

Small renal masses: current concepts regarding the natural history and reflections on the American Urological Association guidelines

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Purpose of review

Although surgical resection is the current standard for treatment of small (<4 cm) renal cortical neoplasms, active surveillance remains an option in selected patients depending on tumor characteristics and surgical risk. We review the natural history of small renal masses according to the current literature, and highlight issues regarding the recent guidelines for the management of T1 renal masses put forth by the American Urological Association.

Recent findings

The natural history of small renal masses is still largely unknown; however, initial size or volume of the mass seems to predict the risk of malignancy in retrospective studies. A new study found that growth rate is inversely related to initial tumor volume, with smaller masses growing faster in the beginning and decreasing in rate of growth as they enlarge. Biomarkers such as carbonic anhydrase IX, vascular endothelial growth factor, and CD147 have demonstrated some value in predicting tumor characteristics and prognosis in renal cell carcinoma. Finally, we suggest modifications to the new American Urological Association guidelines based on the authors' experience in order to optimize the management of renal cortical neoplasms.

Summary

The natural history of small renal masses is not completely understood. Growth rate and tumor size are factors shown to be predictive of tumor biology. Currently, there are no specific tumor markers to determine initial risk or progression to metastatic disease; however, investigation into new molecules is being undertaken. The guidelines presented by the American Urological Association give a formal framework for the management of T1 renal cortical neoplasms; however, we site specific modifications and recommend that they be considered when evaluating patients for treatment.

Keywords

active surveillance, cryoablation, laparoscopy, partial nephrectomy, small renal neoplasm

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Introduction

The incidence of renal cell carcinoma (RCC) has increased significantly in the past three decades with 54 000 new cases and 13 000 deaths estimated in the USA in 2008 [1]. Historically, patients with renal tumors presented clinically with gross hematuria and flank pain. However, frequent use of cross-sectional imaging has led to the detection of asymptomatic localized renal masses found incidentally. The greatest incidence of these tumors is found in patients in the sixth and seventh decades of life [2]. Despite an increase in detection, cancer-specific death rates have not decreased indicating that treatment of these incidental renal lesions may be of little or no benefit to some patients. Surgical resection in

the form of radical nephrectomy historically had been the standard of care for the treatment of renal tumors; however, the surgical management of small renal masses (SRMs) (≤ 4 cm) has changed dramatically with the concept of nephron-sparing surgery and with the expansion of minimally invasive techniques such as laparoscopy, robotic-assisted surgery, and ablative technologies. In addition, observation or active surveillance has emerged as another reasonable treatment alternative to surgery in selected patients. We review the current literature regarding the natural history of SRMs and indications for active surveillance. In addition, we review and evaluate the recently published American Urological Association (AUA) guidelines for the management of T1 renal masses.

Natural history of small renal masses and indications for initial surveillance with possible delayed intervention

RCC is a term used to describe a heterogeneous group of tumors with varied degrees of biologic aggressiveness. The majority of renal cortical neoplasms (80%) are known to be malignant, but only 20–30% of malignant T1a lesions have potentially aggressive features. The natural history of SRM is not well characterized, as the majority of tumors are surgically removed soon after diagnosis. In addition, most series on active surveillance are small, retrospective, single-institution studies with short-term follow-up. Renal biopsies are not routinely performed in the evaluation of SRMs and are not available for many of the tumors undergoing active surveillance. The decision to surgically excise a tumor is usually based on changes in radiographic characteristics such as initial size, growth kinetics, and physician perception of risk. Therefore, the possibility exists that several renal masses may be benign.

Initial tumor size measured on preoperative imaging has been suggested as a variable to help predict the natural history of SRMs [3]. Frank *et al.* [4] reviewed disorder from a large series of 2935 renal tumors from a single institution, which demonstrated that for each 1-cm increase in diameter, there was a 17% increase in the likelihood of the lesion being malignant. In addition, correlations were made between tumor size and final pathological features such as histology and tumor grade. For example, larger lesions were more likely to be a clear cell or high grade as opposed to a papillary or low-grade lesion [4]. Thompson *et al.* [5^{*}] confirmed these findings by reporting another retrospective series of 2675 tumors. A positive correlation existed between tumor size and probability of malignancy with a 16% increase in the odds of cancer detection with each 1-cm increase in tumor size. For tumors with clear cell histology, each 1-cm increase in size increased the odds of high-grade disease by 25% [5^{*}]. Laudano *et al.* [6] demonstrated that initial tumor size predicts RCC histology. Tumors of 4 cm or less that had undergone surgical removal were reviewed. The majority of tumors (87.3%) were malignant, and 74.6% showed clear cell histology. For every 1-cm increase in the diameter up to 4 cm, the malignant tumors were 1.27 times more likely to be a conventional RCC as opposed to another RCC subtype [6]. However, although there may be an association between initial tumor size and disorder, most SRMs are malignant and, in a small number of cases, are found to exhibit aggressive disease. Gill *et al.* [7] reported on 100 tumors after laparoscopic partial nephrectomy (LPN) with a mean size of 2.8 cm. In this cohort, 70% of tumors were found to be malignant and 30% benign, indicating that size is often unreliable in determining malignancy [7].

The greatest risk of observing a clinically localized, enhancing renal lesion is the potential for progression to metastatic disease. The first case of reported progression was described in an active surveillance series of 36 elderly patients who were at high surgical risk. One patient developed metastatic disease 132 months from initial diagnosis [8]. Chawla *et al.* [3] identified only 1% of lesions progressing to metastatic disease after surveillance of 34 months. All three of these lesions demonstrated interval growth during surveillance, and all three patients were symptomatic at the time of progression [3]. The risk of progression of renal masses of 4 cm or less is generally low and, at this time, there are no documented reports of metastasis occurring in the absence of tumor growth. However, there is no noninvasive, absolute or reliable way to distinguish benign from malignant or indolent from aggressive tumors. Patients must be aware that the potential for metastatic disease exists and that there is some level, although quite small, of risk involved in managing a small renal cortical neoplasm with observation alone. In addition, patients should be informed that progression may lead to a loss in the ability to treat tumors with a nephron-sparing approach, and that there are currently no curative therapies for metastatic disease.

At this time, there are no formal defined indications or established protocols for active surveillance of SRMs. However, it is helpful to know which patients are reasonable candidates for observation. Significant medical comorbidity is the most common relative indication for observing an enhancing renal mass. Patients with serious health risks who are deemed poor surgical candidates or who possess a chronic disease such as a secondary malignancy that significantly reduces life expectancy should be counseled regarding the risks and benefits of active surveillance as an initial treatment option. Similarly, some elderly patients with poor performance status and shorter life expectancies are unlikely to suffer sequelae from an untreated localized RCC. Last, some patients may wish to undergo observation on an elective basis despite being young, healthy, or a low-risk surgical candidate.

Imaging of renal masses: size determination and growth rates

Enhancement upon intravenous contrast administration is the hallmark of a renal cortical neoplasm. Therefore, axial imaging modalities such as computed tomography (CT) and MRI are considered the gold standard for the identification of renal tumors. These studies consist of precontrast and contrast phase imaging to adequately measure Hounsfield units. In addition, monitoring the renal lesion with a consistent imaging modality ensures that the tumor characteristics can be accurately compared.

The most common and simplest method of reporting renal lesion growth is to measure the linear growth. When using axial imaging, linear growth assumes that the tumor is spherical and that growth occurs uniformly in all directions. The maximal cross-sectional diameter is measured with the growth rate expressed as the change in diameter per year (cm/year) [9]. When measuring in this fashion, care should be taken to measure the mass at the same level within the kidney on both the new and prior study in order to compare the interval growth. A more accurate way to evaluate growth kinetics is by calculating the volume of the mass. Volumetric growth better quantitates cell number and biologic growth as compared with maximal diameter, and can be determined on the basis of the number of cross-sectional dimensions that are known. Growth can then be expressed as tumor doubling time [10]. The growth rate of cystic renal lesions is difficult in some cases due to the loss or accumulation of fluid that may not represent a true change in the tumor cell mass.

The growth rates of SRM have been reported in several series. In one study [11], seven of 32 renal masses observed were cystic in nature. Growth rates were reported separately and found to be similar at 0.09 and 0.11 cm/year for the cystic and solid masses, respectively [11]. Kouba *et al.* [12] observed 46 masses with a mean follow-up of 36 months and found a mean growth rate of 0.36 cm/year. A meta-analysis demonstrated that most renal masses grow at a relatively slow rate. Combined data from several small observational series included 234 SRMs with a growth rate of 0.28 cm/year. However, it must be noted that growth rates in these series do not necessarily reflect the growth of RCC, as pathologic evaluation was not performed on all lesions. Initial tumor size has been evaluated as a potential predictor of growth. Bozniak [13] did not notice a difference in growth rates when comparing masses of 2 cm or less to more than 2 cm. Chawla *et al.* [3] observed 61 masses for 36 months. Mean lesion size at presentation was 2.97 cm. The correlation of growth rates based on lesion size was not statistically significant [3]. In contrast, Crispen *et al.* [14*] demonstrated an association between tumor volume and growth rates, with smaller tumors exhibiting significantly faster growth than larger tumors. This observation is consistent with Gompertzian kinetics in that a tumor's growth rate is initially exponential and then decreases with increasing size [14*].

Growth rate and disorder

One important factor that urologists use to guide treatment decisions related to the management of SRMs is the growth rate on cross-sectional imaging. It is hypothesized that tumors with faster growth rates are more likely to be malignant than tumors that grow slowly. Kato *et al.* [15]

evaluated 18 RCCs that were surgically removed after observation. Mean growth rate was 0.42 cm/year. A positive correlation was found between growth rates and tumor grade. High-grade tumors grew at a faster rate (0.93 cm/year) as compared with intermediate and low-grade tumors (0.28 and 0.37 cm/year) [15].

Although most incidental SRMs are slow growing, it cannot be safely assumed that lack of growth radiographically correlates with an absolute indolent clinical course. Kunkle *et al.* [16] observed 106 renal masses for at least 12 months. Lesions were grouped together based on growth rates determined by CT or MRI. Group 1 consisted of 35 enhancing masses with a zero or negative growth rate after a mean follow-up of 29 months. Group 2 included 71 lesions showing a median growth rate of 0.31 cm yearly. Extirpation was performed in 17% (six patients) of lesions in group 1 and in 51% of lesions in group 2. Malignancy rates were similar in the two groups, and these data have been used to support the fact that growth rate does not correlate with malignancy. However, the diminutive number of tumors exhibiting zero growth that were removed in this trial precludes any reasonable conclusions regarding the relationship of growth rate and malignancy [16].

Active surveillance and advancements in molecular biomarkers

The active surveillance of a SRM must be viewed by both the urologist and patient as a calculated risk. At this time, the natural history of SRMs is unclear and regular follow-up imaging should be done using a consistent modality (CT or MRI) and compared with prior studies focusing on tumor characteristics such as tumor size (maximal diameter or volume) and number. Measurements of known lesions should be taken at equivalent levels within the kidney compared with earlier studies, and the presence of new lesions or cysts should be closely assessed. Patients should be aware that tumors exhibiting a rapid growth rate, the presence of new tumors on follow-up imaging, or the onset of symptoms related to a renal mass may change the management from observation to surgical resection.

At this time, there are no known reliable tumor markers to evaluate growth rate or metastatic potential. However, certain molecules are being investigated as potential markers for prognosis. Carbonic anhydrase IX (CAIX) is a hypoxia-inducible gene present in RCC cells and regulates the conversion of carbon dioxide to carbonic acid. In one study [17], patients with RCC were evaluated using tissue microarray to evaluate CAIX staining. High levels of CAIX staining had a more favorable prognosis as compared with intermediate and low-staining groups. CAIX was found to be an independent predictor for

prognosis after adjusting for stage, grade, and RCC subtype [17]. Additionally, CAIX levels measured in serum have been found to have a statistically significant relationship with tumor stage, grade, and size. In a subset of patients who suffered recurrence after treatment of local disease, CAIX levels were found to be higher as compared with those without recurrence (168 vs. 77 pg/ml) [18].

Vascular endothelial growth factor (VEGF) is a hypoxia-inducible growth factor responsible for tumor angiogenesis. CD147 is an extracellular matrix metalloproteinase inducer that may lead to tumor invasion and metastasis [19]. Expression of VEGF and CD147 in advanced RCC patients and the prognostic value of these markers was evaluated in specimens from 53 patients with metastatic clear cell RCC and compared with 12 healthy controls. Expression rates in the RCC patients for VEGF and CD147 were 84.9 and 88.7%, respectively, as compared with controls, demonstrating no expression of VEGF and expression of CD147 in two patients. Positive expression of both molecules significantly correlated with a higher tumor, node, metastasis stage and a lower 1-year survival rate as compared with controls [20**].

Reflections on American Urological Association guidelines

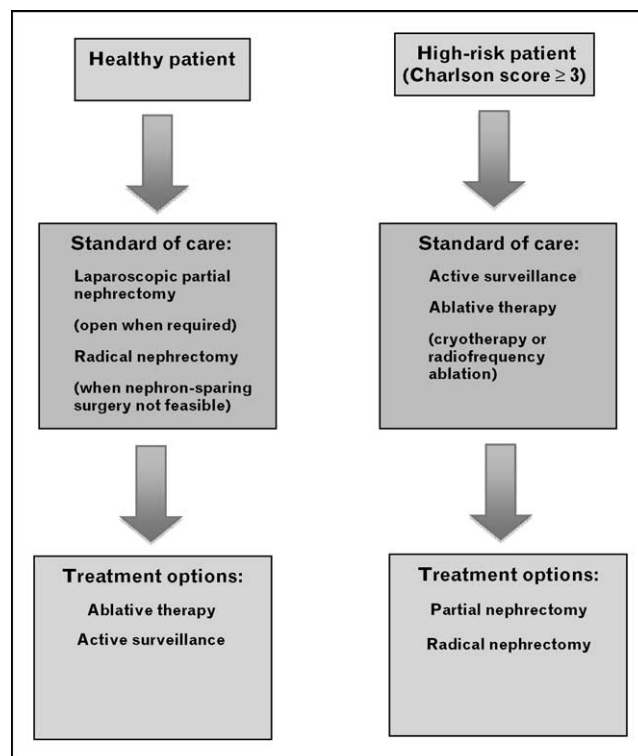
Recent AUA guidelines released in 2009 for the management of T1 renal masses reviewed evidence-based data related to active surveillance, nephron-sparing surgery, and various surgical approaches [21**]. The guidelines suggest that in a healthy individual with a T1a lesion that surgical resection is the standard of care; however, active surveillance is an option for management with an emphasis on counseling patients regarding the risk of disease progression, lack of treatment if metastasis occurs, and potential for the loss of an ability to treat the lesion with a nephron-sparing procedure. In patients with major comorbidities at high surgical risk, active surveillance is a recommendation from the panel, and discussion should involve the aforementioned risks.

Surgical management with radical nephrectomy is appropriate for T1 tumors when a nephron-sparing procedure is not possible. Radical nephrectomy remains a standard in both healthy individuals and high-risk surgical patients for all T1 tumors and is the only standard mentioned for T1b tumors in high-risk surgical patients. Minimally invasive approaches are preferable, when feasible, due to patient benefits such as improved convalescence and recovery. Nephron-sparing surgery is the reference standard for T1 tumors when technically possible and particularly in patients in whom there is a specific indication for nephron-sparing surgery such as a solitary kidney, multiple tumors, or chronic renal insufficiency. Open partial nephrectomy has well established oncologic out-

comes comparable to radical nephrectomy and is preferred for complex cases such as hilar tumors, multiple masses, and in solitary kidneys. LPN is an option for surgeons with advanced experience; however, LPN is associated with a significantly higher number of complications when compared with open partial nephrectomy, higher positive margin rate, and longer warm ischemia times. The duration of warm ischemia has been shown to be an independent predictor of reduced renal function [22].

Ablation therapies using laparoscopic and percutaneous cryoablation and radiofrequency ablation (RFA) are additional minimally invasive treatment modalities that are considered recommended therapies for only T1a lesions in patients with significant comorbidities. They remain an option for healthy T1a individuals and in T1b tumors. Criticisms of ablation therapy are related to an increased risk of local recurrence as compared with partial nephrectomy, poorly defined measures of success, and complicated salvage surgical therapy, if required. In addition, there are variable follow-up methodologies, and most series do not report postablation biopsies. Failure is considered when more than one session of ablation is required to achieve radiographic success defined as no enhancement and no growth in the tumor ablated site. Cryotherapy series report an

Figure 1 Treatment algorithm for T1a (≤ 4 cm) renal cortical neoplasms



overall lower rate of incomplete ablation when compared with RFA. Patients must be counseled regarding the potential need for additional ablative treatments or surgical intervention, and must accept a long-term radiographic surveillance protocol.

If treatment is necessary, ablation therapy should be the standard of management, as it is the least invasive surgical modality and carries the lowest complication rates (Fig. 1). Finally, we recommend not offering ablative therapy for patients with T1b renal tumors (Fig. 2). The guidelines are a thoughtful analysis of contemporary literature. However, in the authors' opinion, there are some subtle discrepancies between the guidelines and the state-of-the-art understanding in small renal cortical neoplasm management that need to be addressed. In healthy individuals with a T1a neoplasm who desire treatment with renal ablation, it should be stressed that repeat ablation is rarely necessary and not technically difficult if needed. Therefore, ablation options should not be excluded in these individuals. High surgical risk T1a patients with a comorbidity index of at least 3 should be managed with active surveillance when possible. If treatment is necessary, ablation therapy should be the standard of management, as it is the least invasive surgical modality and carries the lowest complication rates. Finally, we recommend not offering ablative therapy for

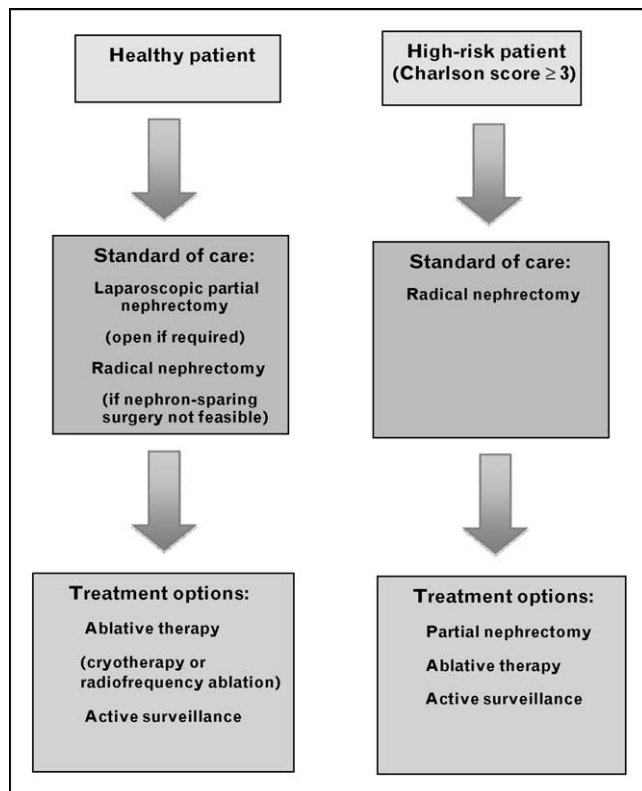
patients with T1b renal tumors. In our experience, these larger tumors exhibit a much higher complication rate, particularly with renal tumor fracture and hemorrhage, and the efficacy of ablation modalities is also diminished in this population.

Conclusion

RCC is a diverse disease process with the majority of lesions demonstrating malignant disorder, but only 20–30% exhibiting aggressive tumor biology. This concept causes the management of SRMs to be challenging and controversial. The natural history of SRMs is not completely known, as the vast majority of masses are either removed at diagnosis or after a short period of observation. In addition, there are no tumor markers or absolute biologic predictors to assess risk or progression to metastatic disease.

Recently, the AUA has created formal guidelines for the management of all T1 tumors with specific standards, recommendations, and options for therapy depending on lesion size and clinical scenario. Although extirpation remains the standard of care for renal masses in most situations, additional series of active surveillance with larger numbers and longer follow-up are necessary to clarify its value.

Figure 2 Treatment algorithm for T1b (4–7 cm) renal cortical neoplasms



References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 178).

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