Percutaneous Renal Biopsy**
There is no current definitive prognostic factor of the natural history of SRMs. Percutaneous renal biopsy (PRB) could be used to determine the pathology of SRMs. Historically, the deficiency in accuracy, a high non-diagnostic rate, and severe complications from puncture limited the application of renal biopsy in SRMs. However, Volpe et al. performed a recent meta-analysis and found the complication rate of PRB was low, the accuracy rate of diagnosis was improved, with sensitivity of 70%–100%, and a specificity of 100%. PRB has been accepted as an aid for SRMs diagnosis. A study with a high-volume of PRB found that the renal biopsy helped with the diagnosis for 90% of patients. Another report found that PRB was deficient for tumor grading and not appropriate for SRMs < 3 cm. However, PRB can provide tumor tissue.
that might be useful to find some predictors of the natural history of SRMs, such as immunohistochemical and genetic biomarkers. Hence, a prospective trial with biopsy before AS to obtain immunohistochemical and genetic biomarkers may help improve our understanding of natural history of SRMs.

Conclusions
The development of imaging procedure has led to an increase of detected SRMs during the last two decade. The largest increase in SRMs is for elderly patients who might not benefit from surgical treatment because of high morbidity and limited life-expectancy. AS has been gradually accepted as an alternative approach to surgery for SRMs, especially among elderly people with medical complications. An increasing number of studies on AS for SRMs gave us a unique opportunity to understand the natural history and growth kinetics of SRMs. Most of SRMs exhibited a slow growth rate, even 23%–33% of SRMs had no growth during AS. However, approximate 2% of SRMs developed metastasis during AS, which is of the most concern when considering AS for SRMs. Previous studies tried to characterize the SRMs with rapid growth or metastasis; unfortunately, there is still no consensus. It is relatively accepted that SRMs with a high tumor grade and the subtype of clear cell RCC might present with aggressive growth and metastatic potential. A prospective trial with biopsy before AS to obtain certain immunohistological and genetic biomarkers is required. Molecular markers and genetic markers might be promising predictors of the growth of SRMs. Until definite predictors of growth and metastasis of SRMs are defined, more attention should be paid to the natural history of SRMs.

References
1. Chow WH, Devesa SS. Contemporary epidemiology of renal cell cancer. Cancer J 2008;14:288-301.
2. Chow WH, Devesa SS, Warren JL, Fraumeni JF Jr. Rising incidence of renal cell cancer in the United States. JAMA 1999;281:1628-31.
3. Hollingsworth JM, Miller DC, Daiguardt S, Hollenbeck BK. Rising incidence of small renal masses: A need to reassess treatment effect. J Natl Cancer Inst 2006;98:1331-4.
4. Vasudevan A, Davies RJ, Shannon BA, Cohen RJ. Incidental renal tumours: The frequency of benign lesions and the role of preoperative core biopsy. BJU Int 2006;97:946-9.
5. Kutikov A, Fossett LK, Ramchandani P, Tomaszewski JE, Siegelman ES, Banner MP, et al. Incidence of benign pathologic findings at partial nephrectomy for solitary renal mass presumed to be renal cell carcinoma on preoperative imaging. Urology 2006;68:737-40.
6. Crispen PL, Boorjian SA, Lohse CM, Sebo TS, Cheville JC, Blute ML, et al. Outcomes following partial nephrectomy by tumor size. J Urol 2008;180:1912-7.
7. Remzi M, Ozsoy M, Klingler HC, Susani M, Waldert M, Seitz C, et al. Are small renal tumors harmless? Analysis of histopathological features according to tumors 4 cm or less in diameter. J Urol 2006;176:896-9.
8. Huang WC, Levey AS, Serio AM, Snyder M, Vickers AJ, Raj GV, et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumors: A retrospective cohort study. Lancet Oncol 2006;7:735-40.
9. McKiernan J, Simmons R, Katz J, Russo P. Natural history of chronic renal insufficiency after partial and radical nephrectomy. Urology 2002;59:816-20.
10. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.
11. Huang WC, Elkin EB, Levey AS, Jang TL, Russo P. Partial nephrectomy versus radical nephrectomy in patients with small renal tumors – is there a difference in mortality and cardiovascular outcomes? J Urol 2009;181:55-61.
12. Miller DC, Schonlau M, Livi AM, Lai J, Saigal CS. Urologic Diseases in America Project. Renal and cardiovascular morbidity after partial or radical nephrectomy. Cancer 2008;112:511-20.
13. Campbell SC, Novick AC, Benedegrun A, Blute ML, Chow GK, Derweesh IH, et al. Guideline for management of the clinical T1 renal mass. J Urol 2009;182:1271-9.
14. Hollingsworth JM, Miller DC, Daiguardt S, Hollenbeck BK. Five-year survival after surgical treatment for kidney cancer: A population-based competing risk analysis. Cancer 2007;109:1763-8.
15. Lane BR, Abouassaly R, Gao T, Weight CJ, Hernandez AV, Larson BT, et al. Active treatment of localized renal tumors may not impact overall survival in patients aged 75 years or older. Cancer 2010;116:3119-26.
16. Fujimoto N, Sugiya A, Terasawa Y, Kato M. Observations on the growth rate of renal cell carcinoma. Int J Urol 1995;2:71-6.
17. Bosniak MA, Birmbaum BA, Kirsinsky GA, Waisman J. Small renal parenchymal neoplasms: Further observations on growth. Radiology 1995;197:589-97.
18. Oda T, Takahashi A, Miyao N, Yanase M, Masumori N, Itoh N, et al. Cell proliferation, apoptosis, angiogenesis and growth rate of incidentally found renal cell carcinoma. Int J Urol 2003;10:13-8.
19. Volpe A, Panzaarella T, Rendon RA, Haider MA, Kondylis FI, Jewett MA. The natural history of incidentally detected small renal masses. Cancer 2004;100:738-45.
20. Wehle MJ, Thiel DD, Petrou SP, Young PR, Frank I, Karsteadn N. Conservative management of incidental contrast-enhancing renal masses as safe alternative to invasive therapy. Urology 2004;64:49-52.
21. Kato M, Suzuki T, Suzuki Y, Terasawa Y, Sasano H, Arai Y. Natural history of small renal cell carcinoma: Evaluation of growth rate, histological grade, cell proliferation and apoptosis. J Urol 2004;172:863-6.
22. Lamb GW, Bromwich EJ, Vasey P, Aitchison M. Management of renal masses in patients medically unsuitable for nephrectomy – Natural history, complications, and outcome. Urology 2004;64:909-13.
23. Chawla SN, Crispen PL, Hanlon AL, Greenberg RE, Chen DY, Uzzo RG. The natural history of observed enhancing renal masses: Meta-analysis and review of the world literature. J Urol 2006;175:425-31.
24. Abou Youssef T, Kassouf W, Steinberg J, Aprikian AG, Laplante MP, Tanguay S. Active surveillance for selected patients with renal masses: Updated results with long-term follow-up. Cancer 2007;110:1010-4.
25. Kouta E, Smith A, McRackan D, Wallen EM, Pruthi RS. Watchful waiting for solid renal masses: Insight into the natural history and results of delayed intervention. J Urol 2007;177:466-70.
26. Sia W, Hafez KS, Johnston WK 3rd, Wolf JS Jr. Growth rates of renal cell carcinoma and oncocytoma under surveillance are similar. Urol Oncol 2007;25:115-9.
27. Fernando HS, Duvvuru S, Hawkwyard SJ. Conservative management of renal masses in the elderly: Our experience. Int Urol Nephrol 2007;39:203-7.
28. Matsuoka M, Kawano Y, Morikawa H, Shiga Y, Murata H, Komatsu H. Conservative management of small renal tumors. Hinyokika Kiyo 2007;53:207-11.
29. Lee JY, Kim CK, Choi D, Park BK. Volume doubling time and histological grade, cell proliferation and apoptosis. J Urol 2004;172:863-6.
30. Beisland C, Hjelle KM, Reisaeter LA, Bostad L. Observation should be considered as an alternative in management of renal masses in older and comorbid patients. Eur Urol 2009;55:1419-27.
31. Outcomes following partial nephrectomy by tumor size. J Urol 2007;177:466-70.
32. Rosales JC, Haramis G, Moreno J, Badani K, Benson MC, McKiernan J, et al. Active surveillance for renal cortical neoplasms. J Urol 2010;183:1698-702.
33. Hwang CK, Ogan K, Pattaras J, Master VA. Estimated volume growth characteristics of renal tumors undergoing active surveillance. Can J Urol 2010;17:5459-64.
34. Jewett MA, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active surveillance of small renal masses: Progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44.
35. Li XS, Yao L, Gong K, Yu W, He Q, Zhou LQ, et al. Growth pattern of renal cell carcinoma (RCC) in patients with delayed surgical intervention. J Cancer Res Clin Oncol 2012;138:269-74.
36. Mehrzarin R, Smaldone MC, Kutikov A, Li T, Tomaszewski JJ, Canter DJ, et al. Growth kinetics and short-term outcomes of cT1b and cT2 renal masses under active surveillance. J Urol 2014;192:659-64.
37. Brunoilla E, Borghesi M, Schiavina R, Della Mora L, Dababneh H, La Manna G, et al. Small renal masses initially managed using active surveillance: Results from a retrospective study with long-term follow-up. Clin Genitourin Cancer 2014;12:178-81.
38. Yao L, Zhang L, Li X, He Z, Zhou L. An easy model for prediction of human renal clear cell carcinoma: Curve fitting for three kidney tumors observed for over 10 years. Chin Med J 2014;127:782-3.
39. Friberg S, Mattson S. On the growth rates of human malignant tumors: Implications for medical decision making. J Surg Oncol 1997;65:284-97.
40. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DY, et al. Small renal masses progressing to metastases under active surveillance: A systematic review and pooled analysis. Cancer 2012;118:997-1006.
41. Ozono S, Miyao N, Igarashi T, Nakazawa H, Fukuda M, et al. Tumor doubling time of renal cell carcinoma measured by CT. Indian J Urol 2014;30:153-7.
42. Schwartz M. A biomathematical approach to clinical tumor growth. Cancer 1961;14:1272-94.
43. Lindell RM, Hartman TE, Swensen SJ, Jett JR, Midhun DE, Tazelaar HD, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 2007;242:555-62.
44. Zhang J, Kang SK, Wang L, Toujier A, Hricak H. Distribution of renal tumor growth rates determined by using serial volumetric CT measurements. Radiology 2009;250:137-44.
45. Dodelzon K, Mussi TC, Babb JS, Taneja SS, Rosenkrantz AB. Prediction of growth rate of solid renal masses: Utility of MR imaging features – preliminary experience. Radiology 2012;262:884-93.
46. Nerli R, Devaraju S, Hiremath MB, Guntaka AK, Pame P, Dixit N. Tumor doubling time of renal cell carcinoma measured by CT. Indian J Urol 2014;30:153-7.
47. Kunkle DA, Crispen PL, Chen DY, Greenberg RE, Uzzo RG. Enhancing renal masses with zero net growth during active surveillance. J Urol 2007;177:849-53.
48. Kawaguchi S, Fernandes KA, Finelli A, Robhinet M, Fleshner N, Jewett MA. Most renal oncocytomas appear to grow: Observations of tumor kinetics with active surveillance. J Urol 2011;186:1218-22.
49. Oda T, Miyao N, Takahashi A, Yanase M, Masumori N, Itoh N, et al. Growth rates of primary and metastatic lesions of renal cell carcinoma. Int J Urol 2001;8:473-7.
50. Crispen PL, Wong YN, Greenberg RE, Chen DY, Uzzo RG. Predicting growth of solid renal masses under active surveillance. Urol Oncol 2008;26:555-9.
51. Staepler M, Haseke N, Stadler T, Zilinberg E, Nordhaus C, Nuhn P, et al. The growth rate of large renal masses opposes active surveillance. BJU Int 2010;105:928-31.
52. Mason RJ, Abdollem M, Trottier G, Pringle C, Lawen JG, Bell DG, et al. Growth kinetics of renal masses: Analysis of a prospective cohort of patients undergoing active surveillance. Eur Urol 2011;59:863-7.
53. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: An analysis of pathological features related to tumor size. J Urol 2003;170:2217-20.
54. Kunkle DA, Crispen PL, Li T, Uzzo RG. Tumor size predicts synchronous metastatic renal cell carcinoma: Implications for surveillance of small renal masses. J Urol 2007;177:1692-6.
55. Cary KC, Sundaram CP. Watchful waiting in the treatment of the small renal mass. Indian J Urol 2009;25:489-93.
56. Lane BR, Babineau D, Kattan MW, Novick AC, Gillis ES, Zhou M, et al. A preoperative prognostic nomogram for solid enhancing renal tumors 7 cm or less amenable to partial nephrectomy. J Urol 2007;178:429-34.
57. Birnbaum BA, Bosniak MA, Megibow AJ, Lubat E, Gordon RB. Observations on the growth of renal neoplasms. Radiology 1990;176:695-701.
58. Volpe A, Kachura JR, Geddie WR, Evans AJ, Gharajeh A, Saravanan A, et al. Techniques, safety and accuracy of sampling of renal tumors by fine needle aspiration and core biopsy. J Urol 2007;178:379-86.
59. Silverman SG. Percutaneous biopsy of renal masses: Sensitivity and negative predictive value stratified by clinical setting and size of masses. AJR Am J Roentgenol 2001;176:695-701.
60. Rybicki FJ, Shu KM, Cibas ES, Fielding JR, vanSonnenberg E, Silverman SG. Percutaneous biopsy of renal masses: Sensitivity and negative predictive value stratified by clinical setting and size of masses. AJR Am J Roentgenol 2003;180:1281-7.

Received: 27-12-2014 Edited by: Huan Liu and Yi Cui
How to cite this article: Zhang L, Li XS, Zhou LQ. Natural History of Small Renal Masses. Chin Med J 2015;128:1232-7.
Source of Support: Nil. Conflict of Interest: None declared.