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The Evolving Management of Small Renal Masses

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Abstract

The incidence of small renal masses (SRMs) continues to rise, largely due to the widespread use of cross-sectional imaging for abdominal symptomatology. Clinical management must balance the risk of disease progression from renal cell carcinoma (RCC) in these tumors against the potential morbidities of treatment, particularly in elderly patients or those with multiple comorbidities. Moreover, a significant minority of SRMs represent benign lesions. Here, we review the current data for surgical excision, cryoablation, radiofrequency ablation, and active surveillance of SRMs. Surgical excision, predominantly in the form of nephron-sparing surgery, remains the standard of care due to its durable oncological and favorable functional outcomes. Active surveillance and ablative technologies have emerged as alternatives to surgery in select patients based on short-term oncological data. Nevertheless, the extent to which treatment alters the natural history of SRMs is yet to be established.

Introduction

In 2008 there were approximately 54,400 newly diagnosed cases of cancer of the kidney and renal pelvis in the United States, the majority of which represent renal cell carcinoma (RCC) [1]. Cancer of the kidney accounts for approximately 3.5% of all malignancies, and is the third most common cancer of the urinary tract [1]. Although the overall incidence of RCC has been steadily increasing for the past two decades, in large part due to the increased application of abdominal imaging, there has been a concurrent downward stage migration, with small renal masses (SRMs), defined as lesions with a maximum diameter of 4 cm or less, now accounting for the largest proportion of newly diagnosed renal tumors [2].

Interestingly, despite the increased detection of SRMs, for which the survival rates following surgical excision are between 95–100% [3–4], the mortality rates from RCC continue to increase [5]. As the increasing deaths from kidney cancer have primarily been noted for lesions > 7 cm, these data suggest that the increasing detection, and resulting increased surgical treatment, of SRMs may not be impacting patient survival [5]. Therefore, increasing attention has turned to alternative, less invasive management approaches to patients with SRMs, including the thermal ablative techniques of cryoablation and radiofrequency ablation (RFA), as well as observation or active surveillance (AS).

As the minimally invasive techniques of cryoablation and RFA are potentially less morbid in nature, the treatment patterns for anatomically uncomplicated SRMs have preferentially shifted toward these ablative technologies at some institutions [6]. While the published outcomes to date suggest that ablation may have short-term metastasis-free survival rates comparable to

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surgical excision, it remains unanswered whether treatment actually impacts cancer-specific or overall survival of patients with SRMs, or whether the excellent reported outcomes of patients undergoing such treatments is simply a function of their indolent nature and prolonged natural history. Importantly, a substantial number of tumors included in the outcome analyses from ablative series do not have pathological confirmation of malignancy. Therefore, given the recognized high frequency of benign lesions among patients with SRMs [7], many of the tumors from these series might not have been destined to progress. At the same time, AS has emerged as a management option for the SRM, particularly in elderly and unfit patients. Increasing data has been accumulated on the growth kinetics and metastatic potential of SRMs under AS [8••].

Prospective data comparing the outcomes for patients treated with excision, ablation, and observation are lacking, leaving the optimal management of SRMs in debate. Here, we review existing outcome data for each of these approaches, emphasizing differences in patient selection and definitions of treatment efficacy which encumber our ability to directly compare results from each modality.

Surgical Excision of the SRM

The standard of care for clinically localized RCC remains surgical resection, due to the favorable prognosis associated with surgery, as five-year cancer-specific survival rates following nephrectomy are in excess of 95% [3]. Surgery for renal tumors was initially performed with complete kidney removal, or radical nephrectomy, with partial nephrectomy reserved for patients with a solitary kidney, bilateral tumors, or pre-existing renal disease. Over the last decade, however, the benefits of nephron-sparing surgery (NSS) have increasingly been realized.

Specifically, partial nephrectomy has been shown in multiple series to have equivalent oncological efficacy to radical nephrectomy for renal tumors 4 cm or less [3-4;9]. Moreover, patients undergoing NSS for SRMs have been found to be significantly less likely to develop postoperative chronic kidney disease (CKD) than patients treated with radical nephrectomy [10-11••]. Interestingly, Huang et al. [11••] found that, even in the setting of a normal baseline serum creatinine and contralateral functioning kidney, patients undergoing radical nephrectomy for a SRM were 3.8 times more likely to develop CKD after surgery than patients undergoing partial nephrectomy. The importance of renal preservation is increasingly relevant as emerging evidence has linked CKD to cardiovascular events and death [12]. Therefore, the potential exists that overtreatment of SRMs with radical nephrectomy may in fact be contributing to the seemingly-paradoxical increased overall mortality in these patients [5], specifically by increasing the rate of non-cancer deaths. To this end, Huang et al. [13] recently evaluated the Surveillance, Epidemiology, and End Results (SEER) cancer registry and found a significantly decreased number of cardiovascular events and improved overall survival in patients undergoing partial versus radical nephrectomy for SRMs. Similarly, a series from the Mayo Clinic noted an increased risk of mortality among patients treated with radical nephrectomy compared to NSS for pT1a (< 4 cm) renal tumors [14•].

Unfortunately, however, NSS remains underutilized in the United States. An analysis of the Nationwide Inpatient Sample showed that partial nephrectomy accounted for only 7.5% of kidney cases nationally between 1988-2002 [15•]. Likewise, data from the SEER registry demonstrated that only 20% of renal tumors less than 4 cm are treated with partial nephrectomy [13;16]. The overuse of radical nephrectomy is likely multifactorial in nature. For one, partial nephrectomy for the SRM is potentially more technically challenging than radical nephrectomy. Second, and perhaps more likely, outcome data from renal transplant donors demonstrating no decrease in kidney function on long-term follow-up have been

inappropriately extrapolated to patients with a SRM, perpetuating the misconception that the risk of CKD after radical nephrectomy is insignificant. Significant disparities exist between donor patients and patients presenting with SRMs, including age, smoking status, and the prevalence of comorbidities such as hypertension and diabetes, all of which are risk factors for CKD. Indeed, a recent study noted that 25% of patients with a SRM have pre-existing CKD [11••]. Therefore, the potential impact of radical nephrectomy on the quality and length of survival of patients with a newly diagnosed SRM further supports the use of NSS as the preferred treatment option.

While long-term outcome data for partial nephrectomy primarily reflect the results from the open surgical approach, laparoscopic NSS has shown similarly favorable early results, with a 100% cancer-specific survival reported at three-year follow-up in one series [4]. More recently, robotic-assisted laparoscopic partial nephrectomy has been utilized as a technique to overcome the learning curve associated with pure laparoscopic partial nephrectomy, particularly to facilitate a minimally-invasive approach to complex SRMs [17]. The ability of these techniques to provide equivalent renal functional preservation and durable oncologic efficacy will require future study as additional follow-up becomes available. Regardless of the approach, however, NSS remains the treatment of choice for SRMs, and efforts must continue to educate physicians and patients regarding the benefits of renal preservation.

Thermal Ablation for SRMs

Cryoablation

Cryoablation of SRMs was first described in 1995 [18], and may be performed with open, laparoscopic, or percutaneous image-guided techniques [19]. Cryoablation effects tumor kill through freezing of tissues, specifically by generating an ice ball using liquid argon or nitrogen [19-22]. Ablation can be monitored by a thermocouple or by ultrasound in order to confirm appropriate extension of the ice ball [19-20]. Temperatures less than -20°C are required for appropriate treatment, and such conditions have been experimentally observed 3.1 mm inside the boundary of an ice ball [21]. Hence, in clinical practice, tissues are generally cooled to -40 °C, and the ice ball is propagated 1 cm beyond the tumor's edge [19].

Tumor destruction occurs through rapid freeze-thaw cycles [19], and two freeze-thaw cycles appear to achieve the best tissue ablation [19;23]. Cell death results from protein denaturation and from extracellular ice formation during freezing, which disrupts cell membranes and causes movement of intracellular water with subsequent alterations in cellular pH [22]. Cell death may continue for days after the procedure, due to delayed tissue necrosis from thermal injury to local microvasculature [22;24].

Although the choice of approach to cryoablation (percutaneous versus laparoscopic/open) may in part depend on tumor location, with anterior lesions thought to be less accessible percutaneously, objective comparisons of the outcomes between laparoscopic/open cryoablation versus percutaneous treatment are only recently emerging. Finely et al. [25] reported significantly greater procedure times, narcotic requirements, and hospital stays among 19 patients treated with laparoscopic cryoablation compared to 18 patients who underwent percutaneous cryoablation. Moreover, a separate study found that the percutaneous approach was considerably more cost effective (median cost \$6,861) than laparoscopic cryoablation (median \$29,617) [26]. Nevertheless, a recent meta-analysis found that >75% of reported cryoablation treatments to date have been performed through an open or laparoscopic approach [27•], a finding which may reflect practice pattern bias, in that the majority of newly-diagnosed SRMs are initially evaluated by urologists, who have used surgical approaches preferentially.

Radiofrequency ablation

RFA was first described as a primary treatment modality for renal tumors in 1999 [28]. Ablation occurs as radiofrequency waves are converted to heat, resulting in thermal tissue damage [19]. Specifically, high-frequency alternating current produces rapid heating of tissues by stimulating ionic agitation [29]. Clinically, a temperature between 50-100°C is targeted [29], as denaturation of proteins and destruction of cell membranes occurs when the tissue temperature rises above 50°C; however, vaporization, which results when temperatures above 105°C, renders ablation non-uniform and thereby ineffective. As evidence suggests that the renal vasculature may act as a “heat sink” during RFA, reducing the efficacy of treatment, exophytic tumors have been thought to be better candidates for RFA than central lesions [30]. Although RFA has been applied using open, laparoscopic, and percutaneous techniques, with ultrasound, CT, and MRI guidance [19;31], a meta-analysis found that approximately 94% of patients from the current literature who underwent renal RFA were treated with a percutaneous approach [27•], likely reflecting the utilization of this technology primarily by interventional radiologists.

Results of thermal ablation

Radiographic follow-up after cryoablation or RFA is currently the most common means of assessing treatment effect [32], with enhancement or growth on postcontrast imaging considered evidence of incompletely treated disease [33]. Nevertheless, a particular issue often debated with regard to ablative techniques has been the definition treatment efficacy, as some centers have routinely performed a biopsy after ablation to assess for viable disease, while others have relied upon imaging alone [32;34••]. Importantly, for patients treated with cryotherapy, Weight et al. [34••] demonstrated excellent correlation between post-cryoablation radiographic findings and percutaneous biopsy results, such that no lesion which failed to enhance on post-treatment imaging revealed evidence of viable tumor on biopsy. On the other hand, these investigators found that 45% of renal tumors that failed to show enhancement following RFA demonstrated viable tumor at a six-month post-treatment biopsy [34••]. Their results have been countered by others who argue that heat fixation during RFA preserves tumor architecture and makes a biopsy six months following treatment not a reliable method to assess RFA efficacy [35]. Instead, Raman et al. [36•] reported that, when biopsies were taken at a minimum of one year following RFA in 20 tumors that did not enhance on cross-sectional imaging, none of the biopsies contained ‘viable’ tumor cells.

To our knowledge, only one published study to date has compared the outcomes of cryoablation and RFA performed at the same institution [37], with the remainder of studies containing single-institution reports of a single ablative modality. In that study, Hegarty et al. [37] retrospectively reviewed the Cleveland Clinic experience with laparoscopic cryoablation (179 renal lesions) versus RFA (81 tumors), and noted radiographic evidence of disease persistence in 1.8% of lesions after cryoablation versus 11.1% of lesions after RFA. Interestingly, similar results were found on a recent meta-analysis comprised of 47 studies representing 1375 kidney lesions treated with cryotherapy or RFA [27•]. Here, local tumor persistence/recurrence was noted in 31 of 600 lesions (5.2%) after renal cryoablation versus 100 of 775 lesions (12.9%) after RFA ($p<0.0001$) [27•]. Accordingly, repeat ablation was more common following RFA (8.5%) than cryoablation (1.3%, $p<0.0001$), and patients treated with RFA were more likely to experience progression to metastatic disease than patients who underwent cryoablation (2.5% versus 1%, $p=0.06$) [27•].

As noted, the majority of studies which have evaluated outcomes following renal tumor ablation consist of single institution reports with relatively limited patient numbers and short-term follow-up. As such, comparing the results from these techniques against the results from partial nephrectomy, for which reported series are comprised of considerably larger

numbers of patients, with longer follow-up, remains difficult. For example, Stern et al. [38] reported that, with a follow-up of 30 months after treatment, disease-specific survival after RFA for T1a lesions (93.4%) was comparable to the results of partial nephrectomy for similar stage tumors. Nevertheless, a recent meta-analysis which included 99 studies encompassing 6,471 renal masses demonstrated that SRMs treated with cryoablation or RFA were significantly more likely to experience residual disease following initial treatment (4.6% and 11.7%, respectively) than lesions managed with NSS (2.6%), such that on multivariate analysis patients who underwent cryoablation or RFA had a 7.45 and 18.23 times greater incidence of local recurrence than patients treated with partial nephrectomy [39•] (Table 1). At the same time, however, the incidence of progression to metastatic disease did not differ significantly by treatment modality [39•] (Table 1), which further hints at an inherently indolent biological potential for many SRMs. Other differences of significance included the rates of unknown pathology (0%, 18%, 43%, and 54% following partial nephrectomy, cryoablation, RFA, and observation, respectively ($p=0.0014$)), as well as differences in reported mean duration of follow-up (54.0, 18.3, 16.4, and 33.3 months, respectively ($p<0.0001$)) [39•] (Table 1).

Lastly, few studies to date have examined the effects of thermal ablation on renal function. Indeed, as these techniques by design must extend the ablative field beyond the radiographic boundaries of a lesion in an effort to maximize cell death at the periphery of the tumor, nephrons may be unavoidably sacrificed. Gill et al. [40] examined 56 patients with three-year follow-up after renal cryoablation and reported preoperative and postoperative serum creatinine levels of 1.2 mg/dL and 1.4 mg/dL, respectively. In the 10 patients from this series with a solitary kidney, the mean preoperative and postoperative serum creatinine levels were 2.2 mg/dL and 2.6 mg/dL, respectively [40]. Another series of 14 patients who underwent cryoablation of a tumor in a solitary kidney reported no adverse effect on renal function [41]. Meanwhile, a series of 16 patients with a solitary kidney who underwent RFA demonstrated a decrease in the mean glomerular filtration rate from 54.2 mL per minute per 1.73 m² preoperatively to 47.5 mL per minute per 1.73 m² at last follow-up [42]. Likewise, Jacobson et al. reported on 16 patients with a solitary kidney treated with RFA and found a 13.3% change in creatinine clearance within one week of ablation, and a 9.1% change at a mean follow-up of 15.3 months, with one patient developing chronic renal failure [43]. Thus, the goal of nephron sparing during ablative techniques remains carefully balanced against the possibility of insufficient tumor destruction, and larger studies, with longer follow-up, are needed to define the ability of these techniques to preserve renal function.

Active surveillance

Given the continued increase in death rates from kidney cancer despite the increased detection and treatment of SRMs, the hypothesis has been raised that the treatment of SRMs may not impact mortality [5;44]. Importantly, then, the reported survival rates from surgical excision and thermal ablation must be evaluated in the context of the emerging body of data regarding observation, or AS, of SRMs. Indeed, before any of the ablation technologies are adopted as the standard treatment for SRMs in the frail, elderly, and/or co-morbid, their effect must be contextualized with the natural history of untreated renal tumors, which is emerging from reported series of AS. In fact, a recent meta-analysis demonstrated that the rates of metastatic progression in patients under AS did not differ significantly from patients treated with NSS, cryoablation, or RFA [39•] (Table 1). This further emphasizes a possible overtreatment bias in SRMs, specifically by demonstrating that treatment may not impact the biological potential for many indolent SRMs. However, reports to date regarding the natural history of untreated localized renal lesions have been limited by selection bias.

We performed a meta-analysis of the world literature regarding the natural history of untreated solid localized renal lesions, consisting of 10 reports from 9 single institutional series [8••].

When combined with our experience with AS at the Fox Chase Cancer Center, a total of 234 tumors were included for analysis, with a mean lesion size at presentation of 2.60 cm and a mean follow-up of 34 months [8••]. We determined that the mean growth rate for SRMs was 0.28 cm per year, and that lesion size at presentation did not predict the growth rate ($p=0.46$) [8••]. Furthermore, progression to metastatic disease was identified in only 1% of lesions during follow-up [8••]. In a subsequent study, we found that 26-33% of enhancing renal masses demonstrated zero net growth when observed over a median of 29 months, with no clinical or pathological predictors of this behavior identifiable [45], further emphasizing the potentially indolent nature of certain SRMs.

Likewise, Volpe et al. [46] previously reported that the average growth rate in 32 masses < 4 cm with median follow-up time of 27.9 months did not differ statistically from zero, and that no patient experienced progression of disease. In addition, Abouassaly et al. [47], in a series of 110 patients managed with AS of SRMs (median tumor size 2.5 cm), documented a median growth rate of 0.26 cm per year, again with no deaths during follow-up (median 24 months) attributable to RCC. As with our series, 43% of lesions demonstrated zero net growth, and no significant correlation of growth rate with tumor size at diagnosis was noted [47].

AS of renal tumors with delayed intervention for lesions which demonstrate interval growth is therefore emerging as a viable approach to the management of select patients with SRMs. We recently reported our experience with this practice, consisting of 82 patients who underwent intervention for a SRM (median tumor diameter 2 cm) with at least a six month delay from diagnosis [48]. Median time to treatment was 14 months, with 69% of patients having at least a 12 month delay [48]. Only three patients were upstaged at the time of resection, and no patient progressed to metastatic disease, for an estimated one and three-year recurrence-free survival of 100% and 99%, respectively [48]. Moreover, we [48] and others [49] have noted that delayed management of renal tumors did not impact surgical approach, specifically with regard to patients' candidacy for partial versus radical nephrectomy. Overall, although the collective experience with AS for SRMs has thus far primarily been in elderly or infirm populations, and remains with relatively short-term follow-up, the data reported to date support the continued investigation of AS as an approach to the newly-diagnosed SRM in select patients.

Conclusions

With the prevalence of comorbidities in the population of patients in whom SRMs are increasingly diagnosed, as well as the deleterious impact on non-cancer morbidity of CKD, it has become evident that the goals in managing patients with SRMs extend beyond cancer control. As such, urologists must individually consider the biologic potential of the disease together with the potential consequences of treatment on survivorship when facing patients with a SRM. Given the definitive nature of excision and the longest reported follow-up studies, surgery in the form of partial nephrectomy remains the standard of care. While cancer-specific metrics for ablation appear promising on short-term follow-up, the impact of these modalities on the natural history of many SRMs, as well as on renal function, is unclear. Available data on ablation technologies suggests that cryoablation is superior to RFA, although this may be a function of the application of the technology rather than the technology itself.

Observation of an enhancing renal mass is a calculated risk for the treating physician and the affected patient. Arguments in favor of an initial trial of AS include the often indolent growth rate of SRMs now independently reported in several series, as well as the competing comorbidities which frequently affect patients with a newly-diagnosed SRM. Nevertheless, the relatively uncertain long-term biological potential of untreated renal masses, the absence of serum biomarkers or histological predictors of progression, the lack of standardized radiographic surveillance protocols, and the expanding options for therapy of SRMs, including

minimally-invasive and percutaneous approaches, remain barriers to the widespread application of AS.

Prospective data are limited regarding the optimal management of the SRM. Moreover, as demonstrated on a recent meta-analysis [39•], significant differences have existed in the clinical application of these techniques to date, particularly with regard to patient age and tumor size, reflecting a selection bias that obscures direct comparison of outcomes. In addition, the published series of ablated lesions tend to include shorter posttreatment follow-up compared with studies of tumors managed by surgical excision or active surveillance [39•]. Furthermore, a significant number of tumors treated with ablative technologies or AS have unknown or indeterminate pathological findings, further confounding any comparison of oncological outcomes, as histologically benign tumors are certainly included in the reported outcomes from such series. However, although patient selection biases are inherent to all retrospective analyses, prospective randomized comparisons are both time consuming and costly. Systematic management of SRMs based on clinical and pathologic predictors of disease progression must be the long-term goal. Identification of such predictors, including for example through molecular and genetic testing of needle biopsies [50], should be the short-term objective.

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Table 1
Outcome comparison of various treatment approaches to the SRM. Data adapted from recent meta-analysis [39•].

Treatment modality	Mean follow up (months)	Mean tumor size (cm)	Percentage of lesions with pathologic confirmation	Relative risk of local recurrence (95% CI)	Relative risk of distant metastases (95% CI)
Partial nephrectomy	54.0	3.40	100%	1.00	1.00
Cryoablation	18.3	2.56	82.3%	7.45 (2.24, 6.92)	1.24 (0.10,12.60)
RFA	16.4	2.69	57.2%	18.23 (6.08, 60.64)	3.21 (0.39, 8.19)
AS	33.3	3.04	45.9%	-	0.11 (0.00, 0.14)