Prior to publication, this guideline underwent review by the CUA Guidelines Committee, topic experts, and the CUA Executive Board.

Canadian Urological Association guideline: Management of small renal masses – Full-text

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Summary of recommendations

1. Patients diagnosed with SRM should undergo routine laboratory investigations, including at a minimum a serum creatinine and glomerular filtration rate *(Clinical principle)*.
2. Patients with SRM incidentally discovered on routine imaging should be investigated with a multiphasic, contrast-enhanced abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scan *(Clinical principle)*.
3. For patients with suspected renal malignancy, a baseline chest X-ray is suggested to assess for pulmonary metastases *(Conditional recommendation, low certainty in evidence of effects)*.
4. Patients with SRM and pre-existing renal dysfunction in whom a radical nephrectomy is being considered, may be offered renal scintigraphy when the result may alter their management *(Clinical principle)*.
5. Patients with SRM should be offered a renal mass biopsy when the result of the biopsy may alter their management *(Adopted from Kidney Cancer Research Network of Canada [KCRNC] consensus on the role of renal mass biopsy in the management of kidney cancer; expert opinion)*.
6. Patients with features suspicious of hereditary renal cell carcinoma (RCC) should be offered genetic counselling *(Adopted from CUA guideline on genetic screening for hereditary RCC; expert opinion)*.
7. For patients with SRM suspicious for renal malignancy AND significant comorbidities and/or limited life expectancy, observation (or watchful waiting) is recommended as the preferred strategy for patients *(Strong recommendation, high certainty in evidence of effects)*.
8. For patients with a suspected renal malignancy measuring <2 cm in diameter, active surveillance is suggested as the preferred strategy, given their slow growth rate and low probability of aggressive histology *(Conditional recommendation, moderate certainty in evidence of effects)*.
9. For patients with a suspected renal malignancy measuring 2–4 cm in diameter, active surveillance and definitive treatment (partial nephrectomy or percutaneous thermal ablation) are suggested as management options *(Conditional recommendation, low certainty in evidence of effects)*.
10. For patients with a suspected renal malignancy, the choice of treatment should be personalized using a shared decision-making approach, after proper counselling and while taking into account tumor characteristics, patient factors, and patient preferences and values *(Expert opinion)*.

11. For patients with a suspected renal malignancy who prefer management by upfront definitive treatment, surgery *or* percutaneous thermal ablation are suggested *(Conditional recommendation, low certainty in evidence of effects)*.
12. Patients with a suspected renal malignancy who prefer management by upfront definitive treatment should be informed of the higher uncertainty surrounding the data on the efficacy and harms of percutaneous thermal ablation treatment compared to surgery *(Expert opinion)*.
13. Patients with a suspected renal malignancy who opt to be treated by percutaneous thermal ablation should have a renal mass biopsy performed prior to, or at the time of thermal ablation *(Adopted from KCRNC consensus on the role of renal mass biopsy in the management of kidney cancer; expert consensus)*
14. For patients with suspected malignant SRM undergoing surgery, partial nephrectomy is recommended over radical nephrectomy *(Strong recommendation, moderate certainty in evidence of effects)*.
15. For patients with suspected renal malignancy undergoing partial nephrectomy, a minimally invasive approach (robotic-assisted or conventional laparoscopy) is suggested over an open approach, when technically feasible and oncologically safe *(Conditional recommendation, moderate certainty in evidence of effects)*.
16. For patients with suspected renal malignancy undergoing radical nephrectomy, a conventional laparoscopic approach is recommended over open or robotic-assisted approaches *(Strong recommendation, moderate certainty in evidence of effects)*.
17. For patients undergoing percutaneous thermal ablation for a suspected renal malignancy, cryoablation and radio-frequency ablation are both suggested as options for management, as they yield similar oncological outcomes and adverse events *(Conditional recommendation, moderate certainty in evidence of effects)*.
18. Patients under active surveillance should be monitored until the oncological risk increases, they select intervention, or the benefits of treatment outweigh the competing risks. The factors that define oncological risk are not completely elucidated but the most well-accepted factors are: growth of tumor to >4 cm, consecutive growth rate >0.5 cm/year, progression to metastases, and patient's choice *(Clinical principle)*.
19. Patients with suspected tumor growth on ultrasound imaging should undergo cross-sectional imaging to confirm growth prior to intervention *(Expert opinion)*.
20. For patients with suspected renal malignancy who opted to be managed by active surveillance, routine abdominal ultrasound (assuming good visualization and good agreement in size measurements between ultrasound and cross-sectional imaging) is suggested until definitive treatments are no longer considered (i.e., watchful waiting) *(Conditional recommendation, low certainty in evidence of effects)*.
21. For patients with suspected renal malignancy who opted to be managed by active surveillance, chest X-ray imaging is suggested until definitive treatments are no longer considered (i.e., watchful waiting) *(Conditional recommendation, low certainty in evidence of effects)*.
22. The panel was unable to achieve a consensus as to the frequency of abdominal imaging, which varied from at least once every 3–6 months for the first year and then once every 6–12 months if the lesion remains stable. The same can be said regarding the frequency of chest imaging, which varied from for-cause to once a year *(Expert opinion)*.
23. Patients with RCC who have undergone definitive treatment should be followed with routine chest and abdominal imaging to rule out recurrence or progression to metastasis *(Adopted from CUA guideline for followup of patients after treatment of non-metastatic RCC; expert opinion)*.
24. Patients with an estimated glomerular filtration rate (eGFR) <45 ml/min/1.73m^2 or with progressive chronic kidney disease following definitive treatment should be considered for a referral to a nephrologist (or their general practitioner), especially if associated with proteinuria *(Adopted from CUA guideline for followup of patients after treatment of non-metastatic RCC; conditional recommendation, low certainty in evidence of effects)*.

Introduction

The incidence of small renal masses (SRM) is increasing around the world largely due to the increasing use of abdominal imaging.[1,2] Although 10–30% of these SRM are benign, the increase in SRM detection has also led to an increase in the detection of renal cell carcinoma (RCC).[3-5] In 2020, it was estimated that approximately 7500 Canadians would be diagnosed with a kidney cancer.[6]

There are several well-accepted treatment strategies available to manage SRM, and in the absence of high-quality evidence comparing each option, the best treatment strategy remains debated and may vary by patient. The most accepted treatment modalities include surgical excision (partial/radical nephrectomy), thermal ablation (cryoablation/radio-frequency ablation), and active surveillance. Even though many small cancers behave in an indolent fashion and have a low metastatic potential, the vast majority of patients receive invasive treatments.[3,7] In an attempt to decrease overtreatment of patients with SRM, renal mass biopsies have been proposed as a diagnostic test that may help guide management.[8]

There is no "one-size-fits-all" strategy to the management of patients with SRM; shared decision-making must consider

tumor characteristics, competing medical risks (age, renal function, comorbidities, etc.), and patient values and preferences to produce individualized management plans, recognizing gaps remaining in the natural history of observed renal masses. The objective of this guideline is to provide evidence-based recommendations to help clinicians and patients in the evaluation and management of SRM.

Definition of small renal masses

For the purpose of this guideline, the panel has focused their recommendations on the management small, solid, enhancing renal masses measuring ≤4 cm on cross-sectional imaging and with features suspicious of a cT1a RCC (i.e., no radiographical evidence of tumor thrombus, renal fat, and/or renal sinus fat invasion).

As the management of cystic renal lesions and angiomyolipomas are already the topic of separate guidelines, the review of these entities was not included in the current document.[9,10] *[Editor's note: The CUA guideline on the management of cystic renal lesions is currently being updated and should be available in 2022.]*

Methods

In October 2020, the guideline panel met and discussed key components of the guideline. Several questions were prioritized and were chosen to be developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.[11] A comprehensive literature search was completed in Medline, Embase, and PubMed to identify existing systematic reviews and meta-analyses on the topic, as well as additional relevant observational or randomized controlled studies. Recommendations were based on the most recent and most comprehensive meta-analyses available. When meta-analyses were not available, questions were answered based on selected observational or randomized controlled studies. The evidence was presented in evidence profiles and evidence-to-decision tables using GRADEpro.

The guideline panel developed the recommendations by majority during four teleconference meetings. The panel considered the tradeoff between undesirable and desirable effects of each management strategy, the required resources, and the economical impact of each intervention. In the absence of evidence on the topic, the panel estimated the patients' values and preferences by reflecting on their own values and preferences, were they faced with the decision to choose a treatment for the management of a SRM. Two of the panelists were non-clinician patient participants. They represented the patient stakeholder group Kidney Cancer Canada.

The strength of each recommendation was rated as strong or conditional (weak) as per the GRADE framework. Strong recommendations were made when the desirable benefits of treatment outweighed the undesirable consequences (harms) and are worded as *recommends*. Conditional recommendations were made when the benefits of treatment probably outweighed the harms and are worded as *suggests*. When insufficient evidence was available for a recommendation, the panel reported additional information as clinical principle or as expert opinion. All final recommendations were reviewed and approved by all members of the guideline panel.

Diagnostic evaluation

Bloodwork

1. **Patients diagnosed with a SRM should undergo routine laboratory investigations, including at a minimum a serum creatinine (Cr) and glomerular filtration rate (GFR)** *(Clinical principle)*.

In patients with a SRM suspicious for renal malignancy, routine blood work, such as serum Cr and GFR, is suggested to better counsel patients on the potential harms of treatments. For patients with renal impairment and for whom an invasive treatment is being considered, a urinalysis to screen for proteinuria is also suggested.[12,13] Urine albumin-to-creatinine ratio may also be used. Likewise, a complete blood count and a coagulation study may also be considered for patients being considered for an invasive treatment.[14] Although uncommon, synchronous metastasis can be found in patients diagnosed with a SRM.[15] For patients with features suspicious for liver metastases, liver function tests are suggested.[16] For patients presenting with bone pain, alkaline phosphatase, serum calcium, and lactate dehydrogenase (LDH) should be ordered.[17] For patients where urothelial cancer is suspected, a urine cytology and endoscopic assessment should be performed.[18]

Imaging

2. **Patients with a SRM incidentally discovered on routine imaging should be investigated with a multiphasic, contrast-enhanced, abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scan** *(Clinical principle)*.
3. **For patients with suspected renal malignancy, a baseline chest X-ray is suggested to assess for pulmonary metastases** *(Conditional recommendation, low certainty in evidence of effects)*.
4. **Patients with a SRM and pre-existing renal dysfunction in whom a radical nephrectomy is being considered may be offered renal scintigraphy when the result may alter their management** *(Clinical principle)*.

Most renal masses are incidentally discovered on routine imaging.[1] As many as 10–30% of all SRM are benign, and the majority of malignant lesions have low metastatic potential.[3] An abdominal, multiphasic, contrast-enhanced CT or MRI is mandatory to characterize the mass, as enhancement is the most important criterion to confirm its solid nature.[19] Non-contrast CT scans can also be useful to identify macroscopic fat, a feature consistent with an angiomyolipoma, a benign lesion. Alternatively, a non-enhanced CT after an ultrasound confirming the solid nature of a mass may be acceptable for patients unable to receive contrast due to advanced renal impairment.

Under 2% of malignant SRM will be metastatic at the time of diagnosis.[15] Contrast-enhanced abdominal imaging is useful to exclude the presence of visceral metastases and tumor thrombus. To complete the metastatic workup, the chest should be imaged, as the lungs are the most common site of metastases.[20] Although the sensitivity for metastases is lower with chest X-ray compared to a chest CT,[21] the panel suggests a chest X-ray as the initial imaging of choice, given the low incidence of metastasis and the lower harms and cost to the healthcare system compared to chest CT. If any abnormalities are detected on the chest X-ray, a chest CT should be performed. Bone scintigraphy and brain imaging should only be performed for-cause in patients with symptoms, as most bone/brain metastases are symptomatic at diagnosis.[22,23] Renal scintigraphy may be considered in patients with renal impairment and in whom a radical nephrectomy is considered or in whom the assessment of differential renal function could alter management.

Role of renal mass biopsy

5. **Patients with a SRM should be offered a renal mass biopsy when the result of the biopsy may alter their management** (*Adopted from Kidney Cancer Research Network of Canada [KCRNC] consensus statement on the role of renal mass biopsy in the management of kidney cancer; expert opinion*).[8]

As stated previously, 10–30% of SRM will be benign and the majority of malignant lesions will be of low metastatic potential.[3] Current conventional imaging modalities and other tumor factors typically associated with increased risks of malignancy (i.e., size, growth rate, etc.) cannot reliably differentiate a benign lesion from a malignant one. Consequently, renal mass biopsies have been used as a means to identify the histology of a SRM before treatment, with the objective to inform management and decrease overtreatment.[4,24]

The role of renal mass biopsy in the management of kidney cancer in Canada is the topic of a KCRNC consensus statement that has been endorsed by the Canadian Urological Association.[8] Consequently, only key components will be reviewed here.

Like any other diagnostic test, renal mass biopsy should be offered to patients in whom the result may impact management. A renal biopsy should not be performed for patients where its outcome will not influence treatment decision (e.g., someone not fit for invasive treatment or a patient who seeks surgical removal regardless of histology). A recent meta-analysis by Marconi et al has demonstrated that biopsies yielded a median diagnostic rate of 92% (interquartile rate [IQR] 80.6–96.8%), with a concordance rate for histology and grade (four-tier system) of 90.3% (IQR 84–94.4%) and 62.5% (IQR 52.1–72.1%), respectively.[24] In addition to identifying benign lesions, a renal mass biopsy can also be helpful for risk stratification. Finelli et al used an active surveillance cohort where all patients were characterized by an upfront renal mass biopsy.[25] They found growth rates varied by RCC subtype. Clear-cell RCC had the fastest growth rates (average 0.25 cm/year) and papillary type 1 tumors, the slowest (average 0.11 cm/year).[25] Renal mass biopsies have also been shown to be safe, with a median overall complication rate of 8.1% (IQR 2.7–11.1%), with the vast majority of these complications reported as Clavien-Dindo <2 (>99%).[24] Additionally, although there are some reports of biopsy tract seeding with tumor, the evidence remains controversial and this risk is likely very low.[26,27]

Before proceeding with a renal mass biopsy, the panel believes it is important to inform the patients of its benefits and harms, including the non-diagnostic rate and the unknown false-negative rate; most series do not report the false-negative rate, as masses with a benign biopsy result are not generally removed. False-negative rates have been reported to be as low as 3.5% in one Canadian series and as high as 31.5% in a meta-analysis where "normal parenchyma" biopsies were considered benign histology as opposed to non-diagnostic.[28,29] The authors of this guideline feel it is also important to consider that the diagnostic test characteristics and complication rates reported above are from experienced biopsy centers, and that results may not be generalizable to less experienced centers. Additionally, biopsy outcomes may also be influenced by a number of patient and tumor factors, such as size of the mass, consistency (cystic or necrosis component), location (exophytic vs. endophytic), and skin-to-tumor distance.[5,28,30] Thus, the decision to proceed with a biopsy should be made through a shared decision-making approach after weighing the potential benefits and harms of the diagnostic test and discussing the patients' preferences and values.

Role of genetic assessment

6. **Patients with features suspicious of hereditary RCC should be offered genetic counselling** (*Adopted from Canadian Urological Association guideline on genetic screening for hereditary renal cell cancers; expert opinion*)

The role of genetic testing in the management of kidney cancer is extensively discussed in a separate CUA clinical practice guideline by Reaume et al.[31] Briefly, as suggested by the aforementioned guideline and endorsed by this panel, patients with the criteria presented in Table 1 should be offered genetic counselling and referred for genetic assessment.

Management of small renal masses

7. **For patients with a SRM suspicious for renal malignancy AND significant comorbidities and/or limited life expectancy, observation (or watchful waiting) is recommended as the preferred strategy for patients** *(Strong recommendation, high certainty in evidence of effects)*.
8. **For patients with a suspected renal malignancy measuring <2 cm in diameter, active surveillance is suggested as the preferred strategy, given their slow growth rate and low probability of aggressive histology** *(Conditional recommendation, moderate certainty in evidence of effects)*.
9. **For patients with a suspected renal malignancy measuring 2–4 cm in diameter, active surveillance and definitive treatment (partial nephrectomy or percutaneous thermal ablation) are suggested as management options** *(Conditional recommendation, low certainty in evidence of effects)*.
10. **For patients with a suspected renal malignancy, the choice of treatment should be personalized using a shared decision-making approach, after proper counselling and while taking into account tumor characteristics, patient factors, and patient preferences and values** *(Expert opinion)*.

Table 1. Criteria that should prompt genetic counselling

Patients with any renal tumor AND any of the following: a. Bilateral or multifocal tumors b. Early age of onset (≤45 years of age) c. 1st or 2nd degree relative with any renal tumor d. History of pneumothorax, lymphangiomyomatosis or childhood seizure disorder* e. Presence of skin leiomyomas or fibrofolliculomas/trichodisomas* f. Concomitant tumors*: Pheochromocytoma, paraganglioma, hemangioblastoma (retina, brainstem, cerebellum or spinal cord), early one onset of multiple uterine fibroids *Personal history or presence in 1st degree relative
Patients with non-clear-cell carcinoma with unusual associated features (e.g., chromophobe, oncocytic, or hybrid tumors)
Patients who report a family member with a known clinical or genetic diagnosis that renders him/her at higher risk of being diagnosed with kidney cancer

Adapted from Reaume et al.

There are currently three well-documented management options for the treatment of SRM. Current evidence comparing each of these treatment options is of low quality and no one option has been demonstrated to be superior to another in a randomized controlled trial. Thus, the choice of treatment should be personalized using a shared decision-making approach, after proper counselling, according to each patient's values and preferences, and while factoring the patient's competing risks and tumor characteristics (Fig. 1). A summary of characteristics that may influence treatment decision is presented in Table 2. Prediction tools to estimate risk of other-cause mortality are available (e.g., https://studies.fccc.edu/nomograms/3) and can be helpful to guide management. A decision aid has also been developed to inform patients diagnosed with a SRM and may help facilitate shared decision-making (*https://decisionaid.ohri.ca/docs/das/Small_Kidney_Tumour_Treatment.pdf*).[32] The evidence supporting each recommendation and the different treatment strategies are summarized below.

Expectant management: Active surveillance vs. watchful waiting

Active surveillance is a strategy where patients are followed with serial, scheduled imaging to monitor the mass. With active surveillance, patients are offered a definitive treatment if there is evidence of disease progression or if their preferences change during the course of management. A comprehensive description of the indications for definitive treatment while on active surveillance is detailed below. This strategy differs from watchful waiting (the preferred strategy reserved for patients with limited life expectancy), where treatment is only considered for palliation of symptoms that may arise from disease progression rather than an attempt at cure. Patients managed by watchful waiting do not require regular imaging followup unless clinically indicated.

A meta-analysis of patients with a SRM has demonstrated that active surveillance was associated with a cancer-specific survival similar to other treatment strategies and has demonstrated a low associated risk of developing metastasis after short- to mid-term followup.[33] Results from the largest, multicenter, prospective study (Delayed Intervention and Surveillance for Small Renal Masses [DISSRM]) has demonstrated that most tumors grow slowly (median growth rate <0.1 cm/year) and that approximately 10–15% of patients will discontinue active surveillance in favor of definitive therapy over time.[34-36] Compared to the active surveillance cohort, the immediate intervention cohort had higher quality of life scores at baseline and throughout followup, but men-

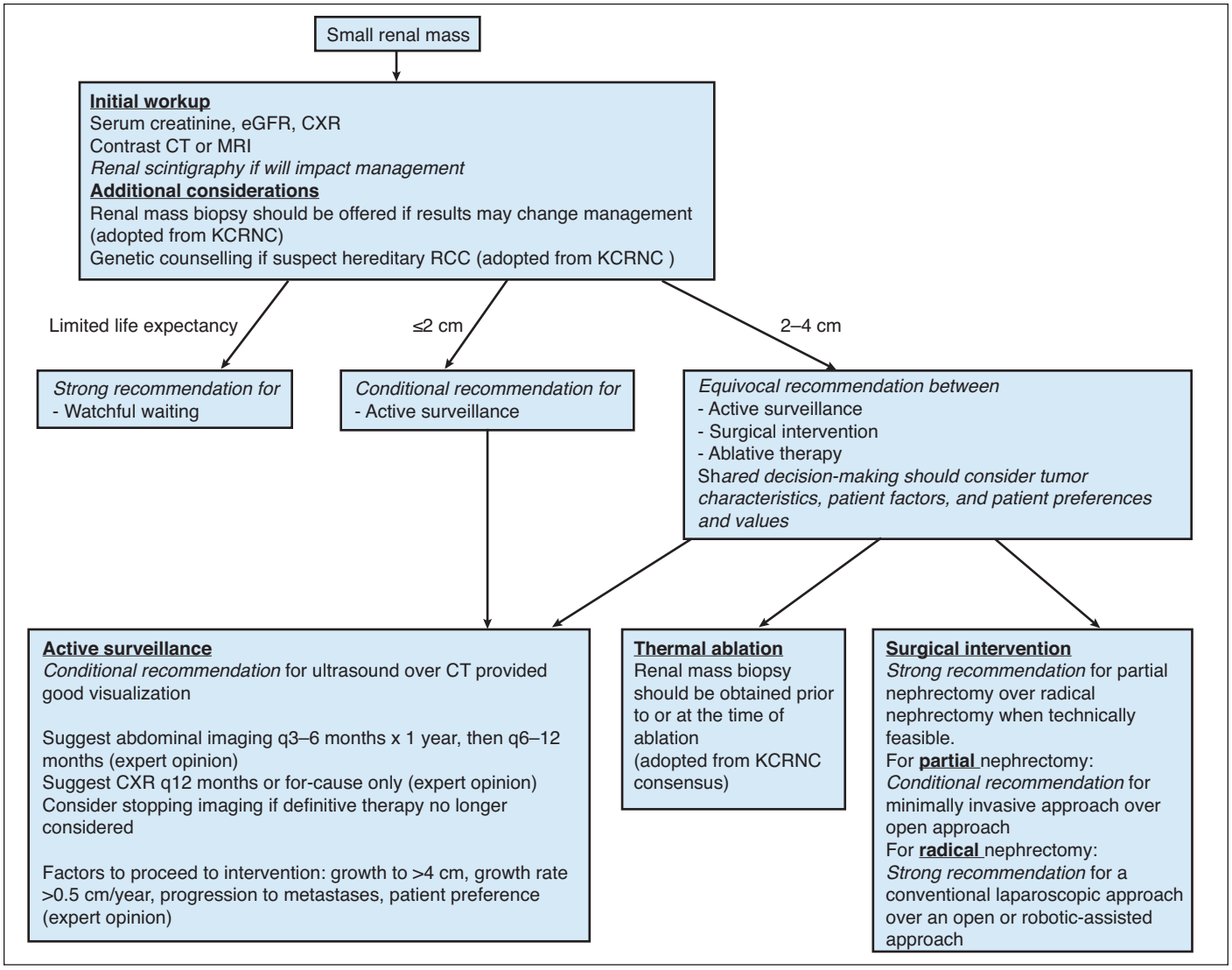

Fig. 1. Algorithm for the management of small renal masses. CT: computed tomography; CXR: chest X-ray; eGFR: estimated glomerular filtration rate; KCNRC: Kidney Research Network of Canada; MRI: magnetic resonance imaging.

tal health domains (including depression/anxiety domains) were not negatively affected while on active surveillance, and even improved over time.[37]

Importantly, although active surveillance was initially reserved for older, comorbid patients, recent evidence has demonstrated that this strategy is also safe among younger patients.[38] Evidence from the DISSRM registry demonstrated that there was no difference in terms of cancer-specific survival and overall survival among patients <60 years of age managed by either definitive treatment (n=156) or active surveillance (n=68). Rate of progression to definitive treatment was lower among patients that presented with a lesion <2 cm compared to patients who presented with a lesion that measured 2–4 cm (15.1% vs. 33.3%).

One caveat that should be discussed with patients about this management strategy, is that most active surveillance series are of relatively short followup (median 42 months, range 1–137 months) and based on older, more comorbid patients compared to surgical series.[39] Nevertheless, given the relatively high probability of benign histology (>20%) and indolent nature of most malignancies in this size range(>85%),[3] active surveillance is suggested as the preferred management strategy for patients with a lesion measuring <2 cm. Immediate, definitive treatment remains an option and should be discussed with patients to ensure they are fully informed. In patients with a lesion measuring 2–4 cm, there was no consensus on the preferred management strategy. **Although the panel members all recognized that active surveillance should be offered as an option to these patients, nearly 40% of the panel members felt that definitive treatment (surgery or thermal ablation) should be considered as the option of choice.** Given the varied

Table 2. Characteristics that may influence treatment decision

Patient	Tumor	Hospital-level
Patient preferences	Size	Access to healthcare
Age	Location	Access to thermal-ablative therapies locally
Comorbidities, including renal function	Number of lesions	Access to minimally invasive surgery locally
Frailty index score	Renal mass biopsy histology	
Medical history	Renal tumor complexity (nephrometry score)	
Surgical history		
Familial history		
Presence of symptoms		

growth rates by histological subtype, biopsy may also inform the management decision for patients considering active surveillance.[25] As stated, risks of active surveillance may be influenced by the characteristics presented in Table 2.

Definitive treatments

Surgery vs. percutaneous thermal-ablation

11. **For patients with a suspected renal malignancy who prefer management by upfront definitive treatment, surgery *or* percutaneous thermal ablation are suggested** *(Conditional recommendation, low certainty in evidence of effects).*
12. **Patients with a SRM should be informed of the higher uncertainty surrounding the data on the efficacy and harms of percutaneous thermal ablation treatment compared to surgery** *(Expert opinion).*
13. **Patients with a suspected renal malignancy who opt to be treated by percutaneous thermal ablation should have a renal mass biopsy performed prior to, or at the time of thermal ablation** *(Adopted from KCRNC consensus statement on the role of renal mass biopsy in the management of kidney cancer; expert consensus).*[8]

As stated, there is currently no randomized controlled trial comparing the outcomes of surgery and percutaneous thermal ablation for the management of patients with a SRM. A number of meta-analyses have compared the short-term and long-term outcomes of surgery and thermal ablation with the caveat that the data are based mostly on retrospective studies and are, therefore, prone to selection bias.[33,40-47] The non-randomized evidence seems to suggest that thermal ablation yields similar oncological outcomes compared to surgery. There is some evidence that seems to suggest that local recurrence is higher after thermal ablation than with partial nephrectomy;[41] however, when multiple ablative treatments were considered, local recurrence-free survival was comparable to partial nephrectomy.[47,48]

The most recent meta-analysis on the topic was performed by the European Association of Urology Renal Cell Cancer Guideline Panel and reported in 2020.[41] In this meta-analysis, 26 observational studies, totalling 16 780 patients, were included. The risk of bias assessment revealed high or uncertain risk of bias across all studies, owing to the included studies being retrospective, observational studies with poorly matched controls and relatively short followups. The data seem to suggest that percutaneous ablation is safe in terms of adverse events and complications, but its long-term oncological outcome compared to partial nephrectomy is uncertain. Compared to thermal ablation, surgery also has the advantage of providing definitive pathology specimen, which may be important for genetic counselling consideration.

Nevertheless, given the evidence, the panel is unable to suggest one approach over the other in patients who choose to undergo definitive treatment. Patients with a SRM should be informed of the higher uncertainty surrounding the data on the efficacy and harms of percutaneous thermal ablation treatment compared to surgery. Thus, the choice of treatment must be individualized according to each patient's values and preferences and according to patient, tumor, and hospital-level characteristics (Table 2). Importantly, patients choosing percutaneous thermal ablation as their treatment of choice should have a renal mass biopsy performed prior to, or at the time of thermal ablation to obtain histological confirmation and to help tailor the followup strategy.

Partial vs. radical nephrectomy

14. **For patients with suspected malignant SRM undergoing surgery, partial nephrectomy is recommended over radical nephrectomy** *(Strong recommendation; moderate certainty in evidence of effects).*

Surgical removal of a localized renal mass can be done through a radical or partial nephrectomy. Current evidence is mostly based on observational studies, either retrospective or prospective in design. So far, only one randomized controlled trial which closed prematurely due to poor accrual, has compared the oncological outcomes of patients with a localized renal mass (<5 cm in diameter) treated with a radical nephrectomy or a partial nephrectomy between 1992 and 2003. The results of this study showed comparable 10-year cancer-specific survival for both options, but an improved 10-year overall survival in favor of radical nephrectomy, with only a fraction of deaths (12 of 117) due to renal cancer.[49] These results have long been debated for a number of reasons, including its poor accrual, relatively high crossover rate, incomplete central pathology review, and most importantly, the overwhelming number of observational studies favoring partial nephrectomy over radical nephrectomy.[50,51]

A Cochrane review published in 2017 demonstrated that time to death of any cause was decreased using partial nephrectomy compared to radical nephrectomy (hazard ratio [HR] 1.5, 95% confidence interval [CI] 1.03–2.18).[52] This review was based on low-quality evidence, given the available data. Additionally, there was no difference identi-

fied between both approaches in terms of significant adverse events (risk ratio [RR] 2.04, 95% CI 0.19–22.34) and time to recurrence (HR 1.37, 95% CI 0.58–3.24). The absence of difference in the rate of significant harm with regards to both surgeries is especially true for easily resectable tumors in the presence of a normal contralateral kidney.[49] Although debated, one of the potential explanations for the improved survival is that partial nephrectomy results in an increased renal function preservation and subsequent decrease in cardiovascular events compared to radical nephrectomy.[53-57]

Therefore, given the overwhelming number of observational studies demonstrating equivalent oncological outcomes, increased renal function preservation, and comparable significant harms (at least in easily resectable tumors), partial nephrectomy is recommended as the preferred approach when technically feasible in expert hands.

In older patients and in those with more comorbidities/limited life expectancy, the potential benefit of partial over radical nephrectomy is less clear. Likewise, the benefit of partial over radical nephrectomy for patients with complex renal masses is subject to some debate, given the higher incidence of significant complications and potentially higher upstaging to pT3a.[58-62] Consequently, for some patients, the increased risk of harms may outweigh the potential benefits of partial nephrectomy. Thus, radical nephrectomy should be reserved for patients in whom a partial nephrectomy or percutaneous thermal ablation cannot be performed even in experienced centers or for patients who are unwilling to accept the short-term risks of partial nephrectomy/thermal ablation compared to radical nephrectomy. A consideration should also be given for a preoperative renal mass biopsy in patients for whom a radical nephrectomy is planned to avoid removal of the entire organ for a benign lesion.

Nephrometry scoring systems have been developed to aid in communicating renal tumor complexity in a standardized fashion — whether in clinical or research contexts — and to predict treatment outcomes. The most commonly used systems are the RENAL (radius, exophytic/endophytic, nearness, anterior/posterior, location), PADUA (preoperative aspects and dimensions used for an anatomical), and SPARE (Simplified PADUA Renal) nephrometry scores (Table 3).[63-65] The first two nephrometry scoring systems are the most extensively studied and have been shown to be predictive of length of hospital stay, tumor pathology, surgical margins, tumor growth rate, renal function outcomes, and survival.[59] The RENAL nephrometry score has also been shown to be useful for predicting outcomes and complications following percutaneous ablation.[58,60] One caveat of using these scoring systems includes interobserver variability in assessments and inconsistent associations with outcome measures.[66] Further work is needed to determine to what extent formal nephrometry scores improve upon subjective estimation of tumor complexity by individual surgeons. Nonetheless, nephrometry scoring systems represent a common language that can standardize classification of renal tumor complexity, allow for comparison of surgical outcomes, improve patient coun-

Table 3. Renal nephrometry scoring systems

R.E.N.A.L.[63]	PADUA[64]	SPARE[65] Simplified PADUA system
R: Radius (maximal diameter) ≤4 cm: 1 point >4 cm & <7 cm: 2 points ≥7 cm: 3 points	Longitudinal (polar) location relative to sinus lines* Superior/inferior: 1 point Middle: 2 points	Maximal tumor diameter ≤4 cm: 0 points >4 cm & <7 cm: 2 points ≥7 cm: 4 points
E: Exo/endophytic properties ≥50% exophytic: 1 point <50% exophytic: 2 points Entirely endophytic: 3 points	Exophytic rate ≥50% exophytic: 1 point <50% exophytic: 2 points Entirely endophytic: 3 points	Exophytic rate ≥50% exophytic: 0 points <50% exophytic: 1 point Entirely endophytic: 2 points
N: Nearness to collecting system ≥7 mm: 1 point >4 mm & <7 cm: 2 points ≤4 mm: 3 points	Renal rim location: Lateral: 1 point Medial: 2 points	Renal sinus Not involved: 0 points Involved: 3 points
A: Anterior/posterior location Descriptor - no points given	Renal sinus Not involved: 1 point Involved: 2 points	Renal rim location: Lateral: 0 points Medial: 2 points
L: Location relative to polar lines* Entirely above upper or below lower polar lines: 1 point Lesion crosses polar line: 2 points >50% of mass is across polar line, or mass crosses axial renal midline, or mass is entirely between polar lines: 3 points	Urinary collecting system Not involved: 1 point Dislocated/infiltrated: 2 points	Scoring: Low complexity: 0–3 points Moderate complexity: 4–7 points High complexity: ≥8 points
Scoring: Low complexity: 4–6 points Moderate complexity: 7–9 points High complexity: 10–12 points	Maximal tumor diameter ≤4 cm: 1 point >4 cm & <7 cm: 2 points ≥7 cm: 3 points	
	Scoring: Low complexity: 6–7 points Moderate complexity: 8-9 points High complexity: 10–14 points	

selling, and inform surgical decision-making. Renal tumor complexity should be factored into management decisions of a SRM and formal nephrometry scoring can be helpful in this regard.

Minimally invasive surgery vs. open surgery

15. **For patients with suspected renal malignancy undergoing partial nephrectomy, a minimally invasive approach (robotic-assisted or conventional laparoscopy) is suggested over an open approach when technically feasible and oncologically safe** *(Conditional recommendation, moderate certainty in evidence of effects)*.
16. **For patients with suspected renal malignancy undergoing radical nephrectomy, a conventional laparoscopic approach is recommended over open or robotic-assisted approaches** *(Strong recommendation, moderate certainty in evidence of effects)*.

Partial nephrectomy can be performed through different approaches — open, conventional laparoscopy, or robotic-assisted. A number of meta-analyses have compared open to minimally invasive partial nephrectomy. All three techniques seem to offer similar oncological outcomes; however, minimally invasive techniques are generally associated with significantly less blood loss (and blood transfusion), shorter hospitalization stay, less severe postoperative complications, and potentially, better renal function preservation.[67-69] There does not seem to be any clinically significant difference between conventional laparoscopy and robotic-assisted partial nephrectomy in terms of oncological and functional outcomes, although robotic-assisted surgery is potentially associated with higher incidence of major bleed and shorter ischemia time, albeit early in the robotic experience era.[67-69] Thus, given the evidence, when technically feasible and oncologically safe, minimally invasive techniques — conventional laparoscopy or robotic-assisted partial nephrectomy — should be favored over open partial nephrectomy. However, open partial nephrectomy remains appropriate for complex SRM, if the alternative is radical nephrectomy.

If a radical nephrectomy is to be performed, a minimally invasive approach is favored over open surgery. Results from a recent meta-analysis showed that minimally invasive approaches offer key advantages over an open approach, such as decreased hospitalization stay and fewer complications, while providing similar oncological outcomes.[70] Conventional laparoscopy and robot-assisted radical nephrectomy seem to result in similar surgical outcomes, but owing to the higher total cost, higher equity, and the lower surgical complexity of a radical nephrectomy (compared to a partial nephrectomy), conventional laparoscopic radical nephrectomy is strongly favored over robotic radical nephrectomy.[71]

Percutaneous cryotherapy vs. percutaneous radio-frequency ablation

17. **For patients undergoing percutaneous thermal ablation for a suspected renal malignancy, cryoablation and radio-frequency ablation are both suggested as options for management, as they yield similar oncological outcomes and adverse events** *(Conditional recommendation, moderate certainty in evidence of effects)*.

Percutaneous ablation of a SRM is most commonly performed using cryoablation (tissue damage by freezing) or radio-frequency ablation (tissue damage by heat). A number of retrospective studies have compared both these ablative techniques and have concluded that both yield similar oncological outcomes and adverse events.[44,72-75] Consequently, as both techniques have their own advantages and disadvantages, the choice of approach should be based on availability, provider's experience, and tumor-related factors (size, location, adjacent structures, etc.). Regardless on the type of technique chosen, it is the panel's opinion that a renal tumor biopsy should be performed prior to ablation (in a separate setting or at the time of ablation), as this will achieve histological confirmation and will help tailor the frequency of followup imaging. It is also important to note that most series reported their outcomes for tumors <3 cm in size.

Even though the treatment of 3–4 cm tumors is possible, patients should be appropriately counselled as to the higher likelihood of complications and local recurrence compared to <3 cm tumors.[58,76-80] For these patients, although the literature is prone to biases and subject to debate among experts, there is some evidence suggesting that cryoablation leads to lower cancer-specific mortality compared to radio-frequency ablation.[80,81] Thus, when both ablation approaches are available, it would seem reasonable to favor cryoablation for tumors 3–4 cm.

Indications for definitive treatment while on active surveillance

18. **Patients under active surveillance should be monitored until the oncological risk increases, they select intervention, or the benefits of treatment outweigh the competing risks. The factors that define oncological risk are not completely elucidated but the most well-accepted factors are: growth of tumor to >4 cm, consecutive growth rate >0.5 cm/year, progression to metastases, and patient's choice** *(Clinical principle)*.
19. **Patients with suspected tumor growth on ultrasound imaging should undergo cross-sectional imaging to confirm growth prior to intervention** *(Expert opinion)*.

Delayed intervention, including partial or radical nephrectomy, or percutaneous ablation, is instituted in 0–30% of

patients on active surveillance.[82] Indications for intervention vary and involve an assessment of the competing risks of RCC progression vs. other causes of mortality, factoring in patient values and preferences through shared decision-making.

Common reasons for intervention include tumor growth rate and absolute tumor size attained. Both maximum linear tumor diameter and volumetric measurements can be used during surveillance. Volumetric assessments may be more accurate, given that tumors are not always spherical, but at the same time, are less practical and less familiar to clinicians. It is, however, important to note that none of these indications have been validated.

Average growth rate for a SRM during surveillance is typically 0.1–0.25 cm per year.[83-88] Aggressive tumors have a faster growth rate. For example, in a pooled analysis of patients who had metastatic progression on surveillance, average growth rate was 0.8 cm per year.[87] As such, rapid growth rate is an indication for intervention, with important additional considerations, such as age, comorbidities, patient's preference, etc. (Table 2). The DISSRM registry used growth rate >0.5 cm per year as a criterion for progression, while the Renal Cell Carcinoma Consortium of Canada used doubling of calculated tumor volume within 12 months as part of their definition of progression.[25,84] Several limitations of growth rate assessments are important. First, growth rates should be assessed cautiously in patients who would require comparisons of tumor size measured using different imaging modalities. If tumor growth is suspected based on ultrasound, this should be confirmed with cross-sectional imaging prior to intervention. Second, tumor growth may be exponential, and therefore, tumor growth may increase over time. Third, intra- and inter-observer variability in the measurement of tumor diameter on imaging exist and must be considered.[89] Fourth, some tumors may exhibit stochastic growth, further contributing to variability.[25] For patients on active surveillance with concerning tumor growth and without a prior renal mass biopsy, one can be considered if it will change management.

Tumor size is associated with risk of harboring malignancy, the risk of aggressive histology, including high-grade disease,[90,91] the risk of developing metastatic disease,[92-94] and survival outcomes.[95] The Renal Cell Carcinoma Consortium of Canada and the DISSRM registry consider tumor diameter >4 cm as a criterion for progression.[83,84] A larger tumor size and/or change in tumor complexity (as reflected by the nephrometry score) may also limit the feasibility of certain interventions. Clinicians should review images in each instance to ensure a window of treatment opportunity is not inadvertently missed; this should be factored into decision-making.

Several patient factors may also influence decisions on delayed interventions.[96] Patient age, frailty, and comorbidities should all be factored into estimating risk of mortality for competing medical conditions. In elderly, frail, and/or comorbid patients, the risks of intervention are not trivial and there is a stronger rationale for deferring intervention or perhaps for transitioning to watchful waiting. Patient anxiety should also be factored into decision-making, although it should not be the sole criterion for intervention. It is the role of the clinician to provide appropriate counselling to address anxiety, which may include the use of decision aids.[32] One study found that depression and anxiety were not adversely affected while on active surveillance for a renal mass, and in fact, improved with time.[97]

Followup

Followup during active surveillance

20. **For patients with suspected renal malignancy who opted to be managed by active surveillance, routine abdominal ultrasound (assuming good visualization and good agreement in size measurements between ultrasound and cross-sectional imaging) is suggested until definitive treatments are no longer considered (i.e., watchful waiting)** *(Conditional recommendation, low certainty in evidence of effects).*
21. **For patients with suspected renal malignancy who opted to be managed by active surveillance, chest X-ray imaging is suggested until definitive treatments are no longer considered (i.e., watchful waiting)** *(Conditional recommendation, low certainty in evidence of effects).*
22. **The panel was unable to achieve a consensus as to the frequency of abdominal imaging, which varied from at least once every 3–6 months for the first year and then once every 6–12 months if the lesion remains stable. The same can be said regarding the frequency of chest imaging, which varied from for-cause to once a year** *(Expert opinion).*

The objective of active surveillance is to delay treatment until evidence of disease progression. To do so, it is important to obtain routine abdominal imaging during followup. Several imaging modalities may be used, such as ultrasound, CT scan, and MRI. Cross-sectional imaging using CT or MRI provides the most accurate assessment of the size and complexity of a SRM. Ultrasound is an alternative for imaging surveillance, as it is cost-effective, offers adequate assessment of growth, avoids ionizing radiation, and is more readily accessible/available than CT and MRI. For these reasons, abdominal ultrasound is suggested as the imaging of choice during followup for patients on active surveillance. One caveat of ultrasound is that it is operator-dependent and cross-modality comparisons of size measurements with CT/MRI can sometimes be challenging. Therefore, if tumor growth is suspected on surveillance ultrasound or the mass cannot be reliably identified

by ultrasound, an abdominal cross-sectional imaging (CT or MRI) for confirmation is required.

Although a rare event, patients on active surveillance may develop distant metastases. For this reason, most renal mass active surveillance series include chest X-rays as part of their surveillance protocols, while none performed CT scans of the chest routinely.[82] Asymptomatic patients with tumors <4 cm in size have a <1% probability of harboring pulmonary metastases, as assessed by CT chest,[98,99] and data from the DISSRM registry has revealed that all abnormalities noted on the chest X-ray either at baseline or during surveillance were not metastasis-related.[100] The low prevalence of pulmonary metastases combined with the suboptimal sensitivity and specificity limit the utility and cost-effectiveness of chest X-ray surveillance in patients undergoing active surveillance for SRM. Nevertheless, despite its limitation, the panel suggests performing chest X-ray imaging during followup, as the members placed a higher importance on finding metastases than on the potential harms and cost of chest imaging.

Followup schedules for active surveillance are heterogeneous between studies and even within series. To date, the optimal schedule has not been agreed upon.[82] Nevertheless, the panel members believed that patients should be followed with abdominal imaging every 3–6 months for the first year and then every 6–12 months, if the lesion remains stable. Frequency of imaging should be increased for patients demonstrating tumor growth if the patient remains on active surveillance. Patients should be followed with abdominal imaging until definitive treatments are no longer considered. Likewise, there is no agreed-upon optimal followup schedule for chest imaging. The panel members were nearly evenly split as to the frequency of chest imaging and thus, they were not able to achieve a consensus as to its frequency, which varied from for-cause (52.6% of members) to once a year (47.4% of members).

Followup after definitive treatment

23. **Patients with a RCC who have undergone definitive treatment should be followed with routine chest and abdominal imaging to rule out recurrence or progression to metastasis** *(Adopted from CUA guideline for followup of patients after treatment of non-metastatic renal cell carcinoma; expert opinion).*
24. **Patients with an estimated GFR <45 ml/min/1.73m^2 or with progressive chronic kidney disease following definitive treatment should be considered for a referral to a nephrologist (or their general practitioner), especially if associated with proteinuria (***Adopted from CUA guideline for followup of patients after treatment of non-metastatic renal cell carcinoma; conditional recommendation, low certainty in evidence of effects).*

The readers interested in receiving in-depth guidance of the followup of patients with hereditary RCC should review the guideline by Lattouf et al.[101] Likewise, the detailed recommended followup after definitive treatment of incidental RCC is extensively reviewed in the guideline by Kassouf et al. Briefly, studies have shown that patients with pT1a RCC are at low risk of local recurrence or metastases after surgery to remove the mass (5% for recurrence or metastases).[102,103] Recommended surveillance after surgery includes: annual blood test (complete blood count, serum chemistries, and liver function test) and annual chest X-ray, as well as abdominal CT, MRI, or ultrasound at 24 and 60 months. A contrast-enhanced abdominal CT scan/MRI at 3–12 months post-treatment for patients treated with partial nephrectomy is optional to evaluate the residual baseline renal appearance. Due to the higher risk of residual disease and need for retreatment after thermal ablation, a contrast-enhanced abdominal CT scan/MRI is recommended at three, six, and 12 months post-treatment, and then annually, in addition to annual bloodwork and chest X-ray. Patients with postoperative chronic renal failure should be referred to nephrology or to their general practitioner for proper assessment, given the potentially higher risk of developing cardiovascular disorders.[57]

Future directions

Novel non-surgical therapies

In addition to cryoablation and radio-frequency ablation, there are currently three other types of ablative therapies available to treat SRM: microwave ablation,[44,104-107] irreversible electroporation, and stereotactic body radiation therapy (SBRT)

Although promising, as long-term data on the outcomes of these techniques are lacking, the panel still considers these approaches experimental and long-term data will be required before making any recommendations on the role of these newer ablative techniques.

Novel diagnostic imaging

MRI is an increasingly used alternative to CT scan and it is generally perceived as a comparable alternative. There are a number of reports evaluating a potential role for multiparametric MRI (mpMRI) as an imaging tool to help predict histological subtype.[108-110] Recently, a clear-cell likelihood score has been proposed to determine the risk of a lesion being clear-cell RCC using a non-invasive approach.[104,110,111] This score has been proposed as a tool to reduce the number of patients who undergo routine biopsy and to help guide management, although this remains to be validated.

Like mpMRI, 99mTc-sestamibi single-photon emission computed tomography (SPECT)/CT is being evaluated for

detecting oncocytomas and other benign renal lesions.[112-117] Early results appear promising but require further validation before being routinely recommended in Canada.

Novel diagnostic biomarkers

In recent years, there has been extensive research focused on the identification of a reliable biomarker as an adjunct to imaging and an alternative to renal mass biopsy.[118,119] Several studies have evaluated the role of liquid biopsy assays, including circulating tumor cells, circulating cell-free DNA, and microRNAs, as less invasive techniques for early detection of RCC and for discrimination between benign and malignant renal masses.[120-133] Although early detection of RCC through easily available circulating biomarkers is of great interest and a promising research avenue, the diversity of techniques and current lack of validation studies preclude any meaningful conclusions. The panel hopes that recommendations will be made possible by the publication of new studies on the topic for the next iteration of this guideline.

Knowledge gaps

In addition to the lack of high-quality studies comparing the different treatment options for SRM, one other area of clear knowledge gap identified by the panel is the current lack of studies on quality-of-life outcomes and on patients' values and preferences. These types of studies are of great importance to guideline panels that must make recommendations based on the tradeoff of desirable and undesirable outcomes of the management alternatives they are considering using average or typical values and preferences. This concept is highlighted by the widely adopted GRADE framework for clinical guidelines. As values and preferences studies on the topic are currently absent, the panel had to speculate, with the help of patient representatives, on the actual patients' value and preferences for the management of SRM, speculation that may diverge substantially from the true situation. The panels hopes that studies will have attempted to fill this important knowledge gap in time for the next iteration of this guideline.

Summary

The incidence of SRM is increasing and many of these incidentally found lesions will be either benign or of low metastatic potential. Immediate invasive treatment of all patients with SRM leads to significant overtreatment. Importantly, most of the evidence on management options for patients with SRM is based on observational data, which are subject to many biases. Thus, most recommendations are based on evidence with low certainty of effect. The panel hopes that in the near future, higher-quality studies will further refine the management of SRM. In the meantime, it is important to obtain a treatment consensus through a shared decision-making approach after weighing the pros and cons of each option according to each patient's own values and preferences.

Competing interests: Dr. Richard has been an advisory board member for Bayer, Janssen, and Sanofi; and a speakers' bureau member for Abbvie, Amgen, Astellas, Ferring, and Janssen. Dr. Bhindi has been an advisory board member for Bayer and Janssen; and has received speaker honoraria from Merck. Dr. Breau has been an advisory board member for Ferring (bladder cancer). Dr. Kassouf has been an advisory board member for EMD Serono and Pfizer; has received grants and/or honoraria from Abbvie, Astellas, BMS, Ferring, Janssen, Merck, Roche, and Sesen Bio; and has participated in clinical trials supported by Astra Zeneca, BMS, Janssen, Pfizer, Roche, Sesen Bio, and Theralase. Dr. Lavallée has participated in advisory boards for Abbvie, Bayer, Ferring, Sanofi, and Tersera; and has received an unrestricted research grant from Sanofi. Dr. Jewett has been an advisory board member for and received payment from Sesen Bio and Theralase Technologies Ltd. Dr. Kachura participated in the multicenter OPTIMA trial for liver cancer ablation supported by Celsion Inc. Dr. Pouliot has been an advisory board member for Astellas, Bayer, Esai, Janssen, Merck, Sanofi, and Tersera; holds investments in Allogene Therapeutics; and has participated in clinical trials supported by Lantheus, Merck, and Progenics. Dr. So has been an advisory board member for Abbvie, Amgen, Bayer, Ferring, Janssen, Merck, and Tersera. Dr. Rendon has been an advisory board and speakers' bureau member for and has received honoraria from AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Ferring, Jansen, and Sanofi. Dr. Tanguay has participated in advisory boards for BMS, Janssen, Knight Therapeutics, Merck, and Roche; and has participated in clinical trials supported by AstraZeneca and Roche. Dr. Shayegan has been an advisory board member for Astellas, Bayer, and Janssen; and has received a research grant from Janssen. The remaining authors do not report any competing personal or financial interests related to this work.

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