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REVIEW ARTICLE

Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation

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ABSTRACT

Renal cancer represents 2% to 3% of all cancers, and its incidence is rising. The increased use of ultrasonography and cross-sectional imaging has resulted in the clinical dilemma of incidentally detected small renal masses (SRMs). SRMs represent a heterogeneous group of tumors that span the full spectrum of metastatic potential, including benign, indolent, and more aggressive tumors. Currently, no composite model or biomarker exists that accurately predicts the diagnosis of kidney cancer before treatment selection, and the use of renal mass biopsy remains controversial. The management of SRMs has changed dramatically over the last two decades as our understanding of tumor biology and competing risks of mortality in this population has improved. In this review, we critically assess published consensus guidelines and recent literature on the diagnosis and management of SRMs, with a focus on patient treatment selection and use of renal mass biopsy, active surveillance, and thermal ablation. Finally, we highlight important opportunities for leveraging recent research discoveries to identify patients with SRMs at high risk for renal cell carcinoma–related mortality and minimize overtreatment and patient morbidity.

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EPIDEMIOLOGY OF SMALL RENAL MASSES

Although the true incidence of renal masses (including benign lesions) is unknown, the incidence of renal cell carcinoma (RCC) has steadily increased in the United States and worldwide in recent decades, with stage 1 tumors (≤ 7 cm) now accounting for 40% to 50% of new patients with RCC .[1] The increasing incidence of RCC parallels an increase in the use of axial imaging.[2] A small renal mass (SRM) is defined as an incidentally detected, contrast-enhancing solid or cystic lesion that is ≤ 4 cm, consistent with clinical stage T1a RCC.[3] Among surgically treated SRMs, 80% are malignant; however, most are low-grade, early-stage tumors, and the remaining 20% are benign.[4] Despite earlier detection and treatment, epidemiologic studies have demonstrated stable RCC mortality, which suggests possible overdiagnosis and overtreatment.[5]

PATIENT TREATMENT SELECTION

Because of the early detection of SRMs, patients in contemporary series rarely present with local or systemic symptoms (eg, hematuria).[6] The prognosis for a patient with an incidentally detected SRM (pT1a) is favorable, with an estimated 5-year cancer-specific survival (CSS) of 95% to 100%. However, those who subsequently develop metastases (2% of SRMs) face a poor prognosis (5-year CSS of 5% to 10%).[7]

Differential Diagnosis

Contrast-enhancing solid or cystic SRMs are considered suggestive of RCC. The differential diagnosis also includes benign renal lesions (eg, lipid-poor angiomyolipoma [AML], oncocytoma), and rarely, lymphoma, metastasis from another cancer, and sarcoma. Among the 80% of SRMs that are malignant, 20% are high grade or locally invasive (invasion of perinephric fat or venous structures) and the remainder have limited metastatic potential (eg, low grade, chromophobe, type I papillary RCC).[4]

Clinical Evaluation

Smoking, obesity, hypertension, and diabetes are documented risk factors for incident RCC and for the metabolic syndrome, cardiovascular disease, and renovascular disease.[8] Therefore,

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clinicians should assess overall health and performance status (eg, Charlson Comorbidity Index). Baseline creatinine and urine dipstick to assess for proteinuria should be used to assign a chronic kidney disease (CKD) stage.

Imaging Characteristics Used to Assign Risk Stratification

Multiphasic enhanced imaging with either magnetic resonance imaging (MRI) or computed tomography (CT) is preferred for initial characterization of SRMs. SRMs should be characterized as either predominantly cystic or solid. Cystic masses are then classified using the Bosniak system (I-IV).[9] Overall, cystic RCC displays an indolent course regardless of size and Bosniak category.[10] CT and MRI can also reliably discriminate AMLs.[11] However, lipid-poor AMLs are difficult to differentiate from clear-cell RCC (ccRCC).[12] The vast majority of sporadic AMLs demonstrate a negligible growth rate and are asymptomatic; therefore, AMLs can be safely observed.[11] CT and MRI protocols can also help distinguish ccRCC from oncocytoma and papillary and chromophobe RCC; however, the accuracy and generalizability of the results are not entirely reliable.[13,14] CT and MRI are also limited in their ability to differentiate which SRMs will be locally invasive (pT3).[15,16] The value of [^{18}F]fluorodeoxyglucose–positron emission tomography in RCC remains to be determined.[17]

Defining Patient Risk Assessment

Because of competing risks of mortality, especially among elderly and comorbid patients, nomograms have been developed to improve risk prediction of non-RCC mortality. Kutikov et al[18,19] demonstrated that as age and Charlson Comorbidity Index increase among patients with localized RCC (T1-4N0M0), the risk of noncancer-specific mortality increases significantly. These predictive nomograms were generated using an older ($\geq$ 66 years) and surgically treated population, making them less applicable to younger and less comorbid patients. Despite improvements in risk stratification, population-based studies show that only a small proportion of older patients ($\geq$ 70 years old) diagnosed with SRMs are managed with active surveillance (AS) or watchful waiting.[20]

Approximately 10% to 52% of patients with localized RCC have CKD (estimated glomerular filtration rate [eGFR] $<$ 60 mL/min/1.73m^2) at the time of diagnosis. Protein detected on urine dipstick (2+ on dipstick) should trigger quantitative measurement with 24-urine protein or albumin-to-creatinine ratio. Patients with preexisting CKD or proteinuria have decreased overall survival (OS) and are at increased risk for progressive decline in renal function after treatment.[21] Guidelines suggest pretreatment referral to nephrology for patients at high risk for CKD progression (eGFR $<$ 45, confirmed proteinuria, patients with diabetes with preexisting CKD, or if eGFR after surgery will be $\leq$ 30 mL/min/1.73 m^2).[22] Clinicians can also consider split renal function assessment with renal scintigraphy for patients with compromised renal function or multiple/bilateral tumors.[23]

Defining Oncologic and Treatment Risk

Pretreatment nomograms have been developed to improve risk prediction of malignancy, histology, morbidity, and survival. In a recent Agency for Healthcare Research and Quality (AHRQ) comprehensive review and meta-analysis (clinical stage T1 to T2), the strongest factors predictive of malignant pathology were tumor size and sex.[24] Among 12 studies (n = 9,401), each centimeter increase in tumor size was associated with a 33% increased risk of malignancy.[24] On the basis of tumor size alone, the risk of malignancy and metastases varies significantly within the category of an SRM.[7] Among 16 studies (n = 10,475), men were more likely to harbor malignant pathology (odds ratio, 2.7; 95% CI, 2.39 to 3.02). The strength of evidence was low for symptoms at presentation, age, and body mass index.[24] Using clinical (age, sex, smoking) and radiographic (tumor size) characteristics, Lane et al[25] created a preoperative nomogram (n = 851) that achieved a concordance index of 0.64 for benign pathology in tumors $\leq$ 7 cm. Among 2,517 patients with localized RCC (median size, 5.3 cm; range, 0.5 to 20 cm), Raj et al.[26] demonstrated that using preoperative imaging (lymphadenopathy, necrosis, tumor size) and clinical (sex, mode of presentation [incidental *v* systemic]) characteristics achieved a concordance index of 0.80 for 12-year metastases-free survival. Anatomic classification scores have also been used to help standardize treatment reporting, assist in treatment selection, and predict complications (eg, R.E.N.A.L nephrometry score[27]). Increasing R.E.N.A.L nephrometry score has been shown to improve risk prediction of malignancy, grade, and pathologic upstaging.[27]

RENAL MASS BIOPSY

The role of renal mass biopsy (RMB) in the management of SRMs remains controversial because of concerns over diagnostic accuracy, safety, and capacity to affect clinical management.[28] The perceived benefit of RMB is to inform risk stratification, prevent overtreatment of benign/low-grade lesions, and guide treatment selection. The use of RMB has increased over time, with the highest use demonstrated in thermal ablation (TA) or systemic therapy and approximately one in five patients undergoing radical nephrectomy (RN) or partial nephrectomy (PN).[29] The current guideline recommendations for RMB are listed in Table 1.

Technical Aspects

RMB can be performed under ultrasound or CT guidance with similar diagnostic yield.[23] Core biopsy (CB) has superior diagnostic rates compared with fine-needle aspiration alone; however, there does seem to be added diagnostic utility in the combination of a fine-needle aspiration smear with CB.[31,32] Guidelines recommend multiple cores (two to three) with a 16- to 18-gauge core needle.[22] However, an ex vivo comparison of 14-, 18-, and 20-gauge needle biopsies demonstrated that a minimum of an 18-gauge needle resulted in the most accurate histologic diagnosis.[33] Overall, protocols and definitions of success in RMB series vary, making studies difficult to compare.

Accuracy

Two recent reviews have comprehensively evaluated the accuracy and harms of RMB.[24,31] Marconi et al[31] evaluated 57 studies (n = 5,228) and reported a median rate of diagnostic RMBs (diagnosis of malignancy) of 92% (interquartile range, 80% to

Table 1. Review of Published Guideline Recommendations for the Use of RMB in Localized RCC

Guideline	Indications for RMB	Recommendation Against RMB
ASCO, 2017[3]	All SRMs should be considered for RMB when the results may alter management	Predominantly cystic renal masses
	Consider when a mass is suggestive of lymphoma, metastasis, infectious/inflammatory	Renal masses originating from the collecting system or suggestive of urothelial carcinoma
	Not necessary before entering AS protocols	
	Should be performed before TA (as separate procedure)	
AUA, 2017[22]	Consider when a mass is suggestive of hematologic, metastasis, or infectious/inflammatory	Young or healthy individuals unwilling to accept the uncertainties associated with RMB
	Counsel individuals about rationale, positive and negative predictive values, potential risks, and nondiagnostic rates	Frail or older patients who will be managed conservatively regardless of RMB findings
	Before TA for pathologic diagnosis and to guide surveillance	
	Consider after initial 3- to 6-month imaging with AS for further risk stratification	
NCCN, 2017[30]	Consider RMB to obtain or confirm a diagnosis of malignancy and guide AS and TA strategies	Not discussed
	Consider if urothelial carcinoma is suspected (eg, central) or lymphoma (eg, homogenous infiltration)	
EAU, 2015[23]	All patients who are considered for AS protocols	Cystic renal masses
	Before TA for pathologic diagnosis and to guide surveillance	Comorbid or frail patients who will be managed conservatively regardless of RMB findings
		Not required if surgery is planned

Abbreviations: AS, active surveillance; AUA, American Urological Association; EAU, European Association of Urology; NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma; RMB, renal mass biopsy; SRM, small renal mass; TA, thermal ablation.

96.8%). For CB, the recent AHRQ review (> 18 studies; n = 2,203),[24] demonstrated a sensitivity of 97.5%, specificity of 96.2%, and positive predictive value of 99.8% but a poor negative predictive value of 68.5%. Nondiagnostic rates ranged from 0% to 22.6%.[24] The majority of nondiagnostic biopsies corresponded with malignant surgical pathology (90.4%). Repeat RMB after an initial nondiagnostic biopsy yields a higher diagnostic rate (83% to 100%) but may be underutilized.[34] Predictors of nondiagnostic RMB in SRMs are smaller size, cystic masses, nonenhancing (≤ 20 HU), and skin-to-tumor distance of ≥ 13 cm.[35]

Histologic determination of RCC subtype is highly accurate, but the accuracy for grade is less reliable. In the AHRQ review, concordance between histologic subtype and surgical specimens was 96% among SRMs.[31] Oncocytoma remains a challenge, because close to one quarter of patients have RCC on surgical pathology.[36] Fuhrman nuclear grading accuracy compared with surgical specimens is poor, but can be improved using a simplified two-tiered system (high- *v* low-grade).[31,37] Approximately 20% of RMB-determined low-grade (1 to 2) cancers are upgraded to high grade (3 to 4) on surgical pathology.[24] The difficulty in assigning a grade determination is likely a reflection of intratumoral grade heterogeneity previously documented in RCC.[38]

Safety

Overall, complications secondary to RMB are infrequent and include perinephric hematoma, clinically significant pain, gross hematuria, pneumothorax, and hemorrhage.[24] The largest RMB series (n = 529) to date reported a 2% rate of Clavien grade ≥ 2 complications.[34] Clinically significant bleeding after RMB is unusual and generally self-limited.[31] Needle biopsy tract seeding historically has been a concern for clinicians; however, with modern biopsy techniques using a coaxial sheath method, this risk is nearly negligible. All but one case report of needle tract seeding was without the use of a coaxial sheath, and although there is one recent report in the literature, this event remains exceedingly rare.[39,40]

Summary

RMB demonstrates a reliable ability to determine the presence of malignancy and characterize histology in SRMs but is limited for grade. Notably, one third of patients with a nondiagnostic biopsy will harbor malignancy on surgical pathology. These findings led guideline panels (Table 1) to suggest offering RMB as an adjunctive option in the evaluation of patients with localized RCC. A recently proposed algorithm[41] suggests that RMB can be selectively used to improve risk stratification in patients where the clinical management may change on the basis of the results of the biopsy (eg, multiple renal masses or hereditary RCC syndromes). In Figure 1, we summarize the possible clinical scenarios in which RMB may be used for the management of SRMs.

ACTIVE SURVEILLANCE

PN is considered the gold standard treatment of patients with clinical stage T1a tumors. Other management options include AS, TA, and surgery (PN or RN). A summary of the guideline recommendations for AS criteria, triggers for delayed intervention (DI), and follow-up protocols are listed in Table 2. Several recent reviews have summarized existing retrospective AS studies for SRMs.[42]

Survival Outcomes

To date, only two studies have evaluated AS protocols prospectively.[43,44] The details of these two studies are listed in Table 3. Overall, both retrospective and prospective studies have reported cancer-specific and metastasis-free survival of 98% to

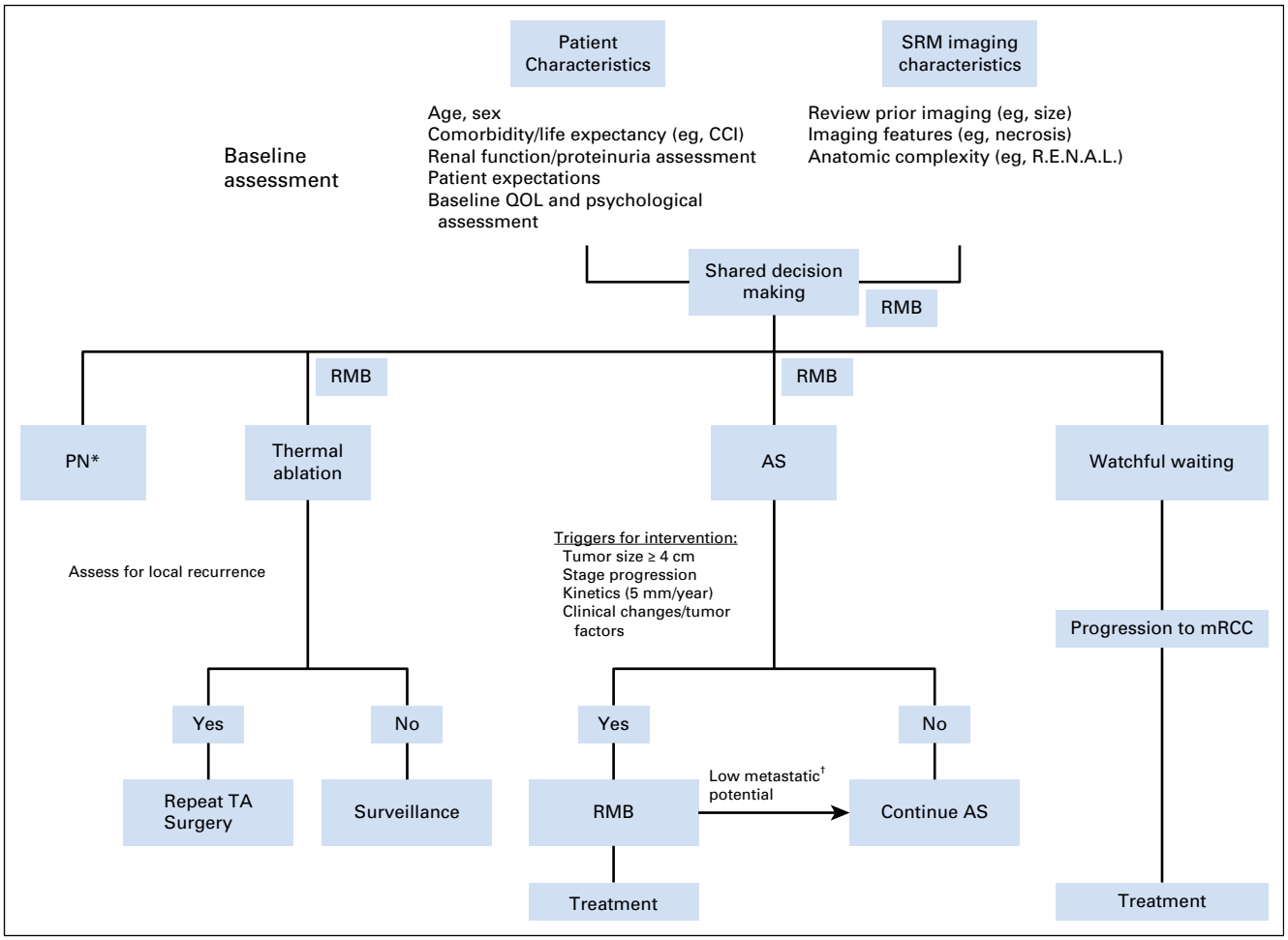

Fig 1. Suggested algorithm for the management of small renal masses (SRMs). Renal mass biopsy (RMB) depicts clinical scenarios in which RMB can be considered. (*) When technically feasible. (†) Benign pathology, chromophobe, papillary type 1, or Fuhrman grade 1 to 2 metastatic renal cell carcinoma (mRCC). AS, active surveillance; CCI, Charlson Comorbidity Index; PN, partial nephrectomy; QOL, quality of life; RCC, renal cell carcinoma; TA, thermal ablation.

100%.[42] OS has ranged from 69% to 94%, reflective of an overall older and comorbid population. In an update on the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) trial (N = 271), investigators reported a mean growth rate of 0.09 (standard deviation, ± 1.51) cm per year, with the highest variability noted within the first year and decreasing with longer follow-up.[45] Notably, patients choosing AS in the DISSRM trial who required DI were still eligible for nephron-sparing approaches.[43]

Triggers for Delayed Intervention

Triggers for DI while receiving AS have been assessed retrospectively. Smaldone et al[46] recently performed a systematic review of 18 series (880 patients, 936 masses) and found that increasing age, initial tumor diameter/volume, and linear/volumetric growth rates were significantly different between those who experienced disease progression (n = 18) compared with those who did not. Among the prospective cohorts, triggers for DI included tumor size > 4 cm, increasing tumor complexity, symptoms (eg, hematuria), infiltrative appearance, patient preference, and/or interval growth (> 0.5 cm/year). Among 447 patients, McIntosh et al[47] demonstrated that 38% of renal masses (median size, 2.1 cm; interquartile range, 1.5 to 3.1) exhibited no initial growth (< 1 mm/year); however, an initial high longitudinal growth rate (> 10 mm/year) was associated with a higher cumulative risk of DI. Growth alone may not be an indication of histology, because both benign and malignant lesions can grow at similar rates and different histologies of RCC demonstrate varied risks of metastases by tumor size alone.[48] However, the development of metastases in AS protocols seems to be preceded by rapid local growth or multiple growth periods.[46,49] Among RMB-diagnosed oncocytic neoplasms, AS has been demonstrated to be safe.[50]

THERMAL ABLATION

To date, no randomized prospective studies have compared TA techniques with surgery (PN or RN) or compared each TA modality (cryoablation *v* radiofrequency ablation). The CONSERVE trial (ClinicalTrials.gov identifier: NCT01608165) was terminated early due to poor accrual to study PN versus TA in masses amenable to both modalities in healthy individuals. A prospective, nonrandomized study evaluating ultrasound-guided percutaneous microwave ablation versus laparoscopic PN for SRMs is currently

Table 2. Summary of Published Guideline Criteria and Follow-Up for AS of SRMs

Guideline	Criteria for AS	Triggers for Intervention*	Surveillance
ASCO, 2017[3]	Absolute indications: high risk for anesthesia or life expectancy < 5 years	Growth > 0.5 cm/year	CXR and axial abdominal imaging (or US) every 3 months for 1 year, twice in years 2-3, and yearly thereafter
	Relative indications: significant risk of ESRD if treated, SRM (< 1 cm), or life expectancy < 10 years	> 4 cm	Modify surveillance on the basis of growth kinetics
	Initial management option for patients who have significant comorbidities and limited life expectancy		
AUA, 2017[22]	Patient factors: elderly, life expectancy < 5 years, high comorbidities, excessive perioperative risk, poor functional status, marginal renal function, patient preference to avoid treatment risk	Not discussed	Initial imaging after 3-6 months
	Tumor factors: tumor size < 3 cm, tumor growth < 5 mm/year, noninfiltrative on imaging, low complexity, favorable histology (if RMB performed), Bosniak 3 or 4 complex cyst, especially if < 2 cm		Decision as to the frequency and imaging modality must be customized and informed by robust communication focusing on goals, risks, and triggers for intervention
NCCN, 2017[30]	Decreased life expectancy or extensive comorbidities that would place them at excessive risk for more invasive intervention	Not discussed	Abdominal CT or MRI within 6 months of surveillance initiation and yearly thereafter
			CXR or CT annually if RMB positive for RCC
			Bone scan/pelvic/head imaging if clinically indicated
EAU, 2015[23]	Elderly and/or comorbid patients with SRM and decreased life expectancy	Not discussed	CT, MRI, or US at 3 and 6 months, then every 6 months until year 3, and then annually
	AML		

Abbreviations: AML, angiomyolipoma; AS, active surveillance; AUA, American Urological Association; CT, computed tomography; CXR, chest x-ray; EAU, European Association of Urology; ESRD, end-stage renal disease; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; RCC, renal cell carcinoma; RMB, renal mass biopsy; SRM, small renal mass; US, ultrasound.
*Depending on the patient's comorbidities and life expectancy.

ongoing (Clinicaltrials.gov identifier: NCT03094949). Most data available are retrospective, include an older and comorbid population, and vary in the rates of use and timing of RMB.

Survival Outcomes

CSS and OS rates are similar across management strategies for T1a RCC, but TA is associated with a higher local recurrence rate.[24] Guidelines generally recommend considering percutaneous TA as an option for clinical T1a masses ≤ 3 cm.[22,23] Both cryoablation and radiofrequency ablation are options and demonstrate no difference in complications, local recurrences, metastatic progression, or CSS.[51] In a recent systematic review and meta-analysis comparing TA (n = 3,974) and PN (n = 2,519), all-cause mortality and CSS was higher among patients undergoing TA and there was no significant difference in local recurrence rate or risk of metastasis.[52] Notably, survival outcomes may depend on histology where ccRCC has a worse prognosis compared with papillary RCC.[53] Options for the management of local recurrence for TA include PN or repeat TA. PN for the treatment of recurrent RCC after TA can be technically challenging, therefore increasing the risk of conversion to RN and complications.[54]

Complications

In a recent systematic review and meta-analysis (n = 3,974), complication rates were lower for TA (odds ratio, 0.49; 95% CI 0.25 to 0.94) compared with PN.[52] Specifically, TA has demonstrated decreased blood loss and transfusion rates compared with PN or RN. TA demonstrates improved renal functional outcomes compared with PN or RN.[52] Not surprisingly, length of hospital stay is shorter with TA compared with PN or RN. Acute kidney injury and minor/major Clavien complication rates are similar among techniques (TA, PN, RN).[55] Renal mass location and complexity need to be considered to prevent complications related to proximity to ureters, ureteropelvic junction, small or large bowel, and nerves. R.E.N.A.L nephrometry scores can help estimate the probability of local tumor progression and potential complications.[56]

RENAL FUNCTIONAL OUTCOMES

Numerous variables can influence renal functional outcomes, including the amount of parenchyma removed/ablated, ischemia type/duration, patient age, comorbidities, and presence of preexisting CKD. Renal functional outcomes favor TA and AS over PN or RN.[36] After PN or RN, eGFR can improve over time, with approximately 40% of patients returning to their baseline renal function after 1 year.[57] Overall, RN has been associated with worse renal functional outcomes compared with either nephron-sparing technique: TA or PN. TA may not adversely affect renal function and therefore may be particularly suited for patients needing maximum conservation of renal parenchyma.

FUTURE DIRECTIONS

Patient Decision Aids

Currently, no published decision aids have been evaluated for kidney cancer. Patients face a range of complex decisions regarding treatment options for SRMs and, often, there is no best treatment choice. Golan et al[58] recently evaluated patient (n = 73) and physician (n = 59) perspectives on RMB and found that both physicians and patients were most uncomfortable about the

Table 3. Comparison of Selection Criteria and Outcomes in Published Prospective AS Protocols

First Author	No.	Inclusion Criteria	Exclusion Criteria	RMB	Surveillance Strategy	Triggers for Intervention	Progression and Survival Outcomes
Pierorazio[43]	223	≥ 18 year	Life expectancy < 2 year	Offered at enrollment (21 SRMs)	4-6 months for 2 years and then every 6-12 months, preferentially with US	Growth rate > 0.5 cm/year	5-year OS: 75%
		Solid, enhancing cT1aN0M0	Suspicion of second malignancy metastatic to kidney			Change in tumor diameter to ≥ 4 cm	5-year CSS: 100%
		Negative chest imaging	Personal history of RCC				No metastases in AS cohort
		Assigned modified cardiovascular index	Hereditary RCC syndrome				Local progression: 36/223 (16.1%)
Jewett[44]	178	Incidental	Life expectancy < 2 year	All (101 SRMs)	CT, MRI, or US at 3 and 6 months, then every 6 months until year 3, and then annually	Change in tumor diameter to ≥ 4 cm	Total: 27/178 (15%)
		cT1aN0M0	SRM diagnosed > 12 months before		Pathologically benign tumors were imaged annually	Doubling of tumor volume	Metastases: 2/178 (1.1%)
		Unfit for surgery because of age, comorbidity, refusal of treatment	Systemic therapy for other malignancies			Metastases	Local: 25/178 (14%)
		Negative CXR	Hereditary RCC syndrome				Survival (mean follow-up 28 months): 10 non-RCC–related deaths (5.6%), 1 RCC-related death (0.7%)

Abbreviations: AS, active surveillance; CSS, cancer-specific survival; CXR, chest x-ray; CT, computed tomography; MRI, magnetic resonance imaging; OS, overall survival; RCC, renal cell carcinoma; RMB, renal mass biopsy; SRM, small renal mass; US, ultrasound.

Table 4. Summary of Genomic/Transcriptomic Prognostic Markers for Survival After Surgery Studied in Localized RCC

First Author	No. (discovery plus validation), TNM Stage	RCC Histology	Technology	Tissue Source	Key Genomic Findings	Survival Outcomes	C-Index	Models Compared
Manley[60]	203, T1-3N0-1M0-1*	Clear cell	DNA (somatic and germline)	Primary tumor (FFPE)	*KDM5C*	Associated with inferior RFS and CSS	N/A	SSIGN
Manley[61]	1,049, T1-4N0-1M0-1	Clear cell	DNA (somatic and germline)	Primary tumor (FFPE)	*SETD2, TP53*	Associated with inferior RFS (*SETD2*) and CSS (*TP53*)	N/A	SSIGN
Brooks[62]	72 + 380 + 157, T1-4N0-1M0	Clear cell	RNA	Primary tumor (FFPE)	34-gene classifier, (ccA/ccB)	Associated with RFS, CSS and OS at 5 years	0.65	SSIGN, UISS
Morgan[63]	303 + 262, T1-T3N0M0	Clear cell, papillary, chromophobe	RNA	Primary tumor (FFPE)	31-gene cell-cycle progression score; (high/low risk)	Associated with CSS and cancer recurrence at 5 years	0.87	Karakiewicz nomogram
Rini[64]	942 + 626, T1-4N0-1M0	Clear cell	RNA	Primary tumor (FFPE)	16-gene assay; (low/intermediate/high)	Associated with CSS at 5 years	0.81	Leibovich score

Abbreviations: CSS, cancer-specific survival; FFPE, formalin-fixed, paraffin-embedded; N/A, nonapplicable; OS, overall survival; RCC, renal cell carcinoma; RFS, recurrence-free survival; SSIGN, score on the basis of stage, size of tumor, grade, and presence of necrosis; UISS, UCLA Integrated Staging System.
*Restricted to tumors ≤ 4 cm.

negative predictive value of RMB. However, most patients (approximately 60%) would opt for RMB after being informed of the imperfect accuracy of the procedure. More studies are needed to help patients navigate the complex options surrounding the management of SRMs.

Criteria for AS

Currently, no standard composite model is used to assess the appropriateness of AS for a given patient. However, existing nomograms are consistent in finding tumor size to be an important predictor of malignancy. Therefore, within the SRM category, there exists a range of risk on the basis of tumor size alone.[4] The importance of assessing competing risks in this population warrants exploration of novel markers of overall frailty and performance status. For example, frailty index has been evaluated across multiple cancer types and is a strong marker for treatment morbidity and OS.[59] Composite nomograms, also incorporating tissue-based biomarkers, are needed to assist clinicians and patients in deciding whether to pursue AS.

Biomarkers

The aim of tissue markers in the clinical scenario of an SRM would be to (1) aid in histologic diagnosis, (2) detect genomic/transcriptomic markers associated with aggressive disease, and (3) diagnosis of benign tumors. Table 4 lists current tissue biomarkers available for localized RCC that are used to risk stratify patients after treatment. Notably, these biomarkers are derived from formalin-fixed paraffin-embedded tissue from the primary tumor and may be evaluated from RMB specimens. The use of tissue-based biomarkers must be balanced with the reality that they may be costly. One potential solution for this would be the use of immunohistochemistry or radiomics (combining the mutational status of specific genes with radiographic findings). Finally, other clinical host biomarkers, such as body composition and neutrophil-to-lymphocyte ratio have been associated with a poor prognosis in localized RCC and should be explored among patients with SRMs.[23,65]

Imaging

Novel imaging modalities to improve the characterization of SRMs are urgently needed. Recent reports describe using ^{99m}Tc-sestamibi single-photon emission CT to differentiate renal oncocytomas and hybrid oncocytic/chromophobe tumors from RCC; however, although promising, these methods still require further validation.[66] Prostate-specific membrane antigen–targeted ^{18}F-DCFPyL positron emission tomography/CT has also demonstrated activity in patients with RCC and requires further evaluation.[67] Radiomics can be used along with clinical and radiographic findings and is a growing field of interest.[68] Improvements in CT and MRI-based sequencing also need to be explored (eg, postcontrast time-attenuation curves and lesion homogeneity on CT can be used to differentiate different histologies).[69] Fusion technology akin to what is used in prostate cancer for fusion biopsies is also being explored.[70]

In conclusion, with a rising incidence of SRMs and negligible improvement in mortality, clinicians and researchers are challenged to improve risk prediction and explore novel diagnostic avenues to improve patient care. Recognizing the importance of competing risks in this comorbid population has led to the increased use of AS and nephron-sparing approaches. Use of RMB remains controversial and requires standardization of definitions and protocols for proper prospective assessment. Furthermore, improved methods for risk prediction of OS and CSS that combine patient performance status, clinical and radiographic features, and tissue-based markers are urgently needed. These efforts should also be coupled with measures to improve imaging diagnostic techniques and tools to assist patients in navigating complex decision making surrounding SRMs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Current Management of Small Renal Masses, Including Patient Selection, Renal Tumor Biopsy, Active Surveillance, and Thermal Ablation

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