Active Surveillance for Small Renal Masses

Shagnik Ray, BA, Joseph G. Cheaib, MD, MPH, Phillip M. Pierorazio, MD
Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, MD

Active surveillance (AS) is a safe and reasonable management strategy for many patients with small renal masses (SRM) suspicious for a clinical T1a renal cell carcinoma based on excellent metastasis-free and cancer-specific survival. However, the expansion of robotic extirpation of SRM has outpaced the adoption of AS, resulting in the possibility of overtreatment for select patients with SRM, especially the elderly and comorbid. In this review of AS for SRM, with a focus on the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry, we detail the rationale behind AS, review lessons learned from the past decades of literature, and offer suggestions for appropriate patient selection and follow-up. An improved understanding of the data supporting AS will empower physicians and patients to more comfortably pursue AS to avoid overtreatment and provide individualized care to patients with SRM.

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KEY WORDS

Small renal mass • Active surveillance • Renal cell carcinoma • Renal mass biopsy • Chest imaging

Small renal masses (SRM) are solid renal cortical neoplasms smaller than 4 cm in maximum diameter suspicious for a clinical T1a renal cell carcinoma (RCC).[1,2] With the widespread use of cross-sectional imaging, SRMs are most often discovered incidentally and at an increasing frequency, accounting for almost half of new RCC diagnoses.[3-6] The diagnosis of a new SRM is a challenging one for physicians and patients given their biologic heterogeneity ranging from benign entities to aggressive RCC.[7,8] The potential for an aggressive malignant mass historically prompted urologists to pursue surgical management for the majority of patients. Partial nephrectomy, when feasible, is now the preferred surgical strategy for SRM given the excellent oncologic outcomes and preservation of renal function.[9] However, 20% to 40% of SRMs are benign, leading to an estimated 5624 potentially

unnecessarily surgically resected benign SRM in the United States annually.[10] Of malignant SRM, 70% to 80% are low-grade, early-stage RCC with rates of metastatic disease of ~2% for 4 cm tumors and <1% for tumors 3 cm or less.[11-14] Notably, death due to competing risks is higher than cancer-specific mortality for all patients with cT1a RCC regardless of age group, management strategies, and comorbidities.[15]

Over the past two decades, active surveillance (AS) involving stringent clinical follow-up and scheduled imaging evaluation has emerged as a safe alternative management strategy for patients with SRMs.[16] A systematic review by Mir and colleagues evaluated 28 AS studies and confirmed low rates of metastatic progression (1%–6%) and cancer-specific mortality (0%–18%) for untreated SRM despite an other-cause mortality of 0% to 45%.[17] Despite these data, robotic surgical extirpation has outpaced the adoption of AS for SRMs, raising concern that this diffusion of robotic technology has propagated the overtreatment of SRMs, particularly among elderly and comorbid individuals.[18]

With limited and mainly retrospective evidence supporting AS, the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry was opened in 2009. This multi-institutional, prospective cohort study was designed to report the outcomes of patients undergoing AS versus primary intervention for newly diagnosed SRM and was developed initially at Johns Hopkins University (Baltimore, MD) with expansion to Columbia University Medical Center (New York, NY) and Beth Israel Deaconess Medical Center (Boston, MA), and is currently the world's largest prospective program with over 400 AS patients (median follow-up, 3.0 years [IQR 1.1-5.0]; 126 patients [23%] followed for ≥5 years).[19] In this review of AS for SRM, we detail lessons learned about AS over the past decade with a focus on the DISSRM Registry.

AS Basics

AS is currently endorsed to varying degrees by different medical societies including the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), and the American Urological Association (AUA). The NCCN recommends AS as an option for select asymptomatic patients; ASCO notes that AS should be an initial management option for patients who have significant comorbidities and limited life expectancy; and the AUA suggests that AS is an optional initial management strategy for any patient with a SRM <2 cm or for larger tumors in patients with advanced age or comorbidities.[20-22] Currently, only 10% to 20% of eligible patients undergo AS.[13] Unfortunately, there are no established protocols for AS, with different prospective trials utilizing different eligibility and follow-up criteria.[17]

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AS is not synonymous with "observation" or "watch and wait," but instead entails a highly individualized follow-up strategy involving serial imaging evaluating growth of masses. Shared decision making is an essential component of the process, with the urologist and patient discussing imaging modality (eg, cross-sectional vs ultrasound) and timing (eg, 3 months vs 6 months) with each imaging result. Notably, delayed intervention does not compromise outcomes with this strategy.[17] Ideally, this strategy includes formal decision-making tools whenever possible to discuss the risks and benefits of intervention uniquely tailored to a patient's disease and life circumstances. According to the AUA, AS is most appropriate for patients in whom the anticipated net benefit of AS is modest to significant when compared with treatment.[22] This is different from expectant management or observation, which is better suited for patients in whom treatment poses an unacceptably higher risk than surveillance. Contrasting this, for patients in whom the anticipated oncologic benefits of intervention outweigh the risk of treatment and competing risks of death, urologists should recommend active intervention.

Selecting Patients for AS

Without any standardized criteria for which patients are most appropriate for AS for their SRM, different studies have used different inclusion and exclusion criteria when enrolling patients. The DISSRM Registry has inclusion criteria of ≥18 years of age and solid renal mass <4 cm (cT1a) on axial imaging along with exclusion criteria of no familial RCC syndromes or no suspicion of another metastatic cancer to the kidney.[19] Enrolled patients undergo consultation with their urologist and pursue either AS or intervention (Figure 1). Patients who pursue AS versus intervention are older (70.8 years vs 61.8 years; $P < 0.001$), in worse health (Eastern Cooperative Oncology Group score [ECOG] 2-4 in 6.0% of AS patients vs 2.4% of intervention patients; $P = 0.02$, or Charlson Score 0 in

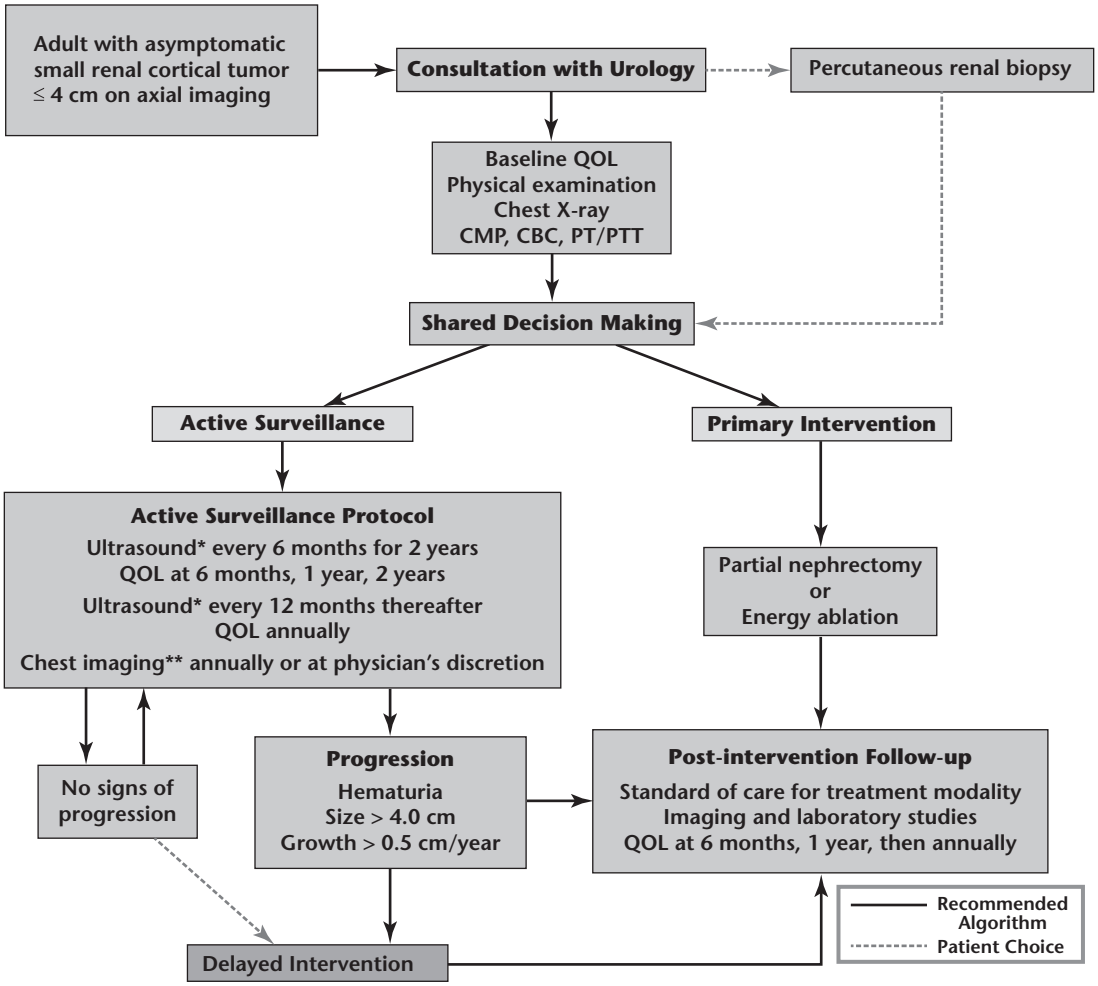

Figure 1. Algorithm for management of patients with a small renal mass in the Delayed Intervention and Surveillance for Small Renal Mass (DISSRM) Registry. Axial imaging entails CT or MRI. CBC, complete blood count; CMP, comprehensive metabolic panel; PT/PTT, prothrombin time/partial thromboplastin time; QOL, quality of life. *Ultrasound is the preferred imaging modality; however, CT or MRI is typically used in an alternating fashion with ultrasound and may be used at the discretion of the physician in the case of uncertainty or changes in ultrasound findings. **Chest imaging (eg, chest radiograph) is no longer recommended on an annual basis without cause. Please refer to the body of the text and Figure 3.

43.9% of AS patients vs 60.1% of intervention patients; $P < 0.001$), and have smaller tumors (diameter for AS patients 1.8 cm vs diameter in intervention patients 2.5 cm; $P < 0.001$).[19] We acknowledge AS as an initial management option for all patients with SRM, and as the primary option for patients with tumors <2 cm or those of advanced age with medical comorbidities. This shared decision making with the patient requires consideration of operative morbidity, patient preferences, and patient-reported physical health and well-being.

Currently, the role of percutaneous renal mass biopsy (RMB) in AS patients with SRMs is unclear, with RMB not always performed on patients making the decision to undergo AS. Although urologists are often hesitant to pursue RMB given potential morbidity, RMB has been shown to be safe with a <5% risk of significant complication and a <0.01% risk of tumor seeding with modern techniques.[23] Although RMB has sensitivity, specificity, and positive predictive value above 95%, some have argued that it does not affect clinical management as it is not able to reliably detect high-grade RCC secondary to intra-tumoral grade heterogeneity (40%-60%), has a high non-diagnostic rate (14%), and poor negative predictive value (68.5%).[7,24,25] Therefore, RMB is not necessary to initiate AS of a SRM, but can provide

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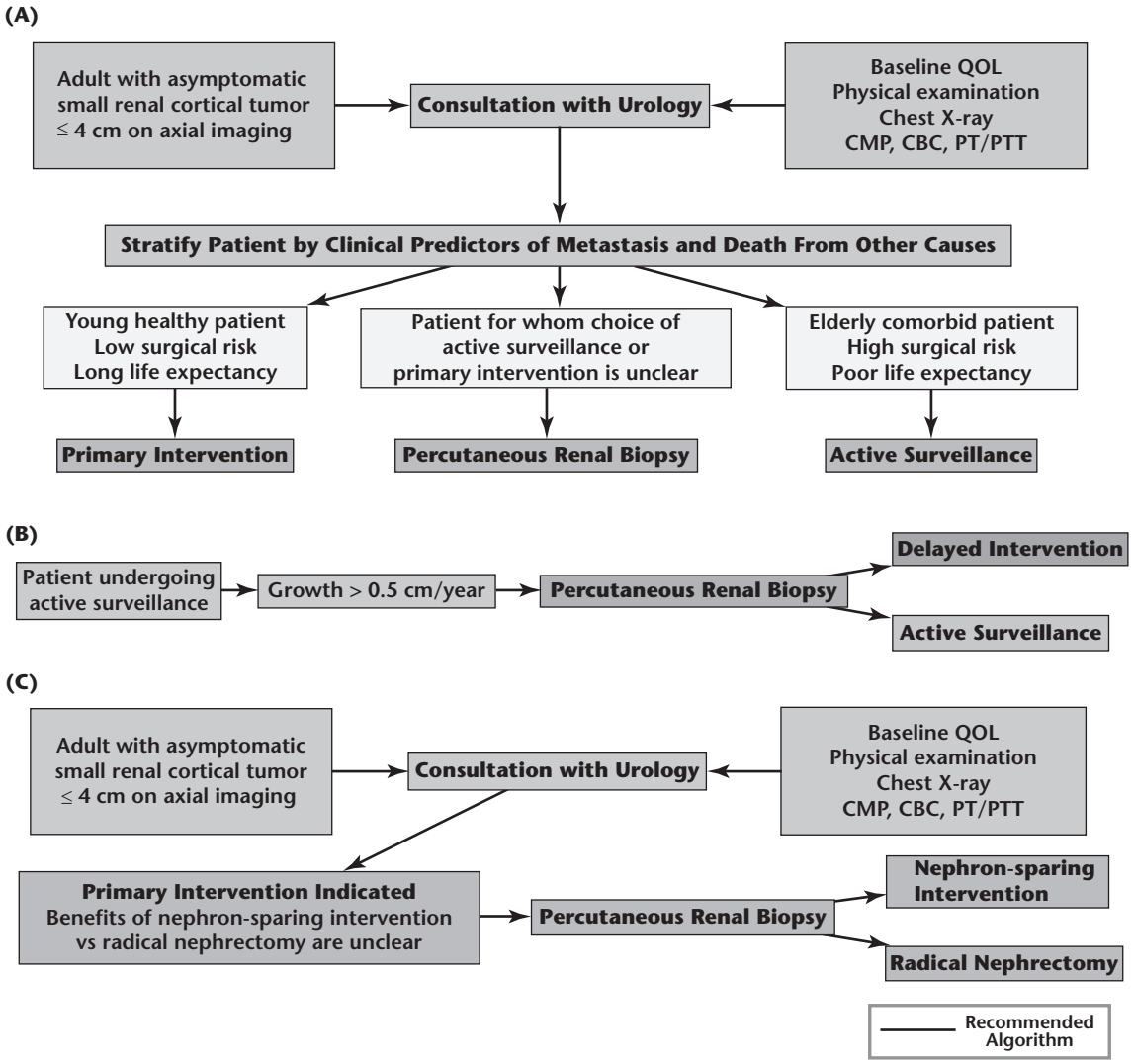

Figure 2. Examples of indications for percutaneous renal mass biopsy of small renal masses. (A) Determining initial management for whom the decision between active surveillance and primary intervention is unclear in a patient who would clearly choose intervention based on a histologic diagnosis. (B) To distinguish rapidly growing benign lesion (ie, oncocytoma) from malignant in a patient on active surveillance whose small renal mass grows > 0.5 cm/year. (C) Determining whether nephron-sparing intervention or radical nephrectomy is appropriate in a patient for whom primary intervention is indicated but the benefits of both are unclear. For example, radical nephrectomy may be more justified in the setting of renal cell carcinoma than a benign entity. CBC, complete blood count; CMP, comprehensive metabolic panel; PT/PTT, prothrombin time/partial thromboplastin time; QOL, quality of life.

helpful diagnostic information in select patients for whom management can be individualized based on tumor histology and biology. Stratifying patients based on clinical predictors of metastasis and death from other causes should determine when RMB is needed (Figure 2). Young, healthy patients with minimal surgical risk should pursue surgery regardless of any negative result on a RMB because of the aforementioned heterogeneity of renal masses, and thus typically do not require RMB. Older comorbid patients with major surgical risk and poor life expectancy will benefit most from AS regardless of any positive result on RMB given their frailty and high cancer-specific survival of SRM, and likewise will not require RMB. However, in patients for whom AS and surgery are both appropriate options, in patients for whom the benefits of nephron-sparing intervention versus radical nephrectomy are unclear, or in patients on AS with SRM with elevated growth rate within the first year of AS, RMB can help with decision making and thus be performed. Of note, RMB has most recently been pursued in 20% of patients per year from 5% of patients per year in the most recent DISSRM update, a trend that will likely continue.[26]

Following Patients on AS

The DISSRM protocol is detailed in Figure 1. Of note, for the patients

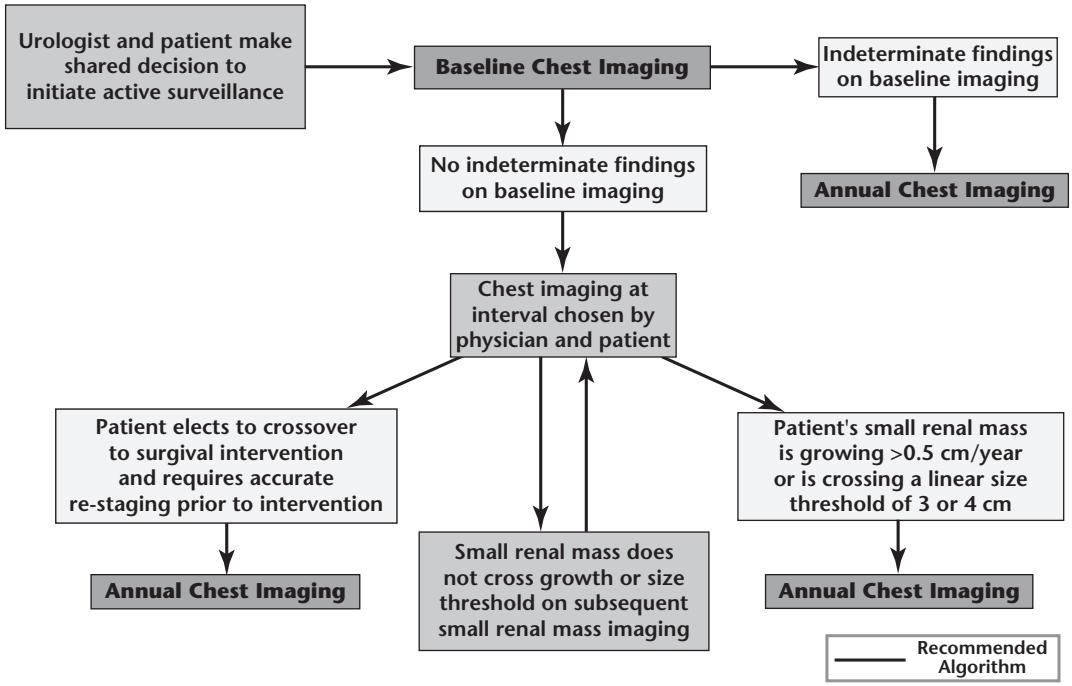

Figure 3. Indications for annual chest imaging during active surveillance.

undergoing AS, the surveillance protocol entails initial axial imaging, chest radiography, laboratory evaluation (complete metabolic panel, complete blood count, coagulation factors), physical examination, and baseline quality-of-life evaluation. Serial imaging is performed every 6 months for 2 years and then annually thereafter. Ultrasound is the preferred imaging modality given lack of ionizing radiation and relatively low cost; however, alternating ultrasound and axial imaging is performed in most patients. Renal function is assessed by laboratory evaluation at least annually. Following this protocol, patients who underwent AS and primary intervention, 5-year cancer-specific survival was 100% and 99%, respectively, and 5-year overall survival was 75% and 92%, respectively.[19]

Initially, chest imaging was recommended on an annual basis. However, given the low metastatic potential of SRM while on AS, the low likelihood of routine chest imaging to detect distant metastases in patients with SRM that do not progress in size, and the detection of incidental findings, routine chest imaging is not necessary in all patients and no longer routinely performed.[17,27] A recent analysis of the DISSRM Registry's chest imaging data found that of 268 patients on AS, 51 (19%) had abnormal baseline chest imaging findings, 22 (43%) of which were actionable (eg, pulmonary nodules suspicious for benign or malignant disease, anterior mediastinal masses, thyroid nodules); and 217 (81%) had normal baseline chest imaging, of which 23 (11%) developed abnormal findings on subsequent yearly chest imaging and 10 (43%) were actionable; no patient developed metastatic RCC.[28] Based on these findings, yearly chest imaging for all patients on AS for their SRM results in unnecessary testing and costs without major changes in care. Considering a low rate of metastatic progression for stable SRM, our group suggests pursuing annual chest imaging for certain groups of patients as detailed in Figure 3, in those most at risk for pulmonary metastasis.

SRM Growth Rates and Progression for AS

For patients on AS for SRM management, identifying appropriate triggers for delayed intervention is essential. Triggers for intervention in the DISSRM Registry include tumor size (>4 cm), tumor growth rate (>0.5 cm/year), development of symptoms (hematuria without other cause), elective crossover (change in patient preference or

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changes [improvements] in patient health), or metastatic disease.[16] The linear growth rate (change in maximum tumor diameter over time typically expressed in cm/year) historically is identified as the most common objective factor to identify adverse biological behavior in a SRM.[13] However, there is significant variability in growth rates with limited implications for metastatic biology. The systematic review by Mir and colleagues showed linear tumor growth rate varied greatly among published AS studies for localized renal masses, with a median rate of 0.37 cm/year (IQR 0.15-0.7) for *c*T1-2 masses (ranging from 0.22 cm/year [IQR 0.11-0.27] for *c*T1a to 0.45 cm/year [0.34 and 0.57 in 2 series] in *c*T1b-2).[17] The DISSRM Registry and the Renal Cell Carcinoma Consortium of Canada (RCCCC) experiences with prospectively followed patients with SRM on AS entailed low median linear tumor growth rates of 0.09 and 0.12 cm/year, respectively.[26,29]

Although the overall median linear tumor growth rates are positive across multiple studies, a proportion of patients with SRM on AS have 0 or negative growth rates. Mir and colleagues reported zero tumor growth in 10% to 44% of patients.[17,26,30] Furthermore, recent data on growth rates of SRM in the DISSRM Registry show that SRM tend to have a non-linear growth pattern, with periods of positive, 0, and negative growth over time.[26] This analysis of SRM growth kinetics found that 41% of SRM ($n = 114$) had 0 or negative growth rate in the DISSRM Registry, with 33% of patients in the RCCCC and the 36% Fox Chase Cancer Center AS cohort (FCCC) having consistent 0 or negative growth.[29,31] Furthermore, growth rate variability in the DISSRM Registry has been noted to be highest in the first year with a decrease in variability with longer follow-up, seeming to reflect measurement variation and mathematical artifact rather than tumor biology.[26] Most SRM with elevated growth rates in the first 6 months did not demonstrate continued growth at future follow-up intervals.[19] Therefore, we recommend avoiding intervention when an elevated SRM growth rate is encountered in the first year of AS given the high linear growth rate variability in conjunction with the relatively indolent nature of SRMs. Shorter interval repeat imaging and consideration of renal mass biopsy may better risk stratify patients in this situation.

A recent report from DISSRM ($n = 317$ patients on AS; median follow-up, 2.9 years; 203 patients with >5 years of follow-up) found 5- and 7-year progression-free survival rates of 76% and 48%, respectively. An elevated linear growth rate was responsible for 30.3% of progressions ($n = 20$) in patients who did not pursue intervention.[32] The remaining patients ($n = 46$; 68.2%) who progressed were mainly crossover events from AS to delayed intervention. About half ($n = 24$; 52.2%) were clinically indicated whereas the remaining 22 (47.8%) were elective based on patient preference. Of these clinically indicated crossover events, 96% ($n = 23$) were secondary to a linear growth rate >0.5cm/year. As expected, patients who underwent delayed intervention had significantly higher median growth rate compared with those who stayed on AS (0.38 vs 0.05 cm/year; $P < 0.001$), a finding confirmed in systematic review.[17,33] More recently, McIntosh and colleagues found that patients with elevated growth rate were more likely to undergo delayed intervention compared with those with low or zero growth rate but had similar cancer-specific survival rates of 99%, clearly demonstrating how increasing growth rate predicts intervention but does not predict survival outcome in these patients.[31] Therefore, linear growth rate is a prominent trigger for progression and delayed intervention across AS cohorts, but may not actually indicate the metastatic potential of these SRM.

Cancer-specific death and metastatic disease progression do not appear to be associated with tumor growth rate. In the DISSRM Registry, although progression rates can be high secondary to increased tumor growth rate, the cancer-specific survival rate at 8 years was 100% without any patients experiencing metastatic disease. Similarly, the prospective RCCCC and FCCC cohorts failed to find a correlation between growth rate, metastatic disease, or cancer-specific mortality given the low rates of metastatic events.[32,33] In a systematic review by Smaldone and colleagues regarding the progression of SRM on AS to metastasis, the overall rate of metastatic progression was 2% and 23% of the metastatic renal masses showed no growth during surveillance.[13] Mir and associates showed that the linear growth rate for patients who experienced metastasis was not significantly different than the overall growth rate of clinically localized renal masses. Furthermore, as both benign and malignant lesions can grow at similar or non-zero rates, growth rate thresholds alone should not be used as a predictor of mass histology or malignant potential.[34,35]

Therefore, the implications of linear growth rate in the setting of AS requires reconsideration. The historic threshold of >0.5 cm/year for progression during AS was based on retrospective data, and

perhaps a more relevant and useful threshold may exist. Contrasting this, we recommend intervention based on overall tumor size as it has been shown to be the best predictor of malignant histology, aggressive pathology, and oncologic outcomes.[19,36,37] Additionally, in the context of the typically non-linear growth of SRMs, multiple consecutive positive growth periods may be associated with unfavorable pathology; however, prospective and unbiased data are lacking.[38] A SRM with elevated growth rate certainly indicates lack of physician and patient comfort with continued surveillance; however, growing data indicates that a biopsy, biomarker, or novel imaging modality be used rather than surgical intervention.

Conclusions

Our current understanding of tumor biology confirms AS as a reasonable and safe primary management strategy for select patients with SRM suspicious for cT1a renal cell carcinoma. To date, early prospective trials demonstrate that AS is non-inferior to primary intervention based on excellent metastasis-free and cancer-specific survival. RMB can be useful to risk-stratify select patients but is not a requisite for AS. Yearly chest imaging is not required for safe AS. Definitions of progression during AS need further refinement, with tumor size rather than growth rate predicting tumor biology. Current society guidelines support the use of AS in patients with SRM <2 cm and in those with competing health risks with SRM <4 cm. ■

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MAIN POINTS

- Our current understanding of tumor biology confirms active surveillance (AS) as a reasonable and safe primary management strategy for select patients with small renal masses (SRM) suspicious for cT1a renal cell carcinoma.
- Early prospective trials demonstrate that AS is non-inferior to primary intervention based on excellent metastasis-free and cancer-specific survival. Renal mass biopsy can be useful to risk-stratify select patients but is not a requisite for AS.
- Yearly chest imaging is not required for safe AS.
- Definitions of progression during AS need further refinement, with tumor size rather than growth rate predicting tumor biology.
- Current society guidelines support the use of AS in patients with SRM <2 cm and in those with competing health risks with SRM <4 cm.

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