Active Surveillance in Renal Cancer

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Introduction

The American Joint Committee on Cancer (AJCC) tumour-node-metastasis (TNM) staging for renal cancer defines a small renal mass (SRM) as stage T1a [1]; a solid renal cortical neoplasm that is less than or equal to 4 cm in greatest dimension and limited to the kidney [2].

The last few decades have seen the emergence of nephron sparing approaches to manage the SRM. The preferred surgical option and current standard of care is a partial nephrectomy which has been shown to provide excellent oncologic outcomes with preservation of renal function [3]. Non-surgical thermal ablative techniques including cryoablation and radiofrequency ablation have also been shown to have very low rates of local tumour progression and metastatic disease.

The emergence of Active Surveillance (AS) as an oncologically safe and effective management option for the SRM has also gained traction over the last decade. Approximately 20–40% of SRM's are benign [4] and a large proportion, 70% to 80% of malignant SRM's are low grade renal cell carcinomas. The rates of metastatic disease for tumours 3 cm or less are <1% and approximately 2% for 4 cm tumours [5, 6].

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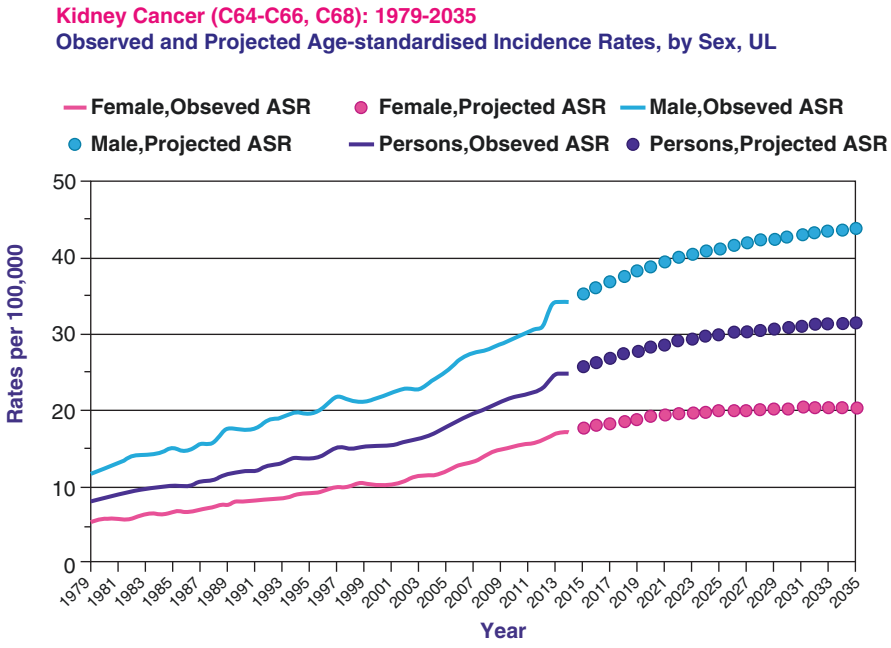

Fig. 1 The observed and projected age-standardised incidence rates, by gender, of renal cancer in the United Kingdom

Active Surveillance

Active surveillance (AS) is a form of expectant management defined as a scheduled serial assessment to evaluate tumour progression and growth rate with a view to initiating curative management once specified criteria are met. AS differs from 'watchful waiting' or 'observation' where serial assessment may be used for diagnostic and monitoring purposes without a specified schedule and may be based on subjective patient symptoms with a view to palliation if needed. AS offers a significant benefit of avoiding side effects from unnecessary treatment whilst providing clinicians and patients with a more proactive method of monitoring tumours [7].

AS of SRMs has evolved as a safe management option over the last few decades. AS may be used in conjunction with a delayed intervention as an option for patients who:

- Wish to avoid surgery
- Are willing to accept the risk of potential tumour progression compared to curative management
- Are considered high risk for surgical therapy [8].

Evaluation of AS as a management option requires thorough assessment of patient baseline/functional status, tumour, and treatments (see Table 1).

Table 1 Important factors when considering active surveillance [8–12]

Patient factors	Tumour factors	Treatment factors
Age	Imaging – Degree of infiltration – Endophytic/exophytic component – Degree and pattern of enhancement	Risk of tumour progression and/or metastasis and the subsequent effect on: – Renal function – Suitability for other management options – Patient's well-being
Co-morbidities	– Renal tumour biopsy – Histological subtype – Grade – Tumour biomarkers	Triggers for delayed intervention
Life expectancy	Progression and expected growth rate (e.g., compared to previous imaging)	Efficacy of intervention
Functional status		Availability of management options
Patient expectations		
Psychological outcomes		
Renal function		

Patient Selection

With the majority of SRMs now being diagnosed incidentally as result of widespread imaging, the incidence of real cancer is projected to rise (Fig. 1). It is important to consider the investigation and management of these often asymptomatic patients. Active surveillance is considered most useful for those whose tumour appears benign or likely to be indolent. In general, the advice is that larger tumours (>3–4 cm) and those with aggressive appearances (e.g., infiltrative growth patterns) should be managed in a proactive manner as they may be associated with increased risk of progression and metastasis [9].

There is no consensus regarding which patients are most appropriate for AS. The American Society of Clinical Oncology (ASCO) recommend active surveillance as an initial management option for those with significant comorbidities and limited life expectancy. They recommend absolute indications for AS consisting of patients with high risk for anaesthetic and intervention, or life expectancy <5 years. Relative indications include significant risk of end-stage renal disease if the SRM is treated, SRM <1 cm, or life expectancy <10 years.

The Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry (a multi-centre cohort study in United States of America following over 400 AS patients) do not recommend specific criteria for which patients should be managed with AS but found that patients opting for AS compared to intervention were older (70.8 years vs 61.8 years; $P < 0.001$), in worse health (based on performance status) and had smaller tumours (1.8 cm vs 2.5 cm; $P < 0.001$) [11]. The DISSRM

registry acknowledges AS as an initial management option for all patients with SRM, encouraging shared decision-making between patients and clinicians. They also recommend it as a primary management option for patients with tumours <2 cm or those of 'advanced age with medical comorbidities' but do not specify definitions.

Role of Renal Tumour Biopsy

The role of percutaneous renal tumour biopsy (RTB) continues to remain a contentious area. There is no consensus as to whether every patient with a SRM should undergo a biopsy procedure or select cases only on an individualised basis. A diagnosis of malignancy ascertained by RTB is considered fairly accurate with the overall median diagnostic rate as 92%, with a sensitivity and specificity of 99.1% and 99.7% for core biopsy [6, 13].

The ASCO guidelines recommend all patients with a SRM should be considered for RTB, based on tumour-specific findings, competing risks of mortality, and when the results may alter management [12]. Specifically, they recommend RTB may be useful in patients with clinical findings suggesting lymphoma, abscess, or secondary renal metastasis. ASCO also recommend RTB should be considered for patients undergoing AS as the biopsy helps assess metastatic risk and therefore helps with patient counselling and managing patient expectations [12].

American Urological Association (AUA) guidelines recommend RTB in any mass not considered to be a primary solid renal tumour (e.g., haematological, metastatic, inflammatory, infectious appearances) as it will help confirm diagnosis and direct therapy. It does not recommend RTB for young or healthy patients unwilling to accept the uncertainty or who will elect for intervention regardless of the result. Nor does it recommend RTB for older or frail patients who will be managed conservatively. If proceeding with RTB, AUA recommends multiple core biopsies (2–3 cores with a 16–18-gauge needle under CT/US guidance rather than FNA) [8]. Finally, AUA recommends RTB in all patients undergoing thermal ablation as the tissue necrosis post-intervention hinders subsequent histological diagnosis.

European Association of Urology (EAU) guidelines recommend a RTB should be considered in patients who are candidates for AS of small masses, to obtain histology prior to ablative treatment and for the selection of the most suitable medical and surgical management in metastatic disease [10–12]. A RTB is not indicated in frail or comorbid patients that are planned for a watchful waiting approach and masses that are contrast enhancing or cystic, and in whom surgery in planned. RTB of cystic tumour masses are not recommended [14].

A renal tumour biopsy is not without its complications. The non-diagnostic rate has been reported as between 10–20% [5]. Common complications have been reported to include lumbar pain and haematoma (4.3%), of which the majority are self-resolving [15]. The risk of tumour seeding along the tract is relatively rare, especially with the co-axial technique. The Renal Cancer Group from Oxford have reported 7 cases where tumour seeding was identified on histological examination of the resection specimen after surgical resection of the renal cell carcinoma

following diagnostic percutaneous biopsy [16]. Six of the seven cases were of papillary RCC type. The clinical significance of this remains uncertain, only one of the patients developed local tumour recurrence at the site of the previous biopsy.

A multicentre study has shown that in departments where renal tumour biopsies are performed frequently, the likelihood of benign findings at pathology is significantly lower (5% vs. 16%) suggesting renal tumour biopsies could reduce the incidence of surgery for benign tumours and the associated risk and morbidity that is involved [17].

Overall, it is important to consider the role of RTB in AS, as imaging alone cannot provide a definitive diagnosis of malignancy. Factors to take into account when deciding if RTB is appropriate would be whether patients are fit candidates for surgery, the suspected tumour aetiology and whether systemic and/or other non-cancer treatments are indicated.

Imaging Surveillance

Numerous imaging modalities may be used for serial assessment of SRMs. Ultrasound imaging (USS) tends to be low cost, avoids radiation exposure and relatively easily accessible; however, can be operator-dependent and may not provide the level of detail required to fully assess the tumour for signs of growth and/or progression. Thus, often the size/diameter is the key factor reported. Computed tomography (CT) offers detailed assessment of the tumour and is relatively accessible, however it exposes patients to radiation and/or contrast depending on the protocol used, which is not ideal in a population likely to have or to develop reduced kidney function. Finally magnetic resonance imaging (MRI) offers a very detailed assessment of the tumour however is costly, less accessible, and may be contraindicated in certain patients depending on their medical history.

There is no consensus regarding which imaging modality is ideal for AS. Different protocols exist and tend to incorporate a mix of modalities. AUA guidelines recommend cross-sectional imaging and/or USS every 3–6 months alongside assessment of renal function (serum creatinine level, proteinuria) and metabolism (liver function tests); and chest imaging [8]. The ASCO protocol is axial imaging (or USS) every 3 months for the first year, followed by every 6 months in the second and third years, and annually thereafter [12].

The DISSRM protocol consists of USS every 6 months for 2 years and then annually afterwards. They report alternating between cross-sectional imaging and USS for most patients alongside monitoring renal function annually [11]. Following this protocol, there was a 100% and 99% 5-year cancer-specific survival for patients undergoing AS compared to primary intervention. The 5-year overall survival was 75% and 92% respectively [18].

An important factor in deciding the frequency for serial imaging is tumour size and growth rate. Growth is often expressed as maximum tumour diameter over time (e.g., mm/year). Growth is considered the most objective factor to aid identifying sinister SRMs [6].

It is accepted that smaller tumours are often associated with reduced malignancy risk, with SRMs <1 cm considered benign in 50% of cases [8]. However the risk of malignancy increases to 75% in lesions 1–2.9 cm in size. In those lesions diagnosed as renal cell carcinomas, aggressive tumour behaviour has only been observed in 20–25% of cases of lesions <7 cm [8, 12, 13]. Given that a high propensity of SRMs are likely to be benign, there may be an argument for the least invasive and safest imaging modality of USS to be used.

Tumour growth rate and metastatic potential are also factors to consider when deciding frequency and imaging modality. SRMs are considered low metastatic risk as they have an annual metastatic potential of approximately 3%. SRMs tend to grow at a rate of roughly 2–3 mm per year [19]. However, it should be noted that the natural history of SMRs is difficult to ascertain as it was previously thought the gold standard of care was surgical removal soon after diagnosis, which resulted in a lack of long-term data [20]. There is an overall belief that SRMs experience variable growth each year, from positive growth to no growth, therefore deciding when to change to curative intervention should not be based on growth alone [21, 22]. Deciding on frequency of imaging in AS and criteria for when to change from AS to definitive management should incorporate growth alongside other clinical and biochemical factors. The benefit of using AS is that it allows for a personalised and dynamic approach to patients and their SRM.

Currently, there is no widely accepted protocol for optimal imaging modality and frequency in AS but USS is often recommended based on its safety profile allowing it to be used more regularly as needed. Published protocols and guidelines seem to suggest a range of frequencies for imaging from 3 months to annually.

Chest imaging is often considered as part of monitoring for SRMs to detect metachronous or synchronous metastatic disease. A recent study from the DISSRM registry analysed the chest imaging performed on initiation of AS and found that 19% (51/268) of patients had abnormal baseline chest radiographs. Of this, 22 (43%) had pathology which was acted upon (e.g., pulmonary nodules, thyroid nodules, mediastinal masses). Of the 217 who had normal initial chest radiographs, only 23 (11%) developed abnormal findings on subsequently yearly chest imaging with 10 having actionable pathology. No patient developed metastatic RCC [23]. From these findings, it may be recommended to perform chest radiograph or CT monitoring for patients who are high risk of metastatic RCC and/or patients who have abnormal findings on baseline chest imaging.

Parameters to Monitor in AS

There are no set criteria which should trigger a change in management for the SRM undergoing AS. Criteria which may be considered include: tumour size, rate of tumour growth, level of infiltration, surrounding structures infiltrated, clinical

Table 2 Triggers for intervention when on AS from ASCO, AUA and DISSRM guidelines

ASCO [12]	AUA Guidelines [8]	DISSRM [11]
Tumour size >4 cm	Tumour size >3 cm	Tumour size >4 cm
Tumour growth >5 mm/year	Tumour growth >5 mm/ year	Tumour growth >5 mm/year
	Clinical changes in patient/tumour factors	Elective crossover (e.g., change in patient preference or improvement in patient health)
	Stage progression	Metastatic progression of disease
		Development of symptoms (e.g., haematuria without other cause)

AUA American Urological Association, *DISSRM* Delayed Intervention and Surveillance for Small Renal Masses.

changes in patient, change in patient preference. The Table 2 below summarises existing guidelines:

Risks and Benefits of AS

The risks and benefits of AS should be considered with every patient and a balanced discussion should take place prior to commencing AS.

Risks include a small but present risk of cancer progression and potential lack of curative therapies should the cancer metastasize [24, 25]. AS has been associated with relatively low rates of growth and metastatic progression of tumour in short-term follow-up (2–3 years) as it tends to be selected for smaller and more benign-appearing tumours [8]. The window for surgical management may also be missed either due to tumour progression and/or patients' overall health status deteriorating.

Benefits include avoiding overdiagnosis and overtreatment of potentially elderly and comorbid patients. A concern of initiating AS is whether it would have an effect on patients' psychology given that some may interpret it as a more passive form of management. However, it should be emphasized to patients and clinicians alike that AS consists of active monitoring with the view to changing management, if appropriate, when triggers are met. The only study to look at the effect of AS on patients' well-being was a multicentre study which assessed quality of life (QoL) of patients undergoing AS (n = 101) vs immediate intervention (n = 226) and they found that there was no adverse effect on mental health 1 year on [26].

What Do the Guidelines State?

A summary of association recommendations is as follows (Table 3):

Table 3 A summary of guidelines published regarding AS

	American Society of Clinical Oncology (ASCO) [12]	American Urological Association (AUA) [8]	Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) Registry [11]	European Association of UrologY (EAU) [10]
Candidate for AS	Absolute indications High risk for anaesthetic and/or intervention Life expectancy <5 years Relative indications Significant risk of end-stage renal disease if treated SRM <1 cm Life expectancy <10 years	Any renal mass < 2 cm Significant comorbidities Significant life expectancy Risk of intervention outweighs potential benefits of active treatment	Did not recommend specific criteria however found patients opting for AS were: – Older – In worse health (based on performance status) – Smaller tumours (<2 cm)	Significant comorbidities Elderly
RTB	Suggests all patients with SRM should be considered for RTB based on tumour-specific findings, competing risks of mortality and when results may alter management (specifically in patients with clinical findings suggesting lymphoma, abscess or secondary renal metastasis). They recommend considering it in every patient as biopsy may help assess metastatic risk and guide patient counselling.	Suggests RTB for any mass not considered to be a primary solid tumour (e.g., haematological, metastatic, inflammatory, infectious appearances) to help confirm diagnosis and direct therapy. Does not recommend for young or healthy patients unwilling to accept the uncertainty or who elect for intervention regardless of the result. Does not recommend for older or frail patients who will be managed conservatively.	Suggests in patients for whom choice of AS or primary intervention is unclear Patient undergoing AS with growth >5 mm/year	Suggests RTB in patients who are candidates for AS with small masses Suggests RTB prior to ablative therapy Suggests RTB in SRMs to select most suitable medical/surgical management of metastatic disease. Does not recommend for frail or comorbid patients undergoing watchful waiting Does not recommend for masses that contrast-enhancing or cystic tumour masses Does not recommend for patients undergoing surgery

Table 3 (continued)

AS protocol suggested	Axial abdominal imaging (or USS) every 3 months in the first year, twice in the second and third years, and annually afterwards.	Cross-sectional imaging +/− USS every 3–6 months. Consider alternatives to contrast when possible or necessary (doppler, diffusion weighted images, etc). Consider renal function assessment (serum Cr, proteinuria), liver function tests and chest imaging.	USS every 6 months for 2 years and then annually afterwards. Recommend alternating between cross-sectional and USS. Monitor renal function annually. Recommend annual chest imaging if baseline chest radiograph is abnormal.	Does not specify
Triggers for intervention	Tumour size>4 cm Tumour growth >5 mm/year	Tumour size >3 cm Tumour growth >5 mm/year Clinical changes in patient/tumour factors Stage progression Benefits of treatment outweigh the risk	Tumour size >4 cm Tumour growth >5 mm/year Elective crossover (e.g., change in patient preference or improvement in patient health) Metastatic progression of disease Development of symptoms (e.g., haematuria without other cause)	Does not specify

AS Active surveillance, *SRM* small renal mass, *RTB* renal tumour biopsy, *USS* ultrasound scan, *cm* centimetre, *mm* millimetre, *Cr* Creatinine.

Key Points

- A Small Renal Mass (SRM) is classified as stage T1a - ≤4 cm
- 20–40% of SRM's are benign
- The risk of metastases from a SRM that is ≤3 cm is less than 1%
- Active surveillance consists of scheduled serial monitoring of the tumour with the view to changing the management approach should specified criteria be met (i.e., tumour growth, tumour progression, patient preference).
- The rationale for Active surveillance is that the slow-growth and low metastatic rates of SRMs could negate the beneficial effect of active management and avoid unnecessary procedures in poor surgical candidates: the elderly and/or comorbid patients with low life expectancy.
- There are patient factors, tumour factors and treatment factors that must be considered as part of the shared decision-making process with the patient
- Renal tumour biopsy should be considered when a histological diagnosis will change management, which ranges from confirming a benign diagnosis, preventing further surgery or to confirm metastatic disease from extra-renal malignancies.
- The non-diagnostic rate of renal tumour biopsy is approximately 10–20%, however, in centres where high numbers of renal mass biopsy is performed, the likelihood of benign surgical histopathology has dropped to ≤5%
- There is no ideal imaging modality type or schedule. Each patient must have an individualised plan based on their tumour characteristics and comorbidities.
- A combination of USS/CT/MRI imaging will provide the most detailed information to aid surveillance planning and protocol
- The patient may choose to come off Active Surveillance at any time with the knowledge that treatment with curative intent is available

Conclusion

The literature on SRMs is limited to case series, observational studies, and non-randomized comparative studies using statistical means to compensate for biases. Of this, most of the literature is based on open surgical approaches while few studies focus on AS [8]. Therefore, the evidence for and against AS ought to be considered in the context of this paucity of literature and could serve as a focus for future research.

Active surveillance proves to be a useful management option of small renal masses. It is particularly useful in elderly and comorbid patients, who are increasing in numbers given our ageing population, however, it should not be underestimated as a management option for others. AS is useful for SRMs, which are statistically likely to be benign and/or remain indolent, and could avoid unnecessary overtreatment.

The most important aspect of a patient's SRM management is the personalised multidisciplinary approach alongside patient preference. AS is a management option that facilitates shared decision-making between the clinician and patient. The highly selective group of elderly and comorbid patients should be offered an individualised AS plan as part of the standard discussion for their SRM management.

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