Review Article

Natural History of Small Renal Masses

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Abstract

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 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.

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Approximately, 20% SRMs present aggressive malignant behavior,[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.[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,[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,[4-7] these studies revealed an encouraging result that SRMs under AS had generally slow growth kinetics and a low rate of metastasis (1.6%) [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 suggested that the growth of RCC might accelerate with the continuation of AS.[38] Hence, the mean growth rate might not precisely reflect the growth of SRMs. Although the previous study demonstrated that the accuracy of ultrasound measuring the size of SRMs was comparable to CT or MRI, the lack of uniform imaging procedures made comparisons difficult.

The growth rate of maximal tumor diameter, also referred as linear growth rate (LGR), is the most common measurement index of SRMs. Using LGR is based on the assumption that the growth of SRMs is spherical and the same in all directions.[39] A meta-analysis involved 234 SRMs from nine Canadian centers treated by AS.[23] In that meta-analysis, the mean size of the SRMs was 2.60 cm, and 86% of the lesions were <4 cm at presentation. During the mean observation period of 34 months, the SRMs revealed a mean LGR of 0.28 cm/year. The growth of these SRMs was slow, although 92% of the masses with pathological results (46% of the cohort) were confirmed to be malignant. A pooled-analysis involving six series with 259 patients and 284 SRMs was reported in 2012.[40] This pooled-analysis demonstrated the mean initial tumor size was 2.3 ± 1.3 cm. 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.[34]

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.[41] However, they are more inconvenient for use in clinical practice. The VGR can be calculated depending on a number of available dimensions and formula; $0.5326 \times yz$, $0.5326 \times y([x + y]/2)$, or $0.5326x^3$.[19] A pooled-analysis in 2012 including 259 patients and 284 SRMs demonstrated that the mean VGR was 6.3 ± 27.4 cm^3/year during a mean AS of 33.5 months,[40] 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^3/year [Table 1]. Crispen *et al*.[31] reported a mean VGR of 17.0 ± 71.6 cm^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:[42,43] $VDT = (T - T_0) \times \log 2/\log (V/V_0)$. T indicates the date of the final imaging procedure, T_0 is defined as the date of initial imaging procedure, V is the volume at final imaging evaluation, V_0 is the volume at initial imaging evaluation. Previous studies reported various mean VDT of SRMs ranging from 460 to 603 days.[16,29,41,44-46] In a prospective study, Jewett *et al*.[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.[29,44,45] The remaining studies employed mathematical formula to calculate the volume.[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.[34,40,47] Kunkle *et al*.[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.[17,20] However, Smaldone *et al*. revealed that no SRMs with zero growth had developed metastasis during AS.[40] 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.

Table 1: Published series on the natural history of renal masses

Authors	Year	Patients/ lesions (*n*)	Mean age (years)	Mean initial MTD (cm)	Mean follow-up (months)	Mean LGR (cm/year)	Mean VGR (cm^3/year)	Progression to metastasis, *n* (%)	Pathologic RCC
Fujimoto *et al*.[16]	1995	6/6	59.7	2.47	24	0.47	9.7	0 (0)	5/5
Bosniak *et al*.[17]	1995	37/40	65.5	1.73	39	0.36	5.26	0 (0)	22/26
Oda *et al*.[18]	2001	16/16	54*	2.0*	25	0.54*	–	0 (0)	16/16
Volpe *et al*.[19]	2004	29/32	71*	2.48	27.9	0.1	3.8	0 (0)	8/9
Wehle *et al*.[20]	2004	29/29	70	1.83	32	0.12	–	0 (0)	3/4
Kato *et al*.[21]	2004	18/18	56.5	2.0	27	0.42	4.4	0 (0)	18/18
Lamb *et al*.[22]	2004	36/36	76.1	7.2	27.7	0.39	–	1 (2.8)	23/24
Chawla *et al*.[23]	2006	49/61	71	2.97	36	0.2	–	1 (1.6)	16/21
Abou Youssif *et al*.[24]	2007	35/44	71.8	2.2	47.6	0.21	2.7	2 (5.7)	6/8
Kouba *et al*.[25]	2007	43/46	67	2.92	32.8	0.7	–	0 (0)	12/14
Siu *et al*.[26]	2007	41/47	68	2.0	29	0.27	–	1 (2.4)	10/16
Fernando *et al*.[27]	2007	13/13	80.4	5.01	38.38	0.17	11.97	1 (7.7)	0
Matsuzaki *et al*.[28]	2007	15/15	67	2.2	38	0.06	0.67	0 (0)	3/3
Lee *et al*.[29]	2008	30/30	65.5	2.6	12.6	0.59	19.1	3 (10.0)	30/30
Beisland *et al*.[30]	2009	63/65	76.3	4.3	33	0.66	–	2 (3.2)	15/18
Crispen *et al*.[31]	2009	154/173	69	2.45	31	0.285	17.0	2 (1.3)	52/61
Rosales *et al*.[32]	2010	212/223	71*	2.8*	35*	0.34*	–	4 (1.9)	32/40
Hwang *et al*.[33]	2010	56/58	64.3	2.1	22	0.21	1.9	0 (0)	10/15
Jewett *et al*.[34]	2011	127/151	73	2.1	28	0.13	–	1 (0.7)	37/46
Li *et al*.[35]	2012	32/32	52.2	2.14	46	0.8	–	0 (0)	32/32
Mehrazin *et al*.[36]	2014	68/72	68.9	5.3	38.9	0.44	–	0 (0)	16/23
Brunocilla *et al*.[37]	2014	62/64	75	2.0	91.5	0.4	4.6	1 (1.6)	14/16
Total		1171/1271	69.5	2.82	34.6	0.33	9.48	19 (1.6)	380/444

*: Median; –: Not stated; MTD: Maximum tumor diameter; LGR: Linear growth rate; VGR: Volumetric growth rate; RCC: Renal cell carcinoma.

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[35,44] reported a faster growth potential of clear cell RCC compared with papillary renal carcinomas. Smaldone *et al*.[40] 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.[51,52] 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*.[54] 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 2–3 cm and 18.7%–22.5% of the SRMs 3–4 cm.[7,53]

Age

Some previous studies discovered no correlation between patient age and the growth rate of SRMs.[50,55] 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*.[44] 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.[36] 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[56] 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*.[57] reported a significant correlation between slow growth and homogeneity on CT. Dodelzon *et al*.[45] 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*.[21] 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.[18] Fujimoto *et al*.[16] 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*.[34] 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.[40] 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 cm^3 vs. 12 cm^3, P < 0.0001), a faster LGR (0.8 cm/year vs. 0.3 cm/year), and a faster VGR (27 cm^3/year vs. 6 cm^3/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*.[16] 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*.[58] 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.[59] Another report found that PRB was deficient for tumor grading and not appropriate for SRMs < 3 cm.[60] 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.

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