# 2022 WUOF/SIU International Consultation on Urological Diseases: Active Surveillance for Small Renal Masses

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## Abstract

With greater awareness of indolence underlying small renal masses (SRM ≤ 4 cm) and the morbidity of invasive treatment, active surveillance for SRM patients is being increasingly utilized on an international level. This synopsis summarizes the 2022 review and expert opinion recommendations provided to the International Consultation of Urological Diseases (ICUD) by 10 urologists from high-volume active surveillance practices at international centers. Topics reviewed include SRM biology and clinical behavior, current national and international guidelines for active surveillance of SRM patients, active surveillance utilization patterns and barriers to implementation, outcomes and limitations of the active surveillance literature, criteria for active surveillance patient selection, protocols for active surveillance management including frequency/modality of imaging and the role of renal tumor biopsy, triggers for delayed intervention during active surveillance including tumor factors and patient factors, and pathological outcomes of delayed intervention. We conclude that despite limitations of the current literature, active surveillance is a safe initial management strategy for many SRM patients. The slow growth and low metastatic potential of SRMs, combined with no evidence to suggest oncologic compromise with delay to treatment, should provide confidence to both patients and providers who are considering active surveillance. Future research for prioritization should include characterization of long-term active surveillance outcomes including rates of metastasis and delayed intervention, standardization of objective tumor progression criteria for triggering delayed intervention, and further delineation of the role for active surveillance in young and healthy patients.

## Introduction

Small renal masses (SRM) are renal cortical neoplasms ≤ 4 cm comprising benign tumors and renal cell carcinomas (RCC) with rare metastatic potential[1]. With greater use of cross-sectional abdominal imaging there has been a significant stage migration towards incidental SRM detection[2,3]. Conversely, RCC mortality has remained stable, establishing a concern for overtreatment of SRM patients and a rationale for active surveillance (AS).

**Key Words**

Small renal mass, active surveillance, management strategies, kidney cancer

**Competing Interests**

None declared.

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### Abbreviations

AS active surveillance
DI delayed intervention
GR growth rate
LE life expectancy
RCC renal cell carcinomas
RTB renal tumor biopsy
SRM small renal masses

AS is semantically distinct from watchful waiting (observation) and includes intention for curative delayed intervention (DI) if necessary, whereas watchful waiting/observation involves only palliative treatment and concedes metastasis when cancer-specific mortality is unlikely[4].

## Heterogenous and Indolent SRM Biology

SRM encompass a variety of benign and malignant histologic subtypes with different genomic and genetic landscapes. Benign tumors represent 20%–40% of SRM[5–8]. Malignant SRM are commonly low-grade and low-stage RCC, with high-grade and/or pT3 tumors accounting for only 10%–25% of surgical cases[5,7]. Regardless of histology, SRM rarely metastasize or become lethal. Risk of death from non-cancer causes is higher in almost all categories of patient age, comorbidity, and tumor size among patients with *c*T1 tumors[9]. Analysis of tumor genomics and genetics by the TCGA and TRACERx next-generation sequencing initiatives indicate that *c*T1a RCC typically has low genetic diversity and chromosomal complexity, which may explain indolent clinical behavior[10–12]. This biology, termed the VHL mono driver subtype, is characterized by limited genetic branching without additional driver mutations, tumor size < 45 mm, and excellent long-term survival, often requiring decades to acquire mutations conducive to metastatic potential[11,12].

## Guideline Support

Commonly used guidelines for SRM patient management include those from the American Urological Association (AUA), European Association of Urology (EAU), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO). There is general agreement that expectant management (AS or watchful waiting/observation) is an option in patients with comorbidities or limited life expectancy (LE), and preferred whenever the anticipated risk of intervention outweighs the oncological benefits of treatment. However, patient selection criteria, role of renal tumor biopsy (RTB), modality/frequency of imaging, and triggers for DI all lack strong consensus recommendations. Current AUA[13,14] and NCCN[15] guidelines each make conditional recommendations to consider AS with potential for DI as a first-line management option in patients with a SRM < 2 cm, regardless of age or health, and in patients with a larger SRM when cystic or with significant comorbidity. EAU and ASCO support RTB to guide AS scanning frequency and/or initial patient selection, while AUA and ESMO recommend consideration of RTB in select cases for additional risk stratification[16–18]. There is general agreement for initial repeat imaging within 3–6 months. Specific patient-related and tumor-related factors favoring expectant management versus intervention are endorsed by the AUA (**Table 1**). However, many patients fall into a gray zone within this dichotomous scheme, and integration of additional factors is needed, as is attention to clinical scenarios in which contrasting factors are simultaneously present.

## Current Utilization and Barriers

AS utilization has remained relatively static over the past 20 years. SEER and NCDB population registries in the United States indicate that AS utilization rates for SRMs remain < 10%[19,20]. In contrast, use of both partial nephrectomy and thermal ablation has increased over this period, including in older patients[21]. There are currently no population-based studies of AS utilization in other countries. Recent reports of high AS utilization at some centers shed new light on potential barriers to broader AS utilization. Roswell Park Cancer Center reported that almost all (> 95%) new SRM patients seen over 5 years elected AS management, regardless of patient age or health[22], while MUSIC registry analyses reported considerably variable AS utilization across regional academic and private practices despite similar patient and tumor features[23]. Hence, factors related to the provider and health care setting, rather than to the patient, appear most important in driving current AS utilization. Provider-related differences may reflect variable awareness and/or certainty in interpreting the current evidence in support of AS.

## Limitations of Active Surveillance Literature

Historically, AS was supported by only retrospective series, and the vast majority of reports are still subject to inherent retrospective design biases[24,25]. Definitions and protocols regarding AS were historically not well established, including substantial contamination with observation patients that potentially exaggerated metastasis rates, with DI deferral being typical upon SRM progression[26]. Reports are further confounded

**TABLE 1.**

Patient and tumor-related factors favoring active surveillance versus intervention according to the AUA guidelines

| | Patient-related factors | Tumor factors |
|---|---|---|
| Favor Active Surveillance/ Expectant Management | Elderly<br>Life expectancy < 5 years<br>High comorbidities<br>Excessive perioperative risk<br>Poor functional status<br>Marginal renal function<br>Patient preference to avoid treatment risks | Tumor size < 3cm<br>Tumor growth < 5mm/year<br>Non-infiltrative on imaging<br>Low complexity<br>Favorable histology (if RTB performed) |
| Favor Intervention | Young<br>Life expectancy > 5 years<br>Low comorbidity<br>Acceptable perioperative risk<br>Good functional status<br>Anticipate adequate renal function following intervention<br>Patient preference for treatment | Tumor size > 3cm<br>Tumor growth > 5mm/year<br>Infiltrative on imaging<br>High complexity<br>Unfavorable histology (if RTB performed) |

by variable inclusion of low complexity cysts (eg, Bosniak I-III) without radiographic evidence of tumor, heterogeneous criteria for DI, and questionable reliability of follow-up to capture all metastatic and/or dying patients. Rarity of SRM metastasis and cancer-specific death has challenged statistical comparisons to immediate treatment in both retrospective and prospective AS cohorts, and surrogates for clinical progression such as growth rate (GR) have unclear relevance to these gold-standard outcomes. It is possible if not likely that a subset of AS "failures," particularly those with early metastasis (< 6–12 months), would not have benefited from immediate treatment[20,27]. Finally, follow-up for most AS studies remains relatively short (typically median 24–36 months), leaving uncertainty regarding the long-term sustainability and safety. More prospective series with long-term follow-up using pre-defined objective criteria for selecting patients and triggering DI are needed.

## Summation of Recent Active Surveillance Literature

Despite its limitations, the summation of published literature indicates that AS is a safe initial management strategy for many SRM patients. A 2018 systematic review of AS series from Mir et al. concluded relatively slow linear growth rates (median 0.37 cm/year overall, 0.22 cm/year for SRMs), and low metastasis and cancer-specific survival rates[28]. These conclusions are supported by more recent prospectively managed cohorts using AS protocols, differing in nuances of their prospective AS pathways but collectively providing strong support for oncologic safety. One of the largest registries is an American multi-institutional prospective cohort study comparing the outcomes of SRM patients undergoing AS versus primary intervention, the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry. Initiated in 2009, DISSRM at last report included 495 AS patients with median follow-up of 3.3 years and a third of patients followed for > 5 years[29]. The 5-year progression-free survival in the AS group was 67% and was driven largely by either rapid GR or patient preference. The 7-year cancer-specific survival (CSS) with AS was 100% and not significantly different from other management strategies (98.8% for partial nephrectomy)[25,30]. Oncological safety of AS was similarly observed among carefully selected SRM patients < 60 years old[31]. The DISSRM registry has also provided data regarding GR variability over time, the minimal utility of routine chest imaging, and comparative outcomes for patient quality of life during AS versus other management strategies[25,32–34].

The prospective Renal Cell Cancer Consortium of Canada recently highlighted histology specific GR outcomes, with an overall average of 2–3mm/year during a median follow-up of 5.8 years[27,35]. RTB was encouraged at enrollment, and papillary type 1 renal cell carcinomas (RCC) demonstrated a significantly more indolent course than clear cell RCC, which had higher

GR and progression rates[35]. GR was variable within an individual patient, and rapidly growing tumors were frequently stable on subsequent imaging, suggesting value to a confirmatory scan. The 5-year progression-free survival was 54%, driven mainly by elevated GR (82% of patients). Only a minority (36%) of 136 patients with biopsy-proven RCC remained on AS at 5 years, and 35% of nephrectomy DI patients had high-grade pathology, suggesting enrichment for adverse pathology (see also Delayed Intervention Pathology, below). Six RCC patients (4%, all clear cell subtype) developed metastasis and 29 (21%) died, including 3 (2%) cancer-related deaths. These long-term outcomes mirror those of malignant SRM surgical series, and support the potential long-term durability of AS in a subset of RTB-confirmed RCC patients.

Fox Chase Cancer Center has a long history of investigating AS for SRMs. In the most recent update, 544 lesions in 457 patients over a median 67 months indicated that 80% of SRMs will grow slowly or not at all, approximately 40% will undergo intervention at 5 years, and cancer-specific mortality is 1%[36]. Data from this cohort support the safety of DI in SRM patients and, as for DISSRM and the Canadian registry, indicates rapid GR is associated with higher rates of intervention.

In a recent cohort series of "universal" AS from Roswell Park Cancer Center, all non-hereditary SRM patients seen by one urologist over a 5-year period were recommended AS if they lacked tumor progression criteria at presentation, which amounted to > 95% of consecutive new SRM patients[22]. Tumor progression criteria used for triggering immediate or delayed treatment were pre-defined as longest tumor diameter (LTD) > 4 cm, GR > 5 mm/year for LTD ≤ 3 cm or > 3 mm/year for LTD > 3 cm, unfavorable RTB histology, cT3a stage, or SRM-related symptoms. Patients meeting any criterion were recommended treatment if LE was > 15 years, observation if LE was < 5 years, and continued AS versus DI if LE was 5–15 years. Most patients tolerated AS, with only 1 patient (1%) crossing over to treatment due to non-tumor factors (anxiety). Of 128 patients, 75% remained DI-free at 3 years, and none developed metastasis, which further supports AS safety.

## Selecting Patients for Active Surveillance

While national and international consensus guidelines recommend AS patient selection based on tumor size, life expectancy, and comorbidities, very few strict size/age/comorbidity cut-offs exist[14,15,33]. Tumor and patient factors to guide AS patient selection are summarized below.

### Tumor Factors

#### Tumor size

There is general consensus for LTD to guide AS patient selection, as the strongest known clinical predictor of SRM malignant histology, adverse pathology, and metastatic potential[5–8,34]. Metastasis rates approach 0% for LTD < 2 cm, ~1% for < 3 cm, 2%–3% for < 4 cm, and increase exponentially for > 4 cm[9,37–43]. Currently, AUA and NCCN recommend consideration of AS independent of health in patients with LTD < 2 cm, while other guidelines are noncommittal regarding an LTD threshold. While < 2 cm is the most ideal for AS patient selection, we believe the current literature supports adequate oncologic safety to consider AS for patients with LTD up to 4 cm. However, more careful selection and/or monitoring (see below, Active Surveillance Protocols / Renal Mass Imaging; and Triggers For Delayed Intervention / Growth Rate) should be considered for patients with LTD 3–4 cm due to the non-negligible metastatic risk at this size.

#### Benign or unfavorable renal tumor biopsy histology

RTB can aid SRM risk stratification by: (1) identifying benign neoplastic histology (renal oncocytoma or angiomyolipoma, AML); or (2) revealing unfavorable RCC histology[17,22,27,44]. Risk of spontaneous hemorrhage observed with larger AML appears to be insignificant among SRMs[45]. Historically, RTB differentiation of oncocytoma from RCC (particularly chromophobe RCC) was challenged by histologic overlap necessitating diagnostic extirpation, but more reliable RTB diagnosis has evolved with immunohistochemistry panels that include the oncocytoma/chromophobe-specific biomarker, CD117, and RCC biomarkers lacking in oncocytoma (eg, CK7, CAIX, AMACR, vimentin); in addition to radiologic approaches that corroborate oncocytoma diagnosis, such as Sestamibi scan and CT-based contrast enhancement measurement (tumor:cortex peak early enhancement ratio, or "PEER" score)[45–50]. Oncologic and functional safety of AS for oncocytomas is generally supported but requires more long-term study[51–54]. SRM patients with RTB favoring oncocytoma are ideal AS candidates, given the indolence of oncocytic SRMs regardless of malignant vs. benign etiology[55]. In contrast, unfavorable RTB histology (nuclear grade > 3, papillary type 2 RCC, translocation RCC, unclassified/indeterminable RCC subtypes) may challenge AS candidacy, although additional study is needed since even adverse histology may have outstanding outcomes among SRM patients[28]. The value of histologic subtyping among favorable RCC histologies (eg, low-grade clear cell vs. papillary type 1 vs. chromophobe) remains unclear, although Canadian

registry investigators observed metastases exclusively with the clear cell subtype, while zero growth occurred more often among non-clear cell subtypes[35].

### Cysts

Predominantly cystic tumors (Bosniak III-IV) are associated with more favorable pathology and prognosis compared to solid tumors of the same size, including only rare metastatic potential[56,57]. Moreover, AS for Bosniak III lesions of all sizes and smaller Bosniak IV lesions is associated with particularly excellent oncologic outcomes. Accordingly, there is general consensus that Bosniak III-IV SRMs comprise an ideal patient subset for AS consideration.

## Patient Factors

### Age and life expectancy

Other cause mortality outweighs the risk of cancer-specific mortality for most SRM patients, particularly in elderly, but also regardless of age, comorbidity, tumor size or initial management strategy elected[43,58–60]. DISSRM and other registries support that patients >70 years old and those with competing risks of mortality (particularly cardiovascular disease)[60] are most likely to benefit from and remain on AS[43,61,62]. Specific LE thresholds have not been routinely addressed. Among patients with LE <5 years, aggressive treatment (predominantly with surgery) has no known benefit but remains common, highlighting a need to better incorporate LE into treatment decision-making[63]. Age- and sex-adjusted LE calculators are available (e.g., https://www.ssa.gov/OACT/population/longevity.html), but methods to adjust based on comorbidities and frailty are not well standardized[64,65]. A health-adjusted renal mass-specific calculator was recently published by Psutka et al. including DISSRM registry patients (https://small-renal-mass-risk-calculator.fredhutch.org)[43]. AS in young, healthy patients remains controversial, given the historical presumption that tumors would eventually grow and require intervention. However, DISSRM registry analysis recently showed that a significant proportion of younger patients (< 60 years old) have a durable absence of significant growth, with 70% remaining on AS after 5 years and metastasis-free[31]. Similarly, a 72% rate of AS continuation beyond 5 years was reported in Roswell Park Cancer Center's recently updated experience of AS recommended to over 200 consecutive progression-free SRM patients without age-related or health-related selection bias, which yielded a relatively young and healthy AS cohort[66]. AS is thus likely to be safe for young, healthy patients with SRMs who wish to avoid immediate treatment, but counseling should mention the uncertainty of long-term (> 10 year) outcomes including DI rates.

### Renal function

Any intervention on a renal unit will adversely affect the estimated glomerular filtration rate, with nephron-sparing approaches generally incurring ipsilateral loss of 10%–20%[21]. AS is the only available management option that may not affect the natural history of chronic kidney disease progression[21,25,67]. Given associated risks for cardiac morbidity and other cause mortality[68], patients at risk for end-stage renal disease upon treatment are ideal candidates for AS[43]. Patients who already have end-stage renal disease may or may not require treatment to be eligible for renal transplant, depending on center-specific requirements[69].

### Illness uncertainty/anxiety

Illness uncertainty and anxiety have historically played a major role in AS patient selection. The impact of the healthcare setting and provider on illness uncertainty is increasingly apparent. With the Roswell Park experience in which nearly all newly presenting SRM patients were recommended AS, there was surprisingly wide acceptance of AS enrollment after informed counseling (95% AS, 1% immediate treatment, 4% unknown), including 100% AS election among patients with follow-up at Roswell Park[22]. A structured AS program, consultation with a RCC expert/specialist, and availability of RTB histology may all influence illness uncertainty and AS enrollment.

## Active Surveillance Protocols

AS protocols include periodic renal mass imaging, renal function monitoring, and periodic staging for metastatic progression, with or without adjunct use of RTB[70]. Meaningful comparisons of protocols have been challenged by the rarity of SRM metastasis or cancer-specific mortality outcomes to evaluate protocol efficacy[21]. In the absence of level 1 evidence, prospective cohort studies with rigorous patient and clinician adherence to meticulously defined eligibility criteria and strict surveillance schedules are critical to determining optimal surveillance protocols.

### Renal Mass Imaging: Timing, Frequency and Modality

Most prospective protocols use multiphasic cross-sectional imaging initially, with a long-term goal for ultrasound of more indolent masses to minimize radiation and contrast exposures[22,30,35]. All major studies to date include initial short-term surveillance, typically within 3–6 months to rule out very rapid growth, and subsequently follow patients at intervals extending from 6–12 months[22,27,30,36]. The next iteration of nuanced imaging may involve intervals based on initial tumor size, as, for example, the

Roswell Park protocol recommends an initial 3-month versus 6-month scan for tumors > 3 cm versus < 3 cm, respectively[22].

### Renal Function and Metastatic Evaluation

Renal functional tests including a serum creatinine should occur at least annually[13,16]. Baseline chest imaging to rule out pulmonary metastasis is recommended[37]. However, the utility of subsequent chest monitoring is questionable, given the metastatic risk approaches 0% in the absence of significant SRM growth[20]; and there are definite psychologic, medical and financial harms to incidental pulmonary findings. Approximately 20% of chest imaging tests evaluated in the DISSRM registry were abnormal, of which most were non-actionable (no metastases)[34]. Annual chest imaging can likely be omitted or at least reduced in frequency unless there is (1) an abnormality on baseline imaging, (2) significant SRM growth, or (3) plans for DI[70].

### Renal Tumor Biopsy

RTB utilization has increased over the past decade because of systematic reviews and meta-analyses supporting a high diagnostic rate and excellent safety profile[71,72]. This evolution in practice is evident from a DISSRM study showing an increase in RTB utilization over the past decade from 5% to 20%, while other contemporary AS cohorts surpass 50%[22,27,32]. While guideline committee recommendations vary, there is growing consensus that RTB can be useful to risk-stratify for AS but is not a requisite. There is also growing consensus to reserve RTB for SRMs with LTD >2 cm, given that smaller sizes have negligible oncologic risk and lower technical success rates[4,7,22]. Some programs, such as at Roswell Park and in Bologna, Italy, additionally endorse RTB in smaller (< 2 cm) tumors whenever there is a rapid GR (> 5 mm/year) to rule out benign tumor histology before DI conversion[22,73]. While some AS centers such as the Canadian registry and Roswell Park endorse routine RTB for AS guidance (i.e, > 50% of patients)[22,35], other contemporary AS programs use RTB more selectively based on variable patient- and program-specific thresholds (8%–24% of patients)[29,36,74,75]. In the DISSRM registry, patients are not routinely biopsied at enrollment, but RTB is recommended for GR >5mm/year or upon surpassing patient-specific LTD size thresholds (2, 3, or 4 cm)[29].

## Triggers for Delayed Intervention

DI should be triggered during AS by any change that causes the oncologic risk to exceed the treatment risk[4,15–17]. This guiding principle mirrors that for initial AS selection, but utilizes growth kinetics and potentially new histology information obtained during AS to further improve risk stratification[22].

As with AS patient selection, DI triggers are divided into tumor factors and patient factors. Recent maturation of oncologic safety data has fostered patient and physician comfort with AS, and DI cases are increasingly triggered by tumor factors rather than patient factors/anxiety. Nevertheless, patient factors remain impactful and drive high variability between different AS programs in contemporary DI rates (11%–50%)[22,27,35,36,74–82].

### Tumor Factors / Progression Criteria for Intervention

Tumor factors for DI have been referred to as progression criteria for intervention (PCI), so as to differentiate from classic clinical progression (i.e. stage, grade, death), since the former may not include the latter[22]. PCI generally fall within 5 categories (acronym: "GLASS"): (1) GR; (2) LTD; (3) Adverse/unfavorable biopsy histology; (4) Stage/infiltration; (5) Symptoms/signs. Based on both incidence and consensus level, GR and LTD are considered major PCI, whereas other GLASS PCI categories are minor. Only few centers use minor PCI, with Roswell Park observing < 3% versus 30% of patients meeting minor PCI versus major PCI, respectively[22]. Greater PCI standardization has been challenged by inconsistent usage of prospectively defined objective PCI thresholds[22,27,35,74–81], as nonspecific subjective tumor thresholds are still commonly reported (eg, "fast" or "significant" growth, "radiological progression," "change in SRM's features," etc.)[73,75–77]. This heterogeneity drives high variability in reported PCI rates (9%–30%)[22,27,75].

#### Growth rate

Rapid GR is the most commonly used PCI in contemporary AS series[22,35,73–75,78,80,82], and also the most common DI trigger when used with other PCI[22,35]. Numerous retrospective studies support GR association with RCC grade[22,74,83–86] metastatic potential[20,75,77,79,80,82,86], and an association between rapid GR and clear cell RCC histology is also reported[35]. However, prospective validation of these associations is still needed[52,75]. A systematic review of early AS series identified a median GR of 6.5 mm/year among metastatic patients compared with 2.5 mm/year in non-metastatic patients[20], and the vast majority of the > 30 AS patient metastases reported to date have had a primary tumor GR > 5 mm/year[29,35,75,77,79,80,82]. However, most of these patients were not followed with prospectively applied PCI and had quite large primary tumors (> 6 cm) at metastasis, and validation in SRM cohorts managed with timely DI conversion is needed[36,78]. Nevertheless, there is consensus, including from ASCO and AUA to use GR of > 5 mm/year to trigger DI[4,15,17]. Studies prospectively using GR > 5 mm/year suggest that 13%–18% of patients meet this threshold during AS[22,56,74,78]. Tumor size-

stratified GR thresholds may have future utility. For example, Roswell Park prospectively uses GR > 5 mm/year for LTD ≤ 3 cm, but GR > 3 mm/year for LTD > 3 cm, based on (1) increased/non-negligible SRM metastatic risk beyond 3 cm; (2) historical reports of SRM metastasis with GR < 5 mm/year but not < 3 mm/year; and (3) high likelihood that a SRM > 3 cm with GR > 3 mm/year will progress based on LTD > 4 cm within 1–3 years anyway[22]. An alternative to linear GR is volumetric growth or doubling rate, as used by the Canadian RCC Consortium and University of Texas Southwestern Medical Center[27,35,80]. However, caution with this approach must be exercised, since minute linear changes in very small SRMs (including those attributable to artifact/inter-observer variability) can yield volumetric doubling, while relatively fast linear growth (eg, ~6–8 mm/year) may fail to meet the volumetric doubling threshold for tumors > 4 cm.

### Longest tumor diameter

In a systematic review of early AS series including over 800 patients, 89% (16/18) of metastatic patients had LTD > 4 cm at metastasis versus 0% (0/18) having LTD < 3 cm[20]. Contemporary AS series similarly support a negligible metastatic rate when <3cm, and a very low metastatic rate for LTD 3–4 cm, with most metastases occurring when > 4 cm[29,56,76,78,80,81,83]. Accordingly, there is strong general consensus for LTD usage as a PCI[4,16,17,87], with 4 cm being the most commonly used threshold. LTD > 4 cm triggered or helped trigger 25% and 50% of DI cases in the Canadian and Roswell Park cohorts, respectively[22,35]. A > 3 cm LTD cutoff for treatment is endorsed by current AUA guidelines, but its reported use is uncommon[4,29,77]. One rationale for using LTD > 3 cm is its association with higher rates of eventual DI[22,29,31]. Nevertheless, a 3 cm threshold likely overtreats many patients, particularly those with slow growth (< 3 mm/year) for whom metastasis rates appear to approach zero and long-term DI avoidance may be possible.

### Adverse/unfavorable biopsy histology

Although the prevalence and diagnostic sensitivity of RTB for adverse histology in SRMs is low, diagnostic specificity is high. Accordingly, any patient with RTB favoring high-grade RCC and/or a more aggressive subtype should be counseled on potentially higher risks with AS continuation, given the higher metastatic risk in surgical series.

### Stage/infiltration

Clinical upstaging from cT1a to cT3a is an independent prognostic variable for metastasis but is a rare event in most AS series. Only one patient (1%) in the Roswell cohort developed cT3a disease (progressing also by both GR and LTD)[22]. Similarly, Canadian investigators reported one (1%) patient with DI triggered by tumor thrombus[75]. Regardless of rarity, detection of cT3a upstaging should trigger DI consideration due to a potentially higher metastatic risk.

### Symptoms/signs

Tumor-related symptoms or signs such as gross hematuria, retroperitoneal bleeding, or paraneoplastic effects are well described for RCC but exceedingly rare in the SRM population. Accordingly, the vast majority of SRMs remain asymptomatic during AS[22,75]. In over 500 patients to date, the DISSRM registry has yet to encounter gross hematuria attributable to a renal mass[29]. Three (18%) patients in a prospective Canadian study and one (1%) patient in the Roswell Park cohort developed gross hematuria, although a renal source is unclear. For symptom development during AS, the first action should be to rule out other sources.

## Patient Factors

With the exception of a few recent AS series in which DI was almost entirely driven by PCI[22,35,73], DI cases in contemporary AS reports are still commonly, if not mostly, performed because of patient factors without PCI development[7,27,74,76,82,88].

### Patient preference/anxiety

Patient preference due to anxiety or disease uncertainty is the most common patient factor triggering DI. This is clearly demonstrated in the DISSRM and Canadian prospective registries where approximately 50% or more of patients who crossover to DI do so without tumor PCI development[27,76,78,82,88]. Illness uncertainty predicts general quality of life, cancer-specific quality of life, and distress which can all impact the success of AS[89]. Interestingly, mental health scores improve over time in patients in a structured AS program such as DISSRM[33]. The increasingly apparent role of the provider and health care setting in influencing AS program acceptance was discussed above. Only rarely did AS patients convert to DI because of anxiety without PCI development in the Roswell Park (1%) and Italian (4%) cohorts, supporting this role[22,73]. Given the impact of illness uncertainty during AS[89], DI conversion may be reduced by empowering the patient upfront with details regarding the very low GR (e.g., average 2–3 mm/year), planned use of PCI thresholds, and negligible expected metastasis rates during PCI freedom. The DISSRM registry demonstrates that patients experience improving mental health domains while they are in structured AS programs, indicating reductions in anxiety and illness uncertainty[33].

### Life expectancy

LE must be carefully considered before DI conversion, since impending metastasis may not increase mortality risk when life expectancy is limited (eg, < 5 years)[90].

In young healthy individuals, PCI development should serve as an absolute indication for DI, whereas AS continuation or observation conversion may be appropriate in elderly patients and/or patients with comorbidities despite PCI development. Improved patient health or resolution of an acute health issue during AS may increase LE and change the risk-benefit ratio towards treatment[82]. More recent cohorts, like that at Roswell Park, have integrated PCI triggers with LE calculations to guide decision-making regarding DI conversion[22].

### Other patient factors

Other patient factors triggering DI are uncommon. The need for unrelated additional surgery is reported as a DI trigger[91], but, other than renal transplantation, is generally not endorsed. Concern for losing a window to perform nephron-sparing treatment may raise consideration for early DI, but the vast majority of DI cases in contemporary AS reports have been amenable to nephron-sparing, suggesting no compromise in renal preservation[22,35,73,74,76–80,88]. Rarely, AS patients may develop end-stage renal disease that requires resection to qualify for renal transplantation eligibility, depending on center requirements[70,79]. Finally, concern regarding patient non-compliance may be an under-utilized reason for DI conversion, given that many metastasis cases during AS have been attributed to poor patient adherence to AS protocols[20,79].

## Delayed Intervention Pathology

Most AS series demonstrate a similar albeit slightly higher rate of malignancy at DI (80%–100%) compared to surgical SRM series[8,22,27,36,73,78,82]. Avoidance of benign resections appears to correlate with degree of RTB usage, with the Canadian consortium and Roswell Park each achieving a 0% benign DI resection rate while using routine RTB to identify benign tumors non-surgically[6,22,27,73,78]. High nuclear grade or pT3 upstaging is uncommon in resected SRM series and AS series, comprising ~5% and 10%–20% of cases, respectively[78,86,92–96]. In contrast, Roswell Park recently reported very high rates (62%) of any adverse pathology at DI surgeries, which may relate to keeping 99% of patients on AS until pre-defined tumor PCI development, potentially enriching DI resections for higher risk tumors[22]. These investigators also found a rapid GR to be associated with higher adverse pathology rates, similar to many retrospective series. However a DI cohort study from the DISSRM registry observed low rates of adverse pathology and zero metastases, regardless of GR[78]. The clinical impact of adverse pathology at DI remains unclear since resected SRM patients have an excellent prognosis regardless of pathology.

## On the Horizon

A variety of technologic advances under active study have the potential to propel the AS field forward. These approaches include the use of novel tumor biopsy-based biomarkers, blood-based biomarkers (e.g., circulating tumor cells/DNA), and urine-based biomarkers, which may improve prognostic accuracy over conventional imaging and biopsy histology. Radiomics guided by automated volumetry and/or artificial intelligence may also further refine current AS strategies.

## Summary

Despite limitations in the current literature, AS appears to be a safe initial management strategy for many SRM patients. The indolent clinical growth and low metastatic potential of SRMs, combined with no evidence to suggest oncologic compromise with delays to treatment, should provide confidence to both patients and providers who are considering AS. Future research in AS patients should prioritize characterization of long-term rates of metastasis and DI, standardization of objective tumor progression criteria for triggering DI, and defining the role of AS in young and healthy patients.

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