Current Role of Active Surveillance in the Management of a Small Renal Mass

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Abstract Renal cell carcinoma accounts for 3–4% of adult malignant neoplasms and over 65,000 new cases of kidney cancer were diagnosed in the USA in 2013 [1, 2]. Widespread use of abdominal imaging is leading to an increased incidence in the detection of small renal masses (SRMs) among other causes [1–4]. In light of recent literature on the role of percutaneous renal mass biopsy and retrospective data analysis, surveillance for renal masses ≤ 4 cm is likely to become more common especially in patients with less aggressive pathology, advanced age and multiple medical comorbidities.

Keywords Small renal mass · Active surveillance · Growth kinetics · Cryoablation

Introduction

Small renal masses are defined as clinically localized tumors measuring 4 cm or less. Renal cell carcinoma accounts for 3–4% of adult malignant neoplasms, with a growing incidence in part due to technological advances and more widespread use of non-invasive abdominal imaging [1, 2, 4]. Nephron sparing surgery is a standard of care for patients with SRMs when it is technically possible, as it offers excellent oncologic outcomes, and higher preservation of kidney function compared to radical nephrectomy [1]. SRMs are often incidentally found in patients

who are poor surgical candidates due to medical comorbidities and advanced age. This leaves clinicians with difficult decisions regarding the management of incidentally discovered SRMs. In recent years, there has been a growing body of data, which suggests that active surveillance (AS) shows no worse outcome in cancer specific mortality when used in certain patient populations.

Active Surveillance for Small Renal Masses

An expanding body of research has become available in recent years arguing for active surveillance citing that non-cancer-related risks often outweigh the cancer-specific mortality for patients with clinically localized renal cell carcinoma (RCC) [3, 4]. In 2009, a multi-institution registry was formed to report outcomes for patients undergoing active surveillance with a small renal mass called DISSRM or delayed intervention and surveillance for small renal masses. Recently, the data from DISSRM has been cited in numerous studies. This registry prospectively followed patients with SRMs ≤ 4 cm who either elected for primary intervention (PI) $n = 274$, or active surveillance (AS) $n = 223$. Intervention was recommended for patients in AS once their tumor growth rate was >0.5 cm/year or once the greatest tumor diameter reached >4.0 cm. Patients who chose primary intervention (PI) then selected either partial nephrectomy (PN), radical nephrectomy (RN), or cryoablation CA for treatment of their tumors. Overall survival for PI was 98% at 2 years and 92% at 5 years compared to 96% for AS at 2 years, and 75% at 5 years. Furthermore, the progression-free survival, including those who chose to cross over from AS to delayed intervention, was 95% at 2 years and 67% at 5 years. Several factors not found to be predictive of overall survival included tumor size, ECOG status, and RENAL nephrometry score. However, factors that did impact on overall survival were both age and cardiovascular index. Of note, statistically significant predictors of disease

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progression in the AS cohort were both age and ECOG score [5]. Overall, this research provides excellent insight into the natural history of SRMs, as well as the outcomes for patient undergoing AS vs. PI. A recent small study including 45 patients under AS for larger renal tumors (cT1b-T2) reported no progression to metastatic disease and no patients with RCC specific mortality at a median follow up of 32 months. This study, while small, supports the plausibility of expectant management for SRMs [2].

Growth Kinetics

The principle risks in active surveillance are the feared progression to metastatic disease, or that by waiting a simple partial nephrectomy is no longer feasible. These risks must be balanced with the individualized risk of intervention for each patient. Many retrospective analyses have proposed active surveillance for small renal masses due the low metastatic potential (2%) for masses ≤ 4 cm [5]. In a prospective study by Mason et al., 82 patients with SRMs were observed over the course of a 3-year period in which only 1 patient developed metastatic disease [6]. Overall, the growth rates for patients in DISSRM ($n = 158$) was a median of (0.11 cm/year). This is consistent with the renal cell consortium of Canada which showed similar results in their study ($n = 178$) with a growth rate on average of 0.13 cm/year [4, 5].

Multiple studies have attempted to outline predictive factors other than the growth rate that can predict the aggressiveness of a tumor. This would be very beneficial when counseling patients, especially for those who chose active surveillance. A recent multicenter prospective study by Organ et al.

observed disease progression in 169 patients diagnosed with presumed RCC on abdominal imaging. Ultimately, this study found that neither tumor characteristics at the time of diagnosis (size, consistency), patient age, nor symptoms were reliable for predicting tumor growth over time. Another study by Schiavina et al. involving 70 patients suggested that male sex and symptomatic presentation are associated with higher growth rates in those managed with active surveillance [7]. Unfortunately, the small number of symptomatic patients (5) make a definitive conclusion difficult to ascertain. Overall, there is conflicting evidence with regard to what is and is not associated with aggressive renal tumors. While some authors conclude that male gender correlates with aggressive tumor biology, others tout that the RENAL nephrometry score is more predictive of aggressiveness [4, 7]. At this time, there is no single characteristic that can be reliably used to determine future tumor behavior, highlighting the need for further investigational studies. The most reliable characteristics that can be extrapolated from recent research seem to be size of tumor at diagnosis as well as tumor growth rate [1, 4, 5]. Table 1 is a comprehensive overview of the recent literature for active surveillance for SRMs. Overall, the trend that can be readily appreciated from the table is the relatively low cancer specific deaths and progression to metastasis. However, where these studies lack is in the duration of follow-up, with the average being approximately 40 months.

Percutaneous Renal Biopsy

Percutaneous renal biopsy (PRB) and its role in the management of SRMs continue to differ throughout the literature.

Table 1 Active surveillance for cT1a renal tumors

Author	Patients/ Tumors	Age (years)	Size (cm)	Growth rate (cm/year)	Follow up (Months)	Delayed surgery <i>n</i> (%)	Progression to metastasis (%)	Deaths, <i>n</i> (%)
Pieroazio et al.	223/240	70.6	1.9	0.11	25.2	21 (9.4)	0	0
Haramis et al.	44/51	71.7	2.67	0.15	77.1	2 (4.5)	0	1 (2.2) ^a
Organ et al.	169/207	72.5	2.15	0.12	20.4	—	—	—
Jewett et al.	178/209	73	2.1	0.13	28	9 (5)	1.1	2 (1.1) ^b
Abouassaly et al.	110/110	81	2.5	0.24	24	4 (3.6)	0	34 (31) ^a
Rosales et al.	212/223	71	2.8	0.34	35	11 (5)	1.9	14 (6.6)
Crispen et al.	154/173	69	2.45	0.29	31	68 (39)	1.3	0 (0)
Brunocilla et al.	62/64	75	2	0.40	91.5	16 (25.8)	3.2	2 (3.2) ^b
Mason et al.	82/84	74	2.6	0.25	36	12 (14.6)	1.2	1 (1.2) ^b
Abou Youssef et al.	35/44	78.1	2.2	0.21	47.6	8 (22)	5.7	9 (25.7) ^a
Volpe et al.	29/32	71	2.48	0.10	38.9	8 (27)	0	2 (6.9) ^a
Chawla et al.	61	—	2.97	0.20	36	20 (32.8)	1.6	0 (0)

^a non-cancer specific-related deaths

^b cancer specific deaths [4–6, 8–16]

Some centers recommend PRB for all patients with SRMs [17]. The European Association of Urology recommends PRB for patients who choose active surveillance, while the American Urologic Association outlines PRB as yet another option for the management of SRMs [5, 18]. The accuracy of PRB has improved over the past few years, with sensitivity ranging from 90 to 100% [19]. Critics of PRB point out that 10–20% of biopsies are non-diagnostic, and cannot reliably distinguish between high and low grade disease. [18–21]. There is a need for further research regarding the efficacy of PRB especially in patients pursuing active surveillance. PRB remains a safe and reliable option to help guide the decision making process for patient and clinicians [19]. It is both useful in patients considering active surveillance as well as at the time of treatment for patients undergoing minimally invasive therapy such as cyroablation and radiofrequency ablation. The highest yield for PRB is for those patients with intermediate risk, and medical comorbidities in which a biopsy confirmation of malignancy would help accurately compare risks of active surveillance vs. primary intervention.

Cyroablation

Cryoablation (CA), either laparoscopic or percutaneous, is becoming a valuable option for patients with small renal masses. The majority of the data surrounding the use of CA is limited to treatment of SRMs in patients who are otherwise poor surgical candidates (elderly, medical comorbidities), making the results of such studies susceptible to selection bias. Regardless, CA remains a viable, minimally invasive treatment modality with low complication rates for small renal masses.

Patient selection for CA is essential, as cryoablation does not offer the same long-term oncologic outcomes as partial nephrectomy. In a case series from Washington University, the reported success rate was 87% of the 124 patients who underwent percutaneous cryoablation (PCA). Mean follow-up was 30.2 months, in which they reported a cancer specific survival rate of 100%, and an estimated disease free survival of 85% at 3 years. Of note, tumor size greater than 3 cm was a predictor of disease recurrence [21]. In another study from the Mayo Clinic, the failure rate was reported at 3.5% of 389 patients who underwent cryoablation, most of which (63%) were diagnosed as RCC prior to ablation. Another study done by the Mayo Clinic published similar outcomes for local tumor recurrence in patients with small (≤ 3 cm), and large (3–8 cm) renal masses which raises the question of 3 cm being a good predictor of disease recurrence [22].

While CA is a minimally invasive option for SRMs, it does not come without risks. Firstly, the higher rate of recurrence, makes this a less ideal option for patients who could otherwise tolerate a partial nephrectomy [23]. Major complications

(Clavien grade 3 and higher) from CA are rare (0–9%) for both laparoscopic and PCA. Overall, the reported complication rates for PCA are lower than those associated with the laparoscopic approach [22, 23]. Furthermore, the overall affect on renal function needs to be considered as CA does not come without consequences, especially in patients with a solitary kidney [22, 23]. There are varying reports regarding the degree of functional renal decline following CA. Some studies report no difference while others report a eGFR decrease of 25 and 28% for LCA and PCA, respectively [22]. Variables associated with a positive outcome included hilar location and smaller tumors, whereas the most significant predictor of functional renal decline was a history of a solitary kidney. While some of these studies show statistically significant renal decline, there has yet to be evidence that this functional decline has clinical significance with regard to progression of CKD or exacerbation of other medical comorbidities [22].

Conclusions

Recent data suggests that 2 years of AS with or without delayed intervention does not significantly affect the overall survival of patients with small renal masses, nor does it significantly increase the risk of progression to metastatic disease. A careful discussion between the clinician and patient are essential in outlining the risks and benefits of different management strategies of SRMs and patient compliance. A growing majority of the US population 65 years or older has one or more of the following conditions: hypertension, heart disease, and diabetes. These common comorbidities compete with cancer specific mortality in patients with an incidentally discovered renal mass. Therefore, risk stratification of each patient's medical comorbidities should be utilized to help guide clinicians in the management of SRM [1]. AS along with delayed intervention have proven to be viable management strategies, and will continue to evolve with the growing understanding of kidney tumor biology.

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