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Active Surveillance of Renal Cortical Neoplasms

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1. Introduction

Over the last two decades there has been an increase in the detection of small (≤ 4 cm) renal cortical neoplasms (RCN) that is attributed to the increase in axial abdominal imaging.[1] Although these lesions are typically asymptomatic in nature, they present a potential management dilemma for the treating urologist. The standard of management in kidney cancer has always been surgical excision with either radical nephrectomy or partial nephrectomy. For tumors <4.0cm, partial nephrectomy is now the surgical standard, which provides equivalent cancer control compared with radical nephrectomy and provides a nephron-sparing treatment.[2]

Historically, the majority of incidental renal masses have been treated relatively soon after detection. While effective, this treatment paradigm has limited our knowledge regarding the natural history of the small renal mass. It has also been observed that despite the increase in the detection of renal cell carcinoma (RCC), that there has not been a significant impact on patient overall survival.[3] Therefore, it is necessary to explore the concept of active surveillance (AS) in small renal masses in order to report the observed natural history and use this knowledge to make accurate and appropriate treatment recommendations to patients. Previously, AS was recommended only for patients with a reduced life expectancy such as the elderly or in patients at high risk for a surgical procedure. Currently, AS is also utilized for healthy patients who reject surgical management or a renal ablation procedure.[2] This chapter will review the natural history of the small renal mass, factors to consider when recommending active surveillance, contemporary treatment outcomes, and the role of the image-guided renal mass biopsy.

2. Natural history

The natural history refers to the behavior of the small renal mass over time with no intervention. The critical questions to be addressed are: can tumors metastasize? When do they metastasize? How do patients know if their tumor is the type that will metastasize? Table 1 shows data from 11 of the larger AS series, which provides some insight into the natural history of these tumors. However the most series are retrospective and vary in terms of selection criteria for inclusion and renal mass monitoring, which introduces selection bias. Therefore, the lack of prospective randomized controlled trials limit the interpretation of the data regarding AS to some degree. Rendon and colleagues followed 13 tumors with a mean

follow-up of 30.7 months and observed a mean GR of 0.22cm/year. There was no progression to metastatic disease.[4] Volpe and coworkers followed 32 tumors in 29 patients for a mean time of 39 months. The mean tumor size was 2.5cm with a mean growth rate of 0.1cm/year. There were no deaths or cases progressing to metastasis.[5] However, most of the literature is composed of small retrospective single center studies with small patient cohorts and short-term follow-up. The majority of tumors on AS are small (≤ 4cm) providing no knowledge about the natural history of larger tumors. In addition, there is no standard in terms of inclusion criteria, surveillance protocol or time for delayed intervention. A meta-analysis in 2006 from 9 different centers observed 234 tumors with a mean size of 2.6cm and an average growth rate of 0.28cm/year. There were 56% of tumors with available pathology and 92% were found to be renal cell carcinoma (RCC). These confirmed RCC lesions grew at a rate of 0.4cm/year, which is considerably faster than the lesions remaining on AS (0.2cm/yr).[6] Recently, the largest single center study on AS demonstrated an average GR of 0.34cm/yr in 223 tumors followed for 35 months. Eleven (5%) patients required some form of delayed intervention. There were 4 patients that progressed to metastatic disease and 1 cancer-specific death.[7]

3. Review of management options for the cT1 renal mass

Historically, the gold standard for the treatment of renal masses of any size was radical nephrectomy. However, the importance of nephron-sparing surgery focuses not only on avoiding chronic renal insufficiency, but also to decrease the incidence of cardiovascular events and death.[8,9,10] Therefore, in patients with a renal mass ≤ 4cm (cT1a), partial nephrectomy is the new gold standard. It has even been suggested that tumors <7cm (cT1b) should be managed with parital nephrectomy when surgically feasible.[2] In addition, the use of minimally invasive techniques should be applied when possible to improve patient related benefits such as reduced post-operative pain, shorter hospital stay and a faster post-operative recovery. In addition to partial nephrectomy, renal tumors can be ablated in the form of cryoablation, radiofrequency ablation (RFA), and high intensity focused ultrasound (HIFU). These modalities provide a minimally invasive treatment option for patients while avoiding surgical resection of the tumor. Both cryoablation and RFA can be performed from a laparoscopic or a percutaneous approach. The surgical approach is usually determined by tumor location with lateral and posterior tumors being treated with percutaneous ablation and anterior tumors treated with laparoscopic ablation. Percutaneous procedures do not require general anesthesia, have minimal post-operative pain, and are usually associated with a short (< 24 hour) hospital stay. Although long-term data are not yet available with these modalities, intermediate-term data demonstrates favorable recurrence and progression free survival.[11,12,13, 14]

The role of AS in the treatment of small RCN is well known and is considered a recommendation for elderly patient and in patients that are considered to be at high surgical risk. AS can be considered an option for healthy patients who have been informed of all treatment options and who insist on avoiding surgical extirpation or ablation. The majority of the urologic literature has demonstrated that most small RCNs have a slow growth rate (GR) and low risk of metastasis.[10] A summary of the contemporary AS series (820 tumors) show a growth rate of 0.27cm/year with 21% undergoing delayed intervention (Table 1). Only 12 (1.6%) lesions progressed to metastatic disease with only 1 cancer specific death. The American Urologic Association guidelines panel for the management of a T1 renal mass

found that only 4 of 390 (1%) patients progressed to metastasis while on AS. This has led them to conclude that the rate of progression is sufficiently low to warrant AS in selected patients.

Active Surveillance Series	Number of patients and tumors	Mean growth rate (cm/year)	Mean follow-up (months)	Number with delayed surgery (%)	Number progressing to metastasis (%)	Cancer specific deaths (%)
Bosniak et al (1995)	37/40	0.36	39	26 (65)	0	0
Kassouf et al (2004)	24/26	0.09	32	4 (17)	0	0
Volpe et al (2004)	29/32	0.1	27.9	8 (27)	0	0
Wehle et al (2004)	29/29	0.12	32	6 (21)	0	0
Lamb et al (2004)	36/36	0.39	24	0	1 (2.8)	0
Chawla et al (2006)	49/61	0.2	36	20	1 (2)	n/a
Kouba et al (2007)	43/46	0.7	35.8	13 (30)	0	0
Abou Youssif et al (2007)	35/44	0.21	47.6	8 (23)	2 (5.7)	0
Abouassaly et al (2008)	110/110	0.26	24	4 (4)	2 (1.8)	0
Crispen et al (2009)	154/173	0.28	31	68 (44)	2 (1.8)	0
Rosales et al (2010)	212/223	0.34	35	11 (5.1)	4 (1.9)	1 (0.5)
Summary totals	**758/820**	**0.27**	**33.1**	**157 (20.7)**	**12 (1.6)**	**1**

Table 1. Summary of Active Surveillance Series

4. Active surveillance: How to decide

Initiating an AS protocol depends on the individual patient's clinical presentation. Many factors such as initial tumor size (ITS), growth rate, patient age, general medical health, and desire for intervention are considered. In addition, about 20% of small renal masses are benign and 50% to 60% are low-grade RCC.[18-20] Therefore only 20% to 30% of small RCNs are considered high-grade with aggressive features.[15-17] Frank and colleagues retrospectively reviewed 2,935 tumors from a single institution to determine if ITS was a predictive factor for malignancy. The average tumor size was 4.2cm and 6.3cm for benign and malignant tumors respectively. For each centimeter increase in diameter of the tumor, there was a 17% increase in the likelihood of the mass being malignant.[17] Additionally, larger malignant lesions were more likely to be high-grade (conventional) renal cell carcinomas (RCC) as opposed to low-grade cancers. However, the large single institution series by Rosales and colleagues and the meta-analysis by Chawla determined that there was no correlation between GR and ITS. Several series on AS have supported these findings and in general, the consensus is that ITS is not a predictive factor for an increase in GR or malignant potential in renal masses <4cm.[14,18-21]

Tumor growth rates in large single institution series and meta-analyses have been shown to be reasonably low (0.28-0.34cm/year) for most tumors.[6,7] Kunkle and co-workers concluded that there was no difference in the incidence of malignancy between tumors with zero growth versus those that do grow. However, this conclusion was based on only 6 tumors excised with no net growth over a 12 month period.[22] It is the author's firm belief that tumors with high growth rates usually represent malignant lesions and require some form of delayed intervention (DI). Crispen and colleagues found that 39% (68/173) of patients on AS underwent DI and the GR was significantly higher than those tumors that remained on AS (p=0.023).[23] Similarly, studies have demonstrated that GRs are significantly higher in confirmed RCC lesions compared with lesions not undergoing treatment (0.4cm/hr vs. 0.21cm/yr and 1.75cm/yr vs. 0.34cm/yr).[6,7]

Another potential predictive factor to consider when deciding on the value of an AS protocol is patient age. Abouassaly and coworkers followed an elderly population of patients (mean age 81 years) for an average of 24 months. The patients had a mean tumor size of 2.5cm and a GR of 0.26cm/yr, which are consistent finding with other contemporary series. At the conclusion of the study 31% of the cohort was deceased, however the disease specific survival was 100%.[24] A meta-analysis by Kouba and colleagues observed that there were slower tumor GRs in patients of advanced age (<60yr. had GR of 0.90 cm/yr vs. ≥60yr. had GR of 0.60 cm/yr, p=0.057). They also demonstrated that patients who underwent DI were significantly younger compared with those that remained on AS (p=0.0006). This suggests that the decision to intervene in younger patients was influenced by both GR and age.[25]

General medical fitness is another important factor when deciding on management. Patients who are high-risk for surgical related and post-operative complications or who are elderly will be better served with an active surveillance protocol or a form of ablative therapy. Many young, healthy patients prefer to be managed with a less invasive treatment as well, and elect to undergo cryoablation or radiofrequency ablation or be placed on active surveillance. Although these are not recommended as a standards or recommendations for these patients, they are options as long as the patients have been informed about risks of disease progression and the necessity of regular and careful follow-up

5. Active surveillance in large (cT1b and cT2) renal cortical neoplasms

Most urologists only consider an AS protocol for patients presenting with a cT1a (≤4cm) mass. However, there are select patients that have larger masses who may be ideal candidates for AS based on their clinical status. Mues and colleagues followed 42 tumors in 36 patients for a mean of 36 months. Average tumor size was 7.13cm and GR was 0.57cm/yr. Three patients underwent delayed intervention for rapid tumor growth. Only 2 (5.6%) patients developed metastasis and there were no cancer related deaths.[26] This data suggests that even larger masses have relatively slow growth rates with low metastatic potential.

6. Outcomes after long-term follow-up

The majority of retrospective studies have relatively short-term follow-up making it impossible to make definitive conclusions about the natural history of these tumors. Table 1 lists several AS series indicating the small number of tumors that have undergone delayed intervention, progression, or death. Abou Youssiff followed 44 tumors with a mean follow-up of 47.6 months. The average growth rate was 0.21cm/year. Two (5.7%) patients developed metastatic disease and there was 1 (2.9%) cancer specific death.[21] Haramis and colleagues reported the only single center experience with a minimum of 5 years follow-up. Fifty-one tumors with a mean follow-up of 77.1 months demonstrated a GR of 0.15cm/yr. Two (4.5%) patients had delayed intervention and there were no patients that developed metastasis or death from their tumor.[27] This represents a selected cohort due to the fact that patients with faster GR underwent DI earlier. However, the evidence suggests that tumors that are amenable to AS for a 5 year period are likely indolent and will not progress to metastatic disease or require intervention.

Patients who develop metastatic RCC generally have a poor prognosis. Large studies shows 12 reported cases on AS progressing to metastatic disease, which represents 1.6% of patients. The mean time to metastasis was 72.5 months with a mean growth rate of 1.04 cm/yr. Dechet and colleagues showed a direct correlation between tumor size and the presence of a synchronous metastasis. The authors compared 110 cases of biopsy proven metastatic RCC to 250 clinically localized tumors. As tumor size increased, there was a statistically significant increase in synchronous metastasis. They found that for every 1 cm of tumor size, the odds of finding a synchronous metastasis increased by 22%.[28] Conversely it has been shown that small tumors can also be dangerous. Minardi and co-workers followed 48 patients who had tumors after partial nephrectomy for a mean follow-up time of 92.9 months. All tumors were pT1a with clear cell renal cell carcinoma histology. Four (8.3%) developed metastatic disease at 24 months.[29] The majority of series that report metastatic disease indicate that there was interval growth in the primary lesion and that most tumors displayed an accelerated growth rate.[7,14,21,23,30,31,32] Therefore, an increased growth rate may be associated with progression to metastatic disease.

7. Role of biopsy

Until recently, renal mass biopsy has been considered unnecessary and contraindicated for the in the work-up of an enhancing solid renal mass. The procedure itself exposes the patient to potential morbidity with complications such as bleeding and hematoma

formation, injury to adjacent organs, infection and pain. The false negative rate for the diagnosis of cancer is high and a sample of benign renal tissue may very well coexist with a cancerous tumor.[33] Also, there is concern related to needle biopsy tract cancer seeding with the technique itself, however there is little data to support this theory.[34] A recent study has indicated that improvements in technique have led to higher levels of diagnostic accuracy (sensitivity of 97.7% and specificity of 100%), however this practice is not considered the standard of care.[35] Rosales and co-workers performed biopsy in only 40 (19%) of their AS series.[7] However, we believe that future patients entering an AS protocol will undergo renal mass biopsy in order to optimize patient selection. New techniques such as immunohistochemical biomarkers and molecular or genomic characterization of tissue may help to identify potentially aggressive tumors that would be more likely to fail AS.

8. Conclusions

Active surveillance is a reasonable treatment option for select patients with a cT1 renal mass. Surveillance is recommended in elderly patients who either have a short life span or who are at high risk for undergoing standard surgical procedures for renal mass treatment. Active surveillance is also an option for healthy patients who do not wish to have surgery performed and who understand the risk of potential disease progression. Growth rate is likely a predictor of malignancy that should be monitored and used to determine if delayed intervention is indicated. Larger tumors (cT1b and cT2) may also be followed under AS in select patients with special attention to changes in GR. The technique and value of renal mass biopsy has changed in the last decade and now provides improved accuracy in diagnosis, which will help determine patient selection for AS protocols. Finally, long-term follow-up has improved our knowledge of the natural history of these tumors and helps urologists to better council patients in the management of their tumors.

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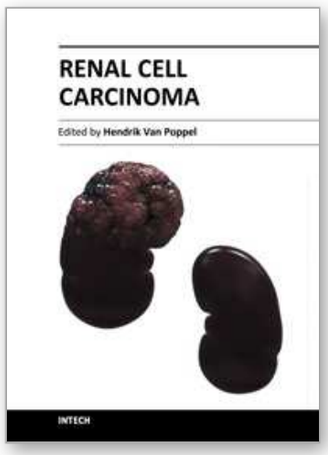

Renal Cell Carcinoma

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Surgical and medical oncologists have been unable to decrease renal cell carcinoma mortality for uncertain reasons, although a lot of progress has been made in diagnosis and imaging, recognition of different genetic and pathological entities, management of localized disease and in the research on new drug treatments for advanced stages of the disease, potentially combined with surgery. The purpose of this book, which tackles a number of separate interesting topics, is to provide further insight into the disease and the management of early and advanced renal cell carcinoma. The volume is divided into different parts; the first part covers the characterization of renal masses and the second part covers rare distinct pathological entity. In the management section, active surveillance, partial nephrectomy and radiofrequency ablation are presented. A separate chapter reviews the management of Von Hippel Lindau disease, and finally, conventional and aberrant signaling pathways are explored.

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