Review Article

Active surveillance in small renal masses

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Abstract

Active surveillance is one of the options available for management of renal masses smaller than 4 cm with a suspicion of malignancy in association with nephrectomy and ablative procedures. In general, small renal masses grow slowly and have a very low metastatic potential, but exceptions occur. Active surveillance is generally offered in the elderly with high comorbidities but there is a lack of validated data in other patient demographics. Data from younger and healthier patients are gradually emerging and have shown promising results but still require further validation. Computed tomography (CT), magnetic resonance imagin (MRI), and ultrasonography (US) are all acceptable imaging modalities for surveillance of renal masses, but CT is the most commonly used. Intervals of surveillance differs from study to study, but the most common schedule is 3, 6, and 12 months after initiation, then annually. The cut off point for delayed intervention is growth > 0.5 cm/year or absolute size > 4 cm. Oncologic outcome is comparable to nephrectomy and ablation in terms of cancer-specific survival. Quality of life for patients undergoing active surveillance is also comparable but is significantly lower in those with confirmed malignant biopsy results. Cost of active surveillance is as a rule more cost effective than nephrectomy or ablation.

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Introduction

Renal cell carcinoma is the 6th most common cancer in males and 10th in females, accounting for 5% and 3% respectively of all diagnosed malignancies.[1] In the Thai population, the age-standardized rate of renal cell carcinoma is 1.2 per 100,000. The incidence of diagnosis of renal mass has been increasing over the past 20 years potentially due to the increased utilization of cross-sectional imaging for various reasons.[2] This also increases the detection of small renal masses (SRMs), defined as a solid renal mass or complex renal cyst sized < 4 cm or a T1a tumor, as the trend is that renal masses are being discovered at a smaller and smaller size.[3]

Due to its low malignancy and metastatic potential, and the fact that most patients are asymptomatic, management of SRMs remains a clinical dilemma between the risk of deterioration of renal function and surgical complications from nephrectomy, and the benefit of early removal and accurate pathologic diagnosis. Active surveillance is one of the available management options according to guidelines from the majority of in-

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stitutions and the referral of patients for periodic monitoring, usually with imaging and laboratory tests, for signs of progression or metastasis with an intention for curative intervention once progression is detected.

This aim of this review is to describe evidence which is currently available with regard to active surveillance of SRMs.

Nature of small renal masses

In contrast with larger enhancing renal masses where the diagnosis of malignancy is relatively reliable from imaging and the aim of treatment is mainly eradication, small enhancing renal masses pose slightly unique challenges for clinical decision making due to uncertainty in diagnosis and the rather indolent biological nature of these potential tumors.

SRMs are known for their low levels of both malignant potential and aggressive nature. Data from renal mass biopsy and molecular profiling have indicated that 20% are benign masses, 60% are indolent RCC and only 20% are potentially aggressive RCC.[4]

Size and growth

SRMs were found to exhibit various growth potentials ranging from no growth at all to a rapid growth, but the majority grow rather slowly. In 2012, Lane conducted a pooled retrospective analysis from 18 studies into a total of 957 SRMs with an average initial size of 2.8 cm and reported an average growth of 3.2 mm/year. The data from the included studies even indicated a proportion of 15-25% which exhibited zero growth.[5] Data from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry, which is a large prospective multi-institutional prospective clinical study regarding outcomes of active surveillance of SRMs, demonstrated a median growth rate of 0.9 mm/year in 271 patients and also reported that 42% of tumors showed zero growth or less (size reduction).[6] Although growth rates vary from patient to patient, there has yet to be a reliable parameter to predict which tumor is more likely to grow, as many authors have failed to demonstrate any correlation between growth rates and specific parameters.[6-8] Even malignant tumors can exhibit zero growth.[9,10]

Although no parameters are predictive of tumor growth, the test of time will. Data from the DISSRM registry have demonstrated that SRMs are more likely to grow (or shrink) during the first 6 months of follow-up than after 1 year of active surveillance.[6]

Metastasis

SRMs do possess a small but non-negligible potential to metastasize. A systematic review in 2012 from a total of 880 patients reported a metastatic rate of 2% during a median follow-up time of 2 years.[10] Data from post-nephrectomy (partial or radical) patients have also demonstrated a similar metastatic rate of 1.8% during 6.9 years of follow-up.[11] A recent systematic review in 2021 collected data from 20 studies and found that 6 studies reported a 0% rate of metastasis while an overall metastatic rate was 2.2% with a median follow up time of between 21-77 months.[12]

While size does not predict growth, it appears to predict metastasis as initial tumor size was found to be larger in patients who developed metastasis than those who did not.[13] Even post-nephrectomy patients with pathologically confirmed RCC still demonstrated similar results with a metastatic rate of 0%, 1.1%, 3.3%, and 6% in tumors smaller than 1 cm, 1-2 cm, 2-3 cm, and 3-4 cm, respectively.[14]

Mortality

As SRMs carry a very low potential for metastasis, the same could be inferred in terms of mortality. McIntosh described a five-year cancer-specific mortality of 1.2%.[8] Data from the DISSRM registry which pooled patients who received any treatment or surveillance showed an even lower mortality with a seven-year cancer-specific survival of 98.8% in the partial nephrectomy group and 100% for radical nephrectomy, ablation and active surveillance group.[15] Overall survival, in contrast, was much lower in the active surveillance group, in comparison with other groups, probably due to older age and higher comorbidity rates of subjects.

Case selection

Patient status

The selection of an appropriate patient remains one of the most challenging and vital aspects of active surveillance, and a well-defined universally accepted group of criteria for eligibility of active surveillance has yet to be established. This is largely due to the paucity of evidence in young and healthy patients.[12] Fundamentally, active surveillance is usually offered to patients with significant competing health risks that might offset the risk of death by cancer progression or renders the risk of interventions to be excessively high.[16] As there has yet to be a randomized trial and the majority of patients who chose active surveillance tend to have old age and high comorbidities, most of the available studies have a median age between 67-83 years.[12]

In comparison, the guidelines from other major institutions including the NCCN, American Urological Association (AUA), and European Association of Urology (EAU) similarly recommend prioritization of active surveillance in elderly patients and those with significant co-morbidities. AUA and NCCN also offer active surveillance as an option for patients with a mass smaller than 2 cm.[17-19] AUA also describe multiple favorable factors for active surveillance including borderline renal function and patient preference, as well as other tumor characteristics such as size < 3 cm, cystic feature predomination, non-infiltrative features, low complexity, growth < 5 mm/year, and favorable histology.

As data supporting the safety of active surveillance in the elderly and those with significant co-morbidities are becoming more reliable, its applicability in young and healthy patients is starting to be recognized as well. Recent data in 2021 analyzing the subgroup of patients from the DISSRM registry with an age younger than 60 years have shown promising results. Of 82 patients, overall survival and cancer-specific survival at seven years were 90.8% and 100%, respectively. Intervention rate was also found to be similar to previous data at 19%. These results are not simply a representation for young patients but represent young and healthy patients as 96% of the active surveillance population has an Eastern Cooperative Oncology Group (ECOG) performance status grade 0-1 and half of the study population has a Charlson Comorbidity Index of zero.[20]

Cell types and renal mass biopsy

As SRMs can vary in nature and consist of both benign and malignant tumors. Renal cell carcinoma (RCC) can also be classified into multiple histologic subtypes including clear cell RCC, chromophobe RCC, papillary RCC, and rarely, collecting (Bellini) duct carcinoma. Different histological subtypes of RCC are known to behave differently, as collecting duct carcinoma is considered to be the most aggressive, followed by papillary RCC type II, clear cell RCC, and papillary RCC type I, respectively.[21] Different levels of aggressiveness also translate into a difference in mortality, as has been indicated in a recent meta-analysis. This study demonstrated a significantly higher mortality in patients with papillary RCC type II than clear cell RCC (HR: 1.2) and similar outcomes between clear cell RCC and papillary RCC type I.[22]

Similar behavior has also been observed in SRMs. Finelli et al. reported a predicted growth rate of 2.5 mm/year in biopsy-proven clear cell RCC and 0.17 mm/year in papillary type I RCC. Chromophobe RCC and papillary type II RCC growth fall in the range between clear cell and papillary type I RCC. It is worth noting that although the average growth is significantly different between subtypes, all subtypes demonstrate a wide heterogeneity of growth ranging from slight regression to rapid progression.[23] In addition to histologic subtype classification, multiple pathologic features such as a high nuclear grading, lymphovascular invasion, sarcomatoid differentiation, and rhabdoid differentiation can adversely affect cancer-specific survival as well.[24]

Although the accuracy and safety of renal mass biopsy is often, historically, of major concern for most clinicians, a growing body of literature may be suggesting otherwise. A systematic review of 17 studies reported a non-diagnostic rate ranging from 0-22%.[25] This number could possibly be reduced further by a repeat biopsy.[26] A more recent study also reported a similar result.[27]

Renal mass biopsy has also been found to accurately diagnose malignancy and histologic subtypes in SRMs. Marconi et al. conducted a meta-analysis which included 33 studies from 1967 to 2011, sensitivity and specificity for the diagnosis of malignancy were 99.7% and 98.2%, respectively, in those with diagnostic biopsy. The reported concordance rate of histologic subtype between biopsy and surgical pathology from multiple studies was 96%.[25,28] However, sensitivity for the detection of tumor grading and adverse pathologic features from biopsy may not be as high.[29]

Another major concern with regard to renal mass biopsy for most clinicians is its incidence of associated complications. Renal mass biopsy can potentially lead to various complications including pain, bleeding complications including hematoma and hematuria, infection, and the area of greatest concern, biopsy tract tumor seeding. Perirenal hematoma is the most common complication of renal mass biopsy at approximately 2-7%, but hematomas that required transfusion only occurred in 0.7% of cases. Hematuria occurred in 3% which were shown to be almost entirely self-limiting.[25] There were also multiple reports of pseudoaneurysm which required angioembolization.[30,31] The risk of needle track tumor seeding is extremely low. There was a single case reporting needle tract seeding diagnosed by radiologic imaging from a mass that turned out to be urothelial carcinoma, but the tract was not confirmed pathologically.[32] Another pathological analysis of perirenal fat and peritumoral fat to specifically detect seeding in another study did not find any evidence of tumor seeding.[33]

As the benefit and safety of renal mass biopsy are becoming more established, renal mass biopsy has, therefore, become more and more utilized over the last decade, especially in SRMs.[34,35] However, as renal mass biopsy still harbors some non-diagnostic risk and demonstrable, though very low, risk of false-negative for malignancy, most guidelines from European and American institutions still regard the use of renal mass biopsy as "consider" and almost unanimously recommend against renal mass biopsy when the result may not alter clinical management (Table 1).

In summary, the selection of patients with SRMs who are eligible for active surveillance is a clinical challenge. To date, available data suggests that old age, high co-morbidity, small size, less aggressive cell types, and absence of adverse features are favorable factors for patient selection for active surveillance.

Surveillance protocols

As the purpose of active surveillance is to delay a primary intervention until a patient actually shows signs of tumor progression and to omit the intervention for those who do not, three components are of utmost importance in doing so; modality of surveillance, interval of surveillance, and triggers for intervention.

Modalities

Since radiographic imaging is used to detect the clinical progression of SRMs, the ideal imaging modality should be able to reliably provide clinicians with tumor characteristics including its size, complexity (in terms of cystic mass), invasion, and any signs of distant metastasis. At the same time there needs to be a minimizing of cost, exposure to ionizing radiation, and adverse effects of contrast media, as patients under active surveillance are deemed to potentially undergo multiple imaging procedures throughout their lifetime.

Computerized tomography (CT) with contrast media is one of the most commonly used imaging

Table 1. Institutional guidelines recommendation for renal mass biopsy (RMB) in the setting of active surveillance

AUA 2021	For patients with a solid or Bosniak 3/4 complex cystic renal mass in whom the risk/ benefit analysis for treatment is equivocal and who prefer AS, clinicians should consider renal mass biopsy (RMB) (if the mass is solid or has solid components) for further oncologic risk stratification
EAU 2021	Perform a percutaneous biopsy in select patients who are considering active surveillance. Use core needle biopsy rather than fine needle aspiration. Do not perform a renal tumor biopsy of cystic renal masses, unless areas with a solid pattern are present. Not indicated for comorbid and frail patients who can be considered only for conservative management.
NCCN 2022	Consider renal mass biopsy at initiation of active surveillance or at follow-up, as clinically indicated.
ASCO 2017	All patients with an SRM should be considered for RTB when the results may alter management. Patients who are considered for an active surveillance protocol may benefit from a biopsy to assess risk for metastasis while undergoing surveillance but not necessary for all patients who undergo surveillance.
ESMO 2019	Renal biopsy is recommended to select patients with small masses for active surveillance, especially because of the incidence of non-malignant tumors in this setting.

modalities in the diagnosis and follow-up of renal masses due to its high availability, accessibility, and accuracy.[12] Therefore, CT is ranked at 9 points in the American College of Radiology (ACR) appropriateness criteria for the diagnosis of renal mass.[36] In addition to the obvious risk of adverse reactions from contrast agents, ionizing radiation exposure is one of the major concerns of utilizing CT for surveillance. From a single triple-phase protocol of KUB system CT scan, patients are usually exposed to an average effective dose of 11.2 mSv of radiation.[37] This seemingly insignificant dose of radiation can accumulate rapidly when performed repeatedly every 3-12 months resulting in a significant amount of radiation.[38] Hence, attention to the minimization of radiation should be ensured in patients undergoing active surveillance. Omission of some phases that may not play an important role in surveillance such as a pre-contrast phase or delayed phase could potentially reduce radiation exposure in some situations. A dual-energy CT scan is also another technique that carries the potential to reduce radiation exposure. The dual-energy CT scan is an emerging imaging technique that uses different energy (kV) of radiation simultaneously, which results in two different image data sets from a single scan. The technique, when used during image acquisition after contrast media injection, creates images that can be processed using a specialized algorithm to create "virtual unenhanced (VUE) images". Thus, the virtual unenhanced images could, theoretically, replace the need to acquire a pre-contrast image and reduce the radiation exposure by up to 33%.[39] In reality, however, the technique still harbors some limitations that hinder its widespread use. In comparison with true unenhanced images, there are some increases in the attenuation value of multiple solid organs in VUE images, including the kidney, which might affect the radiologic interpretation of enhancement.[40] However, another study reported that these variations do not significantly affect the classification of renal mass.[41] In addition, there has yet to be a standardized protocol of dual-energy CT across various manufacturers.[39]

Magnetic resonance imaging (MRI) carries an equally high accuracy as CT in the diagnosis and follow-up of renal masses. It is ranked at 8 points in the ACR appropriateness criteria; one point below CT, owing to its higher cost and lower availability.[36] MRI may be superior to CT in the detection of enhancement in the internal solid part of cysts with wall calcification as the MRI signal is not interfered with by calcification.[42] In addition, MRI is also preferable to CT as it does not expose patients to ionizing radiation. Furthermore, patients with chronic kidney disease (CKD) may be more suitable for MRI as the gadolinium used does not affect renal function. Nephrogenic systemic fibrosis (NSF) is one of the major adverse reactions of gadolinium-based contrast agents (GBCA) and by far the most serious one. It is well known that CKD patients with glomerular filtration rates <30 ml/min/1.73 m^2 are at significant risk of developing NSF. Surprisingly, recent evidence indicated that the risk is only applicable to group I and III GBCAs only. Group II GBCAs are found to expose patients to an extremely low to non-existent risk of developing NSF[43,44], such that the ACR manual on contrast media recommended a routine assessment of renal function to be optional prior to group II GBCAs administration.[45] Therefore, an MRI, if available, could potentially be regarded as the modality of choice for patients with severe renal impairments in the near future.

The advantages of ultrasonography are its high availability, low cost, and lack of ionizing radiation. However, ultrasonography has its limitations due to its lower image resolution especially in patients with obese body habitus, hemorrhage in cystic mass, and cyst wall calcification. Owing to its lower resolution, its ability to detect a renal mass smaller than 2 cm is also much lower than CT.[46] The use of color Doppler imaging has been shown to further enhance the characterization of renal mass.[36] In recent years, contrast-enhanced ultrasonography (CEUS) is emerging as a new technique to improve the image quality and accuracy of ultrasound. CEUS has been demonstrated to have a similar diagnostic value to CT and can even outperform CT scan in the detection of septa, wall thickenings and wall enhancements in cystic renal masses.[47] In terms of surveillance, size measurement of renal mass is also similar to CT, Bertelli et al. demonstrating that median size did not differ between CT and CEUS at all follow-up points during a surveillance period of over 2 years.[48] CEUS is also especially useful in patients with renal impairments as the microbubble-filled contrast agent used in CEUS is not excreted through the kidney.[39]

As the resolution of conventional ultrasound is still inferior to cross-sectional imaging and the contrast media for CEUS is only available in a few selected institutions, the diagnosis of SRM is usually determined by CT or MRI. For surveillance, however, all three modalities were found to be used in various reported surveillance protocols. CT with contrast media was the most commonly used modality for follow-up in 33 studies. The use of MRI for follow-up was reported in 14 studies to be between 6 and 34%. Ultrasonography was reported as being used for follow-up after initial cross-sectional imaging in 11 studies with 2 studies using ultrasonography for follow-up in 100% of cases.[12] This is in accordance with the recommendations from NCCN in which CT or MRI was recommended for the diagnosis and the first follow-up for active surveillance, and could be followed up by CT, MRI or ultrasonography as indicated.[19]

Surveillance intervals and triggers for intervention

While most SRMs usually grow slowly, reports have shown that a minute proportion of SRMs can still grow up to 7 mm per month and most SRMs that do exhibit changes in size do so in the early period of surveillance.[6] Therefore, most surveillance protocols use a follow-up schedule that is most frequent initially then gradually become less frequent as patients go through their surveillance years. Data from a meta-analysis reported that the most commonly used follow-up schedule was at 3, 6, 12 months after initiation of surveillance, then annually afterwards. None of the studies reported on the rationale behind their follow-up schedule nor mentioned the endpoint of surveillance.[12]

Initial data with regard to the trigger for delayed intervention stemmed from the literature on renal masses in patients with von Hippel-Lindau disease who usually develop multiple renal masses and, thus, are usually treated with surveillance until the masses were of a significant size. The cut-off size used in the study was 3 cm in which any masses below this size had shown to develop no metastasis in a median follow-up of nearly 5 years.[49] On the contrary, sporadic renal masses are usually more heterogeneous in tumor biology, therefore, the cut-off from size alone may not suffice. The growth rate of SRMs has been found to be associated with metastasis and no metastasis was found in SRMs with no growth at all.[5,13] As a result, most studies adopt a cut-off at an absolute size of > 4 cm or a growth rate of > 0.5 cm/year with some studies also included the detection of metastasis for triggering a delayed intervention[6,12] (Figure 1).

Outcomes

Oncologic outcomes

Comparison of oncologic outcomes between active surveillance and other treatment options is based on very limited data owing to the lack of prospective randomized studies and the scarcity of long-term outcome. Early data came from the Surveillance, Epidemiology, and End Results (SEER) Program urinary cancer file which enrolled 733 patients from 2000 to 2013. The results have shown a benefit of thermal ablation and cryoablation over deferred therapy, even when adjusted for age, tumor size and grade.[50] However, a more recent prospective data set from the DISSRM Registry which enrolled patients from 2009 onwards has demonstrated a comparable cancer-specific survival among nephrectomy, ablation and active surveillance when adjusted for Charlson comorbidity index, age and sex. Overall survival was lower in the active surveillance arm due to a significantly higher comorbidity but active surveillance was not independently associated with worse overall survival in an adjusted analysis.[15]

Most recent data on active surveillance in young healthy patients eventually confirmed that the lower overall survival in the active surveillance arm could be attributed to old age and high comorbidities. With a 5 year median follow-up time, there was no significant difference in seven-year overall survival between active surveillance and primary intervention; 94% vs 91%, respectively. Cancer-specific survival was 100% in both groups. Furthermore, a delayed intervention may not actually be "delayed" as the term indicates since a subgroup of patients who eventually underwent a delayed intervention, which may represent a more aggressive portion of SRMs, demonstrated a similar 5-year recurrence-free survival to primary intervention; 100% for active surveillance and 96% for primary intervention.[20]

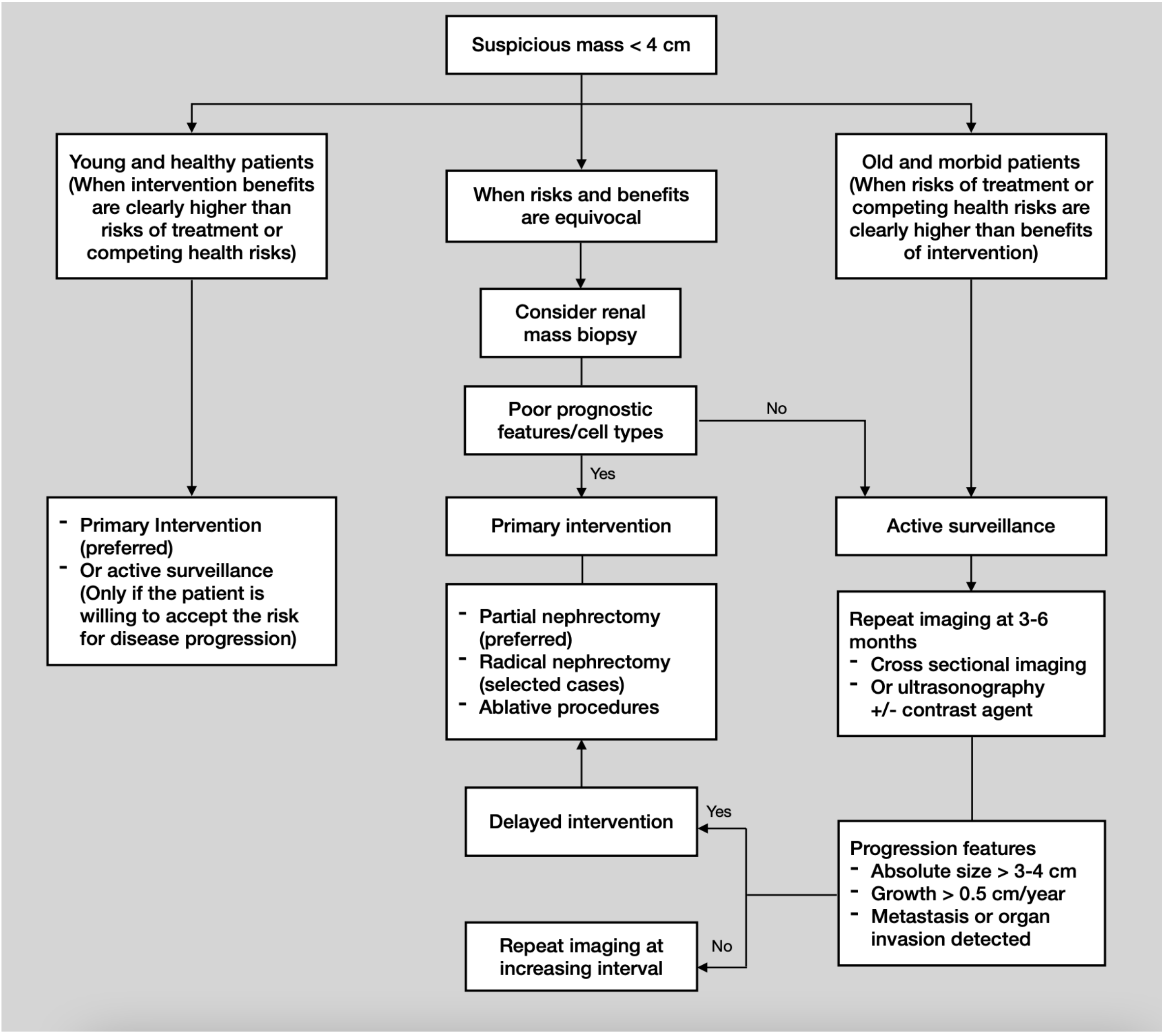

Figure 1. Suggested aigorithm for the management of renal mass smaller than 4 cm with a suspicion of malignancy

Quality of life

In terms of quality of life, active surveillance has its advantages with regard to the possibility of avoiding unnecessary procedures and recovery at the price of stress from uncertainty in relation to the diagnosis. Balancing the two sides of a coin is crucial in advising patients to choose from various treatment options. McAlpine et al. demonstrated that in the 10-year horizon, 70 years old patients would similarly benefit from partial nephrectomy or active surveillance as the gain in Quality Adjusted Life Months (QALMs) was found to be 38 months and 36 months, respectively.[51] When compared with ablative procedures, active surveillance also demonstrated a similar quality-adjusted life expectancy to cryoablation and was significantly higher than radiofrequency ablation.[52]

With regard to psychological distress, Goldberg et al. reported a similar Edmonton Symptom Assessment System - revised score (ESAS-r) and a psychological distress sub-score (PDSS) of ESAS-r between active surveillance and primary treatment. Nonetheless, the similar results between the two groups could possibly rely on the hope of the tumor being benign since a subgroup analysis of patients with biopsy-proven malignancy resulted in significantly higher ESAS-r and PDSS scores than in primary treatment.[53]

Cost

The cost of different management options is one of the factors that could affect a doctor-patient decision, especially in a low-resource setting. Cryotherapy was shown to be over 3,000 Canadian dollars more costly than active surveillance while providing the same quality-adjusted life expectancy (during the average exchange rate of CAD 1.03 to USD 1).[52] Active surveillance was also the option of choice when analysis was carried out using the willingness to pay (WTP) threshold of USD 50,000 per QALY gain while primary treatment was the option of choice when the WTP threshold is raised to USD 75,000.[54] In Thailand, however, these numbers should be regarded cautiously since the WTP threshold in Thailand and the United States are widely different. From a random survey across all regions of Thailand, an average WTP/QALY-gain ranged between THB 59,000 to 285,000 (USD 1,843-8,906 at the exchange rate on Nov 2nd, 2020) and there were no data on the analysis of cost-effectiveness concerning SRMs at this range.[55]

It is also worth noting that most of the quality of life and cost-effectiveness analyses are based on the 60-70 year old patient demographic due to the rarity of long-term outcome data on younger patients.

Conclusion

Active surveillance is a safe, effective, and also cost-effective option for small renal masses in patients in the old age and high comorbidity demographic. Data on active surveillance in young and healthy patients is emerging and could possibly extend the utilization of the active surveillance option for SRMs in a more generalized population in the future. Renal mass biopsy is an effective method for further risk stratification of SRMs prior to the selection of treatment options. Most surveillance protocols use cross-sectional imaging at the first follow-up study which is then followed up by CT, MRI, or ultrasonography, usually over increasing intervals.

References

1. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of renal cell carcinoma. Eur Urol 2019;75:74-84.
2. Lightfoot N, Conlon M, Kreiger N, Bissett R, Desai M, Warde P, et al. Impact of noninvasive imaging on increased incidental detection of renal cell carcinoma. Eur Urol 2000;37:521-7.
3. Nguyen MM, Gill IS, Ellison LM. The Evolving Presentation of Renal Carcinoma in the United States: Trends From the Surveillance, Epidemiology, and End Results Program. J Urol 2006;176:2397-400.
4. Campbell SC, Lane BR, Pierorazio PM. Malignant Renal Tumors. In: Partin AW, Demochowski RR, Kavoussi LR, Peters CA, editors. Campbell-Walsh-Wein Urology. 12nd ed. Philadelphia: Elsevier; 2021. p. 2164.
5. Lane BR, Tobert CM, Riedinger CB. Growth kinetics and active surveillance for small renal masses. Curr Opin in Urol 2012;22:353-9.
6. Uzosike AC, Patel HD, Alam R, Schwen ZR, Gupta M, Gorin MA, et al. Growth Kinetics of Small Renal Masses on Active Surveillance: Variability and Results from the DISSRM Registry. J Urol 2018;199:641-8.
7. Organ M, Jewett M, Basiuk J, Morash C, Pautler S, Siemens R, et al. Growth kinetics of small renal masses: A prospective analysis from the Renal Cell Carcinoma Consortium of Canada. Can Urol Assoc J 2014;8:24-7.
8. McIntosh AG, Ristau BT, Ruth K, Jennings R, Ross E, Smaldone MC, et al. Active surveillance for localized renal masses: tumor growth, delayed intervention rates, and > 5-yr clinical outcomes. Eur Urol 2018;74:157-64.
9. Jewett MAS, Mattar K, Basiuk J, Morash CG, Pautler SE, Siemens DR, et al. Active surveillance of small renal masses: progression patterns of early stage kidney cancer. Eur Urol 2011;60:39-44.
10. Smaldone MC, Kutikov A, Egleston BL, Canter DJ, Viterbo R, Chen DYT, et al. Small renal masses progressing to metastases under active surveillance. Cancer 2012;118:997-1006.
11. Umbreit EC, Shimko MS, Childs MA, Lohse CM, Cheville JC, Leibovich BC, et al. Metastatic potential of a renal mass according to original tumour size at presentation. BJU Int 2012;109:190-4.
12. Rebez G, Pavan N, Mir MC. Available active surveillance follow-up protocols for small renal mass: a systematic review. World J Urol 2021;39:2875-82.
13. Crispen PL, Viterbo R, Boorjian SA, Greenberg RE, Chen DYT, Uzzo RG. Natural history, growth kinetics, and outcomes of untreated clinically localized renal tumors under active surveillance. Cancer 2009;115:2844-52.
14. Lee H, Lee JK, Kim K, Kwak C, Kim HH, Byun S-S, et al. Risk of metastasis for T1a renal cell carcinoma. World J Urol 2016;34:553-9.
15. Alam R, Patel HD, Osumah T, Srivastava A, Gorin MA, Johnson MH, et al. Comparative effectiveness of management options for patients with small renal masses: a prospective cohort study. BJU Int 2019;123:42-50.
16. Wilcox Vanden Berg RN, Basourakos SP, LaRussa S, McClure TD. Management of the Small Renal Mass: a 2020 Update. Curr Oncol Rep 2020;22:69.
17. Ljungberg B, Albiges L, Abu-Ghanem Y, Bensalah K, Dabestani S, Fernández-Pello S, et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur Urol 2019;75:799-810.

18. Campbell SC, Uzzo RG, Karam JA, Chang SS, Clark PE, Souter L. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA Guideline: Part II. J Urol 2021;206:209-18.
19. National Comprehensive Cancer Network. Kidney cancer (Version 2.2022) [Internet]. [cited 2021 Sep 8] Available from: https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
20. Metcalf MR, Cheaib JG, Biles MJ, Patel HD, Peña VN, Chang P, et al. Outcomes of active surveillance for young patients with small renal masses: prospective data from the DISSRM Registry. J Urol 2021;205:1286-93.
21. Deng FM, Melamed J. Histologic variants of renal cell carcinoma: does tumor type influence outcome? Urol Clin North Am 2012;39:119-32.
22. Deng J, Li L, Xia H, Guo J, Wu X, Yang X, et al. A comparison of the prognosis of papillary and clear cell renal cell carcinoma: Evidence from a meta-analysis. Medicine (Baltimore) 2019;98:e16309.
23. Finelli A, Cheung DC, Al-Matar A, Evans AJ, Morash CG, Pautler SE, et al. Small renal mass surveillance: histology-specific growth rates in a biopsy-characterized cohort. Eur Urol 2020;78:460-7.
24. Syed JS, Nawaf CB, Rosoff J, Bryson C, Nguyen KA, Suarez-Sarmiento A, et al. Adverse pathologic characteristics in the small renal mass: implications for active surveillance. Can J Urol 2017;24:8759-64.
25. Marconi L, Dabestani S, Lam TB, Hofmann F, Stewart F, Norrie J, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol 2016;69:660-73.
26. Jeon HG, Seo SI, Jeong BC, Jeon SS, Lee HM, Choi H-Y, et al. Percutaneous kidney biopsy for a small renal mass: a critical appraisal of results. J Urol 2016; 195:568-73.
27. Bada M, Rapisarda S, Cicero C, Mauro MDI, Sebben M, B DEC, et al. The role of renal biopsy to improve small renal mass diagnosis and management: are there predictive factors for a higher detection rate?. The first Italian study of 100 cases. Minerva Urol Nephrol 2021;73:78-83.
28. Amaral BS, Macek P, Arora A, Pazeto CL, Zugail AS, Mombet A, et al. Renal tumor biopsy: rationale to avoid surgery in small renal masses. Curr Urol Rep 2021;22:46.
29. Kapur P, Setoodeh S, Araj E, Yan J, Malladi VS, Cadeddu JA, et al. Improving renal tumor biopsy prognostication with BAP1 analyses. Arch Pathol Lab Med 2022;146:154-65.
30. Maturen KE, Nghiem HV, Caoili EM, Higgins EG, Wolf Jr JS, Wood Jr DP. Renal mass core biopsy: Accuracy and impact on clinical management. Am J Roentgenol 2007;188:563-70.
31. Nuktong D, Sirisreetreerux P, Jenjitranant P, Viseshsindh W. Presentation and treatment of arteriovenous fistula, arteriovenous malformation, and pseudoaneurysm of the kidney in Ramathibodi Hospital. Insight Urol 2020;41:42-7.
32. Tikkakoski T, Paivansalo M, Apaja-Sarkkinen M, Ollikainen A, Lohela P, Matti K. Ultrasound-guided aspiration cytology of renal expansions. Rontgenblatter 1990;43:502-6.
33. Neuzillet Y, Lechevallier E, Andre M, Daniel L, Coulange C. Accuracy and clinical role of fine needle percutaneous biopsy with computerized tomography guidance of small (less than 4.0 Cm) Renal Masses. J Urol 2004;171:1802-5.
34. Ozambela M, Jr., Wang Y, Leow JJ, Silverman SG, Chung BI, Chang SL. Contemporary trends in percutaneous renal mass biopsy utilization in the United States. Urol Oncol 2020;38:835-43.
35. Patel DN, Ghali F, Meagher MF, Javier-Desloges J, Patel SH, Soliman S, et al. Utilization of renal mass biopsy in patients with localized renal cell carcinoma: a population-based study utilizing the National Cancer Database. Urol Oncol 2021;39:79.e1-.8.
36. Heilbrun ME, Remer EM, Casalino DD, Beland MD, Bishoff JT, Blaufox MD, et al. ACR Appropriateness criteria indeterminate renal mass. J Am Coll Radiol 2015;12:333-41.
37. Lukasiewicz A, Bhargavan-Chatfield M, Coombs L, Ghita M, Weinreb J, Gunabushanam G, et al. Radiation dose index of renal colic protocol CT studies in the United States: a report from the American College of Radiology National Radiology Data Registry. Radiology 2014;271:445-51.
38. Lopez PO, Dauer LT, Loose R, Martin CJ, Miller DL, Vano E, et al. ICRP Publication 139: occupational radiological protection in interventional procedures. Ann ICRP 2018;47:1-118.
39. Krishna S, Leckie A, Kielar A, Hartman R, Khandelwal A. Imaging of renal cancer. Semin Ultrasound CT MRI 2020;41:152-69.
40. Sahni VA, Shinagare AB, Silverman SG. Virtual unenhanced CT images acquired from dual-energy CT urography: accuracy of attenuation values and variation with contrast material phase. Clin Radiol 2013;68:264-71.
41. Neville AM, Gupta RT, Miller CM, Merkle EM, Paulson EK, Boll DT. Detection of renal lesion enhancement with dual-energy multidetector CT. Radiology 2011;259:173-83.
42. Israel GM, Bosniak MA. Calcification in cystic renal masses: is it important in diagnosis? Radiology

2003;226:47-52.
43. Bruce R, Wentland AL, Haemel AK, Garrett RW, Sadowski DR, Djamali A, et al. Incidence of nephrogenic systemic fibrosis using gadobenate dimeglumine in 1423 patients with renal insufficiency compared with gadodiamide. Invest Radiol 2016;51:701-5.
44. Michaely HJ, Aschauer M, Deutschmann H, Bongartz G, Gutberlet M, Woitek R, et al. Gadobutrol in renally impaired patients: results of the GRIP study. Invest Radiol 2017;52:55-60.
45. American College of Radiology, ACR Committee on Drugs and Contrast M. ACR Manual on Contrast Media. 2021 [Internet]. [cited 2021 Sep 8] Available from: https://www.acr.org/-/media/ACR/files/clinical-resources/contrast_media.pdf
46. Jamis-Dow CA, Choyke PL, Jennings SB, Linehan WM, Thakore KN, Walther MM. Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. Radiology 1996;198:785-8.
47. Park BK, Kim B, Kim SH, Ko K, Lee HM, Choi HY. Assessment of cystic renal masses based on Bosniak classification: comparison of CT and contrast-enhanced US. Eur J Radiol 2007;61:310-4.
48. Bertelli E, Palombella A, Sessa F, Baldi I, Morelli N, Verna S, et al. Contrast-enhanced ultrasound (CEUS) imaging for active surveillance of small renal masses. World J Urol 2021;39:2853-60.
49. Duffey BG, Choyke PL, Glenn G, Grubb RL, Venzon D, Linehan WM, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol 2004;172:63-5.
50. Uhlig A, Hahn O, Strauss A, Lotz J, Trojan L, Müller-Wille R, et al. Treatment for localized T1a clear cell renal cell carcinoma: survival benefit for cryosurgery and thermal ablation compared to deferred therapy. Cardiovasc Intervent Radiol 2018;41:277-83.
51. McAlpine K, Sud M, Finelli A, Kulkarni GS. Optimizing the management of patients with small renal masses in a Canadian context: A Markov decision-analysis model. Can Urol Assoc J 2021;16:E32-8.
52. Bhan SN, Pautler SE, Shayegan B, Voss MD, Goeree RA, You JJ. Active surveillance, radiofrequency ablation, or cryoablation for the nonsurgical management of a small renal mass: a cost-utility analysis. Ann Surg Oncol 2013;20:3675-84.
53. Goldberg H, Ajaj R, Cáceres JOH, Berlin A, Chandrasekar T, Klaassen Z, et al. Psychological distress associated with active surveillance in patients younger than 70 with a small renal mass. Urol Oncol 2020;38:603.e17-25.
54. Heilbrun ME, Yu J, Smith KJ, Dechet CB, Zagoria RJ, Roberts MS. The cost-effectiveness of immediate treatment, percutaneous biopsy and active surveillance for the diagnosis of the small solid renal mass: evidence from a Markov model. J Urol 2012;187:39-43.
55. Thavorncharoensap M, Teerawattananon Y, Natanant S, Kulpeng W, Yothasamut J, Werayingyong P. Estimating the willingness to pay for a quality-adjusted life year in Thailand: does the context of health gain matter? Clinicoecon Outcomes Res 2013;5:29-36.