



Active Surveillance of Small Renal Masses

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Most renal masses in the United States are incidentally detected via abdominal imaging. This has led to an increase in the incidence of small renal masses (≤ 4 cm). Active surveillance is, an oncologically safe option in slow growing and indolent tumors in other organs and has recently become more widely studied in small renal masses. For selected patients, particularly those who harbor significant comorbidities, active surveillance is a safe option for small renal masses. Renal biopsy may be helpful in the decision making process, but remains an optional component for the active surveillance of small renal masses. UROLOGY 123: 157–166, 2019. © 2018 Elsevier Inc.

Renal cell carcinoma (RCC) represents 3.8% of all new cancer cases within the United States, with an estimated incidence of 65,340 cases in 2018.¹ During the last 2 decades, there has been an annual increase of about 2% in the incidence of RCC worldwide. The incidence of RCC is rising predominantly due to increased use of imaging as well as better resolution of imaging technology.²

Most renal masses in the United States are incidentally detected via abdominal imaging. On computed tomography (CT) scan, a renal mass that enhances with intravenous contrast is considered suspicious for RCC. For years, radical nephrectomy was the gold standard treatment for an enhancing renal mass. Biopsy was discouraged due to fear of spread of tumor cells along the biopsy tract. As such, some patients were over treated for benign or indolent renal tumors. Indeed, as many as 25% of small renal masses (SRMs) are benign tumors.³ In addition, studies found an increased risk for chronic kidney disease (CKD) and end-stage renal disease (ESRD) in patients who had undergone radical nephrectomy compared to partial nephrectomy.⁴ Risk factors for CKD, such as baseline hypertension and diabetes, are seen in many patients with renal masses, even in those with early onset RCC, which may help explain this observation.⁵ Given that the 5-year mortality from ESRD is higher than most newly diagnosed RCCs, urologists have moved toward adopting nephron-sparing approaches for SRMs. The nephron-sparing approach in combination with improved, oncologically

sound biopsy techniques also led to an increase in the practice of preoperative diagnostic biopsy of SRMs.

Active surveillance is a feasible, safe oncologic option in slow growing and indolent tumors in other organs. Active surveillance in prostate cancer in particular has gained favor among urologists, as large studies have shown equivalent oncologic outcomes for deferred treatment.⁶ The concept of active surveillance has begun to be applied to SRMs within the correct clinical setting.^{3,7-9} Herein, we review the practice of active surveillance for SRMs with a focus on accurate diagnosis, oncologic outcomes, and methods of predicting biologic behavior.

METHODS

A systematic search of the literature was performed utilizing the preferred reporting items for Systematic Reviews and Meta-Analyses standards (Fig. 1).¹⁰ Eligibility criteria for our search included original articles with full text available in the English language published from 2013 to 2018. Information sources included the Embase and MEDLINE (PubMed) database (search performed 7/16/18) and websites from the National Comprehensive Cancer Network, American Society of Clinical Oncology (ASCO), American Urological Association (AUA), European Association of Urology (EAU), and Canadian Urological Association.^{3,11-14} The PubMed database search was performed utilizing the terms “active surveillance,” “renal mass,” “renal biopsy,” “cost,” and “imaging”. Limits applied included full-text, English language, and original articles. Articles were selected that presented data from prospective studies, retrospective studies, or meta-analyses. Additional seminal articles (>40 citations) on active surveillance of renal masses were included that were published prior to 2013. Internationally recognized guidelines from selected oncologic/urologic organizations were also included as listed above. Outcomes that were determined to be relevant to the current review included treatment costs, progression of disease, disease specific survival, overall survival, treatment morbidity/mortality, renal biopsy diagnostic accuracy, and renal biopsy diagnostic morbidity in the context of active surveillance for organ confined and SRMs. All papers that met criteria were reviewed and a summary of the results are presented below.

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PRISMA Flow Diagram

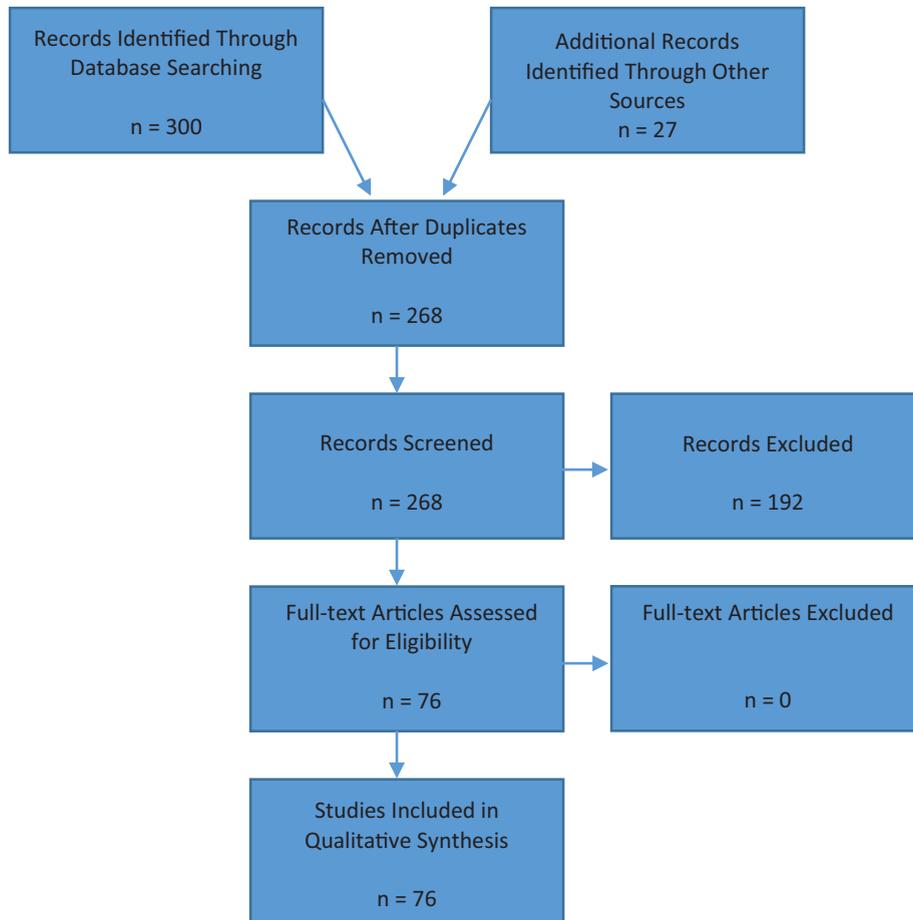


Figure 1. PRISMA flow diagram of search results.

REVIEW

Defining a Small Renal Mass

A SRM is defined by the AUA and ASCO as an incidentally image-detected, contrast-enhancing renal tumor with a maximal diameter ≤ 4 cm and limited to the kidney based on imaging features, which corresponds to a pathologic stage of T1a.^{3,11,15}

Defining of Progression of Small Renal Masses

Progression of disease is an important marker in the management of patients on active surveillance. The current literature utilizes variable definitions for what is considered disease progression, which are predominantly based on tumor size, growth rate, and stage based on imaging (Table 1).^{3,11} The ASCO guidelines consider tumor growth greater than 0.5 cm per year or tumor size greater than 4 cm to be an indicator for possible intervention.³ The AUA guidelines similarly use 0.5 cm per year as a growth cutoff, but applied a more conservative definition of 3 cm for overall tumor size.¹¹ The AUA guidelines also mention that any advancement in stage or metastatic disease to be signs of progression and, therefore potential

triggers to alter management for patients on active surveillance.¹¹

Accuracy of Imaging in Estimating Tumor Characteristics

The choice of active surveillance over definitive therapy is largely guided by clinical factors (life expectancy, comorbidities, etc.), surgical expertise, and the biological potential of the renal mass^{3,11-14} (Fig. 2). Imaging has improved in its ability to determine tumor characteristics, and as such, plays a major role in the decision-making for management of SRMs. Tumor size, in particular, is a critical characteristic to accurately assess by imaging. A study by Syed et al showed a significant association between tumor size and the presence of adverse pathologic features. At least 1 adverse pathologic feature could be found in 49% of tumors 3-4 cm compared to only 22% of tumors ≤ 1 cm.¹⁶ Daugherty et al demonstrated that less than 4% of tumors ≤ 5 cm had metastatic RCC at presentation.¹⁷ In addition, they found that clear cell RCC had the highest risk for metastases compared to other histologic subtypes. Other studies have similarly shown a positive

Table 1. Organization guidelines for active surveillance of small renal masses

Guideline	Criteria for Active Surveillance	Follow up on Active Surveillance	Potential Triggers to Change Management on Active Surveillance	Criteria for When to Perform a Renal Biopsy
ASCO [1]	<ul style="list-style-type: none"> • Patients with significant comorbidities and limited life expectancy <ul style="list-style-type: none"> -Absolute indication: high risk for anesthesia and intervention or life expectancy < 5 y -Relative indication: significant risk of end-stage renal disease if treated, SRM (< 1 cm), or life expectancy (< 10 y) 	<ul style="list-style-type: none"> • Staging chest x-ray and axial abdominal imaging or US every 3 mo (firsty), every 6 mo (second and third y), annually thereafter 	<ul style="list-style-type: none"> • Tumor growth > 0.5 cm/y • Tumor size > 4 cm • Consideration for treatment based on comorbidities and life expectancy 	<ul style="list-style-type: none"> • Not necessary for all patients on AS • All patients with an SRM should be considered for renal biopsy when results may alter management • Recommended prior to ablation therapy • No biopsy for masses that are predominantly cystic, originating in the collecting system, or suspicious for urothelial carcinoma • Not yet standard of care in Canada • Should be reserved for patients in whom the results might change management • At the time of, or prior to, ablation therapy • Consider when a mass is suspected to be hematologic, metastatic, inflammatory or infectious • For a solid renal mass, not required for <ul style="list-style-type: none"> -Young or healthy patients who are unwilling to accept the uncertainties associated with biopsy -Older or frail patients who will be managed conservatively independent of biopsy findings • Patients should be counseled regarding rationale, positive and negative predictive values, potential risks and nondiagnostic rates of biopsy • For patients who elect biopsy, multiple cores are preferred over fine needle aspiration
CUA [2]	<ul style="list-style-type: none"> • SRM in elderly and/or patients with multiple comorbidities at high risk for intervention, and in those with limited life expectancy 	<ul style="list-style-type: none"> • CT or MRI every 3 mo (first y), every 6 mo (second and third y), annually thereafter • US with or without contrast may provide adequate images for measurement 	N/A	
AUA [3]	<ul style="list-style-type: none"> • Patients in who the anticipated net benefit of AS is modest to significant when compared to treatment • For patients with small solid or Bosniak 3/4 complex cystic renal masses, especially those < 2 cm • The anticipated risk of intervention or competing risks of death outweigh the potential oncologic benefits of active treatment • AS with potential for delayed intervention may be pursued only if the patient understands and is willing to accept the associated oncologic risk 	<ul style="list-style-type: none"> • Surveillance imaging initially every 3-6 mo • Chest imaging with plain radiography annually or if intervention triggers are encountered or symptoms arise • The intensity of surveillance can be attenuated if the renal mass exhibits slow growth kinetics, is noted to be radiographically stable or if the patient's medical condition deteriorates • The decision as to the frequency and imaging modality must be customized and informed by robust communication focusing on goals, risks and triggers for intervention 	<ul style="list-style-type: none"> • Tumor size > 3 cm • Stage progression • Tumor growth > 0.5 cm/y • Changes in patient or tumor factors • Progression to metastatic disease 	

Continued

Table 1. Continued

Guideline	Criteria for Active Surveillance	Follow up on Active Surveillance	Potential Triggers to Change Management on Active Surveillance	Criteria for When to Perform a Renal Biopsy
EAU [4]	<ul style="list-style-type: none"> • Offer active surveillance, radiofrequency ablation and cryoablation to elderly and/or comorbid patients with a SRM 	N/A	N/A	<ul style="list-style-type: none"> • Consider in candidates on AS • Consider before ablative treatments • Consider in the setting of metastatic disease • Not necessary before surgical treatment in healthy patients with a long life expectancy and suspicious, contrast enhancing renal mass • Not indicated for comorbid and frail patients who can be considered only for active surveillance regardless of biopsy results
NCCN [5]	<ul style="list-style-type: none"> • Patients with pT1a and decreased life expectancy or extensive comorbidities that would place them at excessive risk for more invasive interventions 	<ul style="list-style-type: none"> • History and physical examination, a comprehensive metabolic panel, and other tests every 6 mo for 2 y and then annually for up to 5 y after diagnosis • Abdominal CT or MRI within 6 mo for 2 y, imaging annually thereafter • Chest imaging annually to assess for metastases in patients with RCC on biopsy • Imaging of the pelvis; CT or MR of the head or spine, if there are neurologic symptoms; or bone scan in cases of elevated ALP, bone pain, or abnormal radiologic findings 	N/A	<ul style="list-style-type: none"> • In selected individuals, needle biopsy may be considered for small lesions to establish the diagnosis of RCC and guide active surveillance strategies, cryosurgery, radiofrequency, and ablation strategies • Should be considered if imaging is suspicious for urothelial carcinoma or lymphoma

AS, active surveillance; ASCO, American Society of Clinical Oncology; AUA, American Urological Association; CT, computed tomography; CUA, Canadian Urological Association; EAU, European Association of Urology; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma; SRM, small renal mass; US, ultrasound.

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last accessed EAU guidelines on renal cell carcinoma on 07/16/2018 at: <http://uroweb.org/guideline/renal-cell-carcinoma/>

5. NCCN guidelines Version 4.2018 Kidney Cancer.

1. Life Expectancy / Overall Health
 - a. Age
 - b. Comorbidities
 - c. Treatment Suitability (anticoagulation/antiplatelet status, renal function, prior surgical history, anesthetic risk)
2. Imaging Characteristics at Time of Diagnosis
 - a. Size
 - b. Location – Accessibility for treatment or biopsy sampling
 - c. Features of adverse pathology (nearness to collecting system, renal sinus fat, hilar vascular structures)
3. Characteristics on Follow-up Imaging
 - a. Size
 - b. Growth rate/velocity
 - c. Features of adverse pathology (nearness to collecting system, renal sinus fat, hilar vascular structures)
4. Pathologic Characteristics on Biopsy (optional)
 - a. Renal cell carcinoma vs benign vs non-renal cortical tumor
 - b. Histologic subtype of renal cell carcinoma
 - c. Grade

Figure 2. Summary of criteria to consider when selecting patients with a small renal mass for active surveillance.

correlation between tumor size, likelihood of malignancy, rate of metastasis, and disease specific survival.¹⁸⁻²¹

Most studies comparing preoperative CT or magnetic resonance imaging (MRI) to final pathologic measurements show a minimal difference in the estimation of tumor size. Some studies have shown that there can be an underestimation of tumor size on imaging vs size on final pathology. Khan et al found that tumor size on imaging was smaller on average by 0.43 cm compared to final size on gross examination.²² This measurement error was independent of imaging modality chosen, whether it be MRI or CT. However, other studies have shown a slight size overestimation for SRMs when comparing renal tumor size on imaging with pathologic measurements.²³⁻²⁵ Kurta et al evaluated 521 patients who had undergone CT scan and surgical resection of a renal mass.²³ They found that CT scan overestimated tumor size by 0.21 cm in patients with tumors between 4 cm and 7 cm. Overall, the size discrepancy at imaging is small enough to suggest that both CT and MRI allow for relatively accurate assessment of actual tumor size.

Safety of Active Surveillance for Small Renal Masses

Minimally invasive, nephron-sparing approaches continue to be the gold standard for the management of SRMs. Although, the majority of patients with incidentally discovered renal masses are candidates for surgical management, patient comorbidities can be a significant limitation for surgical intervention.^{26,27} In a review of the National Cancer Data Base of 109,410 patients, 6.4% underwent observation.²⁸ The authors found patient and disease factors were the strongest predictors of observation. Thereby patients who have the most comorbidities or incurable disease may be more likely to choose active surveillance. Interestingly, the same study also found that racial and socioeconomic factors also significantly predicted observation. Observation rates were higher among poor, African American, and uninsured or socially insured patients, with these groups having 1.2-3.5 times higher

odds of observation ($P < .01$). Sociodemographic factors affecting the choice of active surveillance, has been reported in other studies.²⁹ These studies suggest that some patients may find themselves choosing active surveillance due to the inability to access surgical care and afford definitive therapy.

The risk of surgical intervention weighed against the risk of progression of disease has received increasing attention for patients with SRMs. Several retrospective studies have shown active surveillance for SRMs to be a relatively low risk management option.³⁰⁻³² Bahouth et al evaluated 70 patients clinically staged as T1a, who underwent active surveillance for SRMs with a mean follow-up of 34 months.³³ The majority of masses had a slow growth rate (0.25 cm/y) and 31% showed no growth. Only 10% of masses underwent an intervention and active surveillance did not compromise the ability for eventual definitive nephron-sparing surgery. In another study looking at patients with cystic RCC placed on active surveillance, there was no evidence of metastatic disease found with a median follow-up of 4.3 years.³⁴ Tumors in this cohort had an average size of 3.1 cm. Chandrasekar et al looked at active surveillance of complex renal cysts in a cohort of 336 patients with a median follow-up of 67.1 months.³⁵ Metastatic disease developed in only 1 patient, undergoing active surveillance, which occurred after 12 years of observation. A few prospective multi-institutional clinical trials have also evaluated active surveillance for SRMs.^{36,37} In a study by Pierorazio et al, 158 patients who underwent active surveillance had data available for analysis of growth rate. The progression free survival was 95% at 2 years and 67% at 5 years. No patients undergoing active surveillance died of RCC.³⁶ Similarly, Jewett et al followed 178 patients with 209 SRMs and found a low rate of progression to higher stage (12%) and rare metastases (1.1%).³⁷ These studies and others support active surveillance as a safe option for the appropriately selected patient.³⁸⁻⁴²

Patients who are elderly or have multiple comorbidities may be particularly appropriate for active

surveillance.^{8,9,43-45} Indeed, in the elderly population, rates of choosing active surveillance has been rising over the last decade. Kim et al queried the National Cancer Database from 2002 to 2011 to explore the national treatment trends in patients ≥ 70 years with T1 renal tumors.⁸ Although, most patients were treated with definitive therapy, 12.6% underwent active surveillance. They also found that the rates of active surveillance steadily increased from 9.8% in 2002 to 13.6% in 2011. This increased utility of active surveillance among older patients likely reflects the surgical risk for this population, given the frequency of comorbidities. Patel et al queried the Surveillance, Epidemiology and End Results Medicare database to identify patients with localized SRMs.⁴⁶ They explored associations of specific comorbidities, including congestive heart failure, CKD, peripheral vascular disease, chronic obstructive pulmonary disease, diabetes, and cerebrovascular disease with causes of death. The authors found that these comorbidities were associated with decreased overall survival in patients with SRMs. In addition, even minimally invasive surgical approaches to the management of renal tumors are not without risk. Tomaszewski et al evaluated 1092 patients undergoing partial or radical nephrectomy for localized renal tumors.⁴⁷ The authors found that 16% of patients developed at least 1 medical or surgical complication and 5.7% of patients experienced a major complication. It has been shown that patients who have T1a RCC with significant cardiovascular risk have worse overall survival, which may eliminate the benefit of any cancer-specific survival.²⁶ Tang et al reviewed outcomes of different management modalities in an octogenarian population of 115 patients and found no difference in overall or disease-specific survival among the different management groups, including active surveillance, for those with clinical T1a tumors.⁴³

Overall the literature shows that in the selected patient population, active surveillance can be a safe management option. International guidelines agree that active surveillance should be offered as an initial management option for patients who have significant comorbidities, are high risk for significant morbidity/mortality with intervention, or have a limited life expectancy. Consideration for active surveillance may also be appropriate for patients with a SRM and at high risk for ESRD.^{3,11-14}

Quality of Life for Patients on Active Surveillance

Choosing active surveillance as an appropriate management is not solely dependent on clinical and pathologic factors. Patients must also emotionally deal with delaying treatment, which may be a cause of stress and influence quality of life (QOL). Patel et al conducted a prospective, comparative study of QOL among patients with SRMs choosing active surveillance vs primary intervention.⁴⁸ A QOL questionnaire was completed at enrollment, 6 months, 12 months, and then annually for the duration of the study. The authors found only 4% of patients crossed over to treatment from the active surveillance cohort.

Among the patients who underwent delayed intervention, there was no significant change in mental health scores. Patients who underwent primary intervention had higher QOL scores, but this was due to better baseline physical health than those in the active surveillance group. Mental health scores did not seem to be adversely affected by choosing active surveillance as a management option. However, other studies have shown active surveillance to have a negative impact on QOL. In a prospective trial by Parker et al, 264 patients with clinical T1-T2 disease were enrolled in an active surveillance registry.⁴⁹ The mean age was 72.5 years and the mean tumor size was 2.3 cm. Patients completed questionnaires at the time of enrollment, 6 months, 12 months and 24 months. The authors found that illness uncertainty in patients undergoing active surveillance predicted general QOL, cancer-specific QOL, and intrusive thoughts and avoidance behaviors. Similarly, Alam et al looked at 638 patients enrolled in the Delayed Intervention and Surveillance for Small Renal Masses Registry, of which 339 (53.1%) underwent active surveillance.⁵⁰ QOL scores were significantly lower among active surveillance patients compared to those undergoing partial nephrectomy. These findings remained statistically significant when controlling for time, age, gender, comorbidities, and BMI. Psychosocial interventions may be important in patients undergoing active surveillance to help cope with the uncertainty associated with this management option.

Utilizing Renal Biopsy for Active Surveillance

Percutaneous biopsy of renal masses continues to have an evolving, yet controversial role in active surveillance in terms of risk-stratification and selection of candidates.⁵¹⁻⁵⁴ In theory, renal biopsy could identify high risk features or allow for the identification of benign lesions, which might be useful in guiding management. A patient may also want to know a definitive diagnosis of their renal mass, regardless of the management they choose. A meta-analysis looking at 3113 biopsies demonstrated a low false-positive rate and good diagnostic accuracy in terms of histologic subtype of RCC.⁵⁴ The surgical risks of renal biopsy were found to be limited, with hematoma being the most common at 4.9%.⁵⁴ However, limited tissue sampling remains a significant limitation of renal biopsy, which can lead to under grading secondary to tumor heterogeneity. So, although the sampling of high-risk features may be helpful, low tumor grade features may not necessarily be useful in guiding clinical management. While in most cases accurate histological subtyping can be accomplished on biopsy material, in select cases the diagnosis can be difficult, such as in oncocytic lesions.⁵⁵ It has been recognized that some RCC subtypes can have areas that have the same morphologic features as oncocytoma. Some of these tumors have been recognized to have low metastatic potential, but this does not necessarily apply to all oncocytic RCCs.^{30,56} Special stains and

immunohistochemical (IHC) studies may be helpful in differentiating these lesions.⁵⁵

Renal mass biopsy remains largely unpracticed among urologists both in the United States and abroad. A survey showed that 73% of urologists used renal mass biopsy “never” or “rarely.”⁵¹ In the same survey, urologists decided against renal mass biopsy due to concerns of false-negative results and lack of influence on clinical management. A study looking at clinical parameters influencing the treatment of T1a renal tumors in Germany found that 57% of responders would not perform a renal biopsy.⁵⁷ Interestingly, another study showed no influence of renal biopsy in determining delayed intervention in a group of patients undergoing active surveillance.⁵³

Some studies have shown renal mass biopsy to be a cost-effective method of managing patients with SRMs. A study by Pandharipande et al evaluated the cost-effectiveness of using renal mass biopsy to guide treatment decisions.⁵⁸ They found no difference in life expectancy when using biopsy to triage patients to surgery. They also found that renal biopsy resulted in a cost savings. Similarly, Heilbrun et al evaluated the cost effectiveness of renal mass biopsy in a three-way scenario of active surveillance vs immediate surgery vs biopsy guided decision making.⁵² Immediate surgery held the highest cost, but was the most effective diagnostic strategy and had the longest overall survival. Immediate surgery provided 18.53 life years compared to 18.21 life years for active surveillance. Active surveillance had the lowest cost and was the preferred choice on a cost effectiveness analysis. However, when adjusted for QOL, biopsy guided decision making was superior to immediate intervention in terms of cost-effectiveness.⁵² In contrast, a study by Bhan et al found that the most effective and least costly management option for SRMs, when adjusting for QOL, was active surveillance with no initial biopsy.⁵⁹ Subsequent percutaneous cryoablation was utilized for patients who demonstrated progression on follow-up imaging.

The role of renal biopsy has to be implemented in consideration of each patient's clinical scenario (Table 1). Biopsy of a SRM is not necessary in all patients on active surveillance. Renal biopsy should be reserved for cases in which the information will alter clinical management. Consideration of renal biopsy is recommended prior to ablative procedures as well as in cases of suspected hematologic, metastatic, or infectious/inflammatory lesions. The potential risks, benefits, and nondiagnostic rates associated with renal biopsy should be had with patients considering active surveillance.

Predicting Tumor Aggressiveness

In order for active surveillance to be a safe management strategy for SRMs, there needs to be a way of characterizing tumor aggressiveness and indications as to when a surgical intervention is necessary. Histologic subtype and grade provided by renal biopsy may be helpful in this regard. Some studies have suggested that clear cell RCC

has a tendency to grow faster compared to other histologic subtypes of RCC.⁶⁰ Another study by Zhang et al evaluated 60 patients on active surveillance for a mean of 39.5 months.⁶¹ Mean tumor size increased from 2.3 cm to 4.4 cm during the duration of follow-up. The authors found that high grade clear cell RCC had a greater growth rate than low grade clear cell RCC. Multivariate analysis showed that tumor grade was the only independent variable that predicted a linear growth rate of >0.5 cm/y.⁶¹ A prospective study by Mason et al found tumor size at diagnosis to be the only predictor of growth rate, with a size cut off of 2.45 cm.⁶²

Linear growth rate is an easily measured variable for patients with SRMs undergoing repeat imaging for active surveillance. Linear growth rate of SRMs has been shown by multiple studies to be an objective correlate of tumor aggressiveness to guide patient treatment and serve as a potential trigger for intervention.⁶³⁻⁶⁷ A pooled analysis by Smaldone et al found that a linear growth rate of 0.8 cm/y in those who had progression of disease compared to a rate of 0.3 cm/y in those who did not progress.⁶⁷ Mehrazin et al investigated the association between tumor anatomic complexity via Nephrometry Score and lesion growth kinetics in patients on active surveillance for SRMs.⁶⁸ Their study population had a median age of 71 years and a median tumor size of 2.2 cm at presentation. They found a median linear growth of 0.24 cm/y and no growth in 19% of masses. In their cohort, 1.7% of patients progressed to metastatic disease. Tumors that progressed to definitive therapy demonstrated more rapid growth and tumors that were more anatomically complex were more likely to have rapid growth. Similarly, Hawken et al showed that increased annual growth rate (5.2 mm/y) was associated with adverse pathology.⁶⁹

However, not all studies have shown an association between tumor growth rate and high risk tumor characteristics.^{66,70-72} A study by Jang et al looked at 124 patients with renal masses and delineated groups by favorable (benign or low-grade RCC, pT1-pT2) vs unfavorable (high grade RCC, pT3-pT4) pathology.⁷¹ There was no significant difference in growth rate between the 2 groups. Another study looking at 318 patients on active surveillance found growth rate of SRMs to be variable and not a useful measurement to predict death or adverse pathologic features.⁷² A multi-institutional, prospective study looked at SRMs in 169 patients on active surveillance with treatment delayed until time of progression.⁶⁶ The mean age of their cohort was 72.5 years and the median growth rate was 0.12 cm/y. The study found no predictors of growth rate in their cohort, although the follow-up of the study was short with a median follow-up of 1.7 years. In addition, although some studies have shown a slow growth rate for benign renal masses, such as oncocytoma, others have shown a growth rate similar to RCC.^{30,56,73,74} A study by Kawaguchi et al. showed a growth rate of 0.16

mm monthly for oncocytomas on active surveillance.⁷⁵ These studies raise the concern of relying upon growth rate alone as a marker for intervention and potentially missing the curative window for patients on active surveillance.

Despite the ongoing debate of predictors of growth rate and tumor aggressiveness, the majority of the literature supports the concept that a fast growth rate and tumor size is associated with more aggressive disease.^{62-69,76} As such, it is recommended that tumor growth > 0.5 cm/y be used as a marker for disease progression and consideration of definitive treatment.^{3,11}

FUTURE DIRECTIONS IN ACTIVE SURVEILLANCE

With active surveillance becoming a more acceptable approach to the management of SRMs in the appropriate patient, attention should be turned to ways we can better classify the biologic behavior of renal tumors. Currently, we rely predominantly on histology to help predict aggressive disease. Unfortunately, due to random sampling and tumor heterogeneity, tumor characteristics identified on hematoxylin and eosin staining is limited in its prognostic abilities. IHC techniques and molecular studies may eventually be able to help us to better stratify which are the best patients for active surveillance. Currently, some IHC stains can be applied to biopsy tissue to identify some lesions of low malignant potential that might have previously been classified as conventional clear cell RCC. One such example is clear cell papillary RCC, an indolent renal tumor that shows dual staining for CA9 and CK7.⁷⁷ Other molecular techniques, such as fluorescence in situ hybridization, can be used to help identify tumors that arise in younger patients, such as the MiT family translocation RCCs.⁵ Some of these tumors are thought to be associated with more aggressive disease. Finally, advances in imaging are allowing better discrimination between different histologic subtypes of RCC without the need for tissue sampling.^{78,79}

CONCLUSION

Active surveillance for SRMs is a feasible option for elderly patients and those with comorbidities, especially significant cardiovascular disease. Renal biopsy may be helpful in choosing between management options and should be considered prior to placing a patient on active surveillance if the results of the biopsy will change clinical management. The risks and benefits of renal biopsy must be taken into account when counseling patients. Close follow-up on imaging is recommended for those placed on active surveillance with CT or MRI performed every 3-6 months for the first year, followed by annual assessment. As tumor size has been well correlated to malignant potential, tumor growth rate should be monitored, as well

as any changes in stage, for the possibility for surgical intervention.

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