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## Focal therapy for kidney and prostate cancer

Alexander Kutikov, David A. Kunkle, and Robert G. Uzzo

Department of Urologic Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania, USA

### Abstract

**Purpose of review**—Surgical excision remains the standard of care for treatment of localized small renal masses (SRMs). Laparoscopic and percutaneous minimally invasive ablative technologies are being increasingly employed in current urologic practice. We review recent literature regarding focal ablative treatments of SRMs.

**Recent findings**—Most cryoablations are performed using a laparoscopic approach, whereas radiofrequency ablation (RFA) of the SRM is more commonly administered percutaneously. Pretreatment biopsy is performed more often for lesions treated by cryoablation than RFA with a significantly higher rate of indeterminant or unknown pathology for SRMs undergoing RFA versus cryoablation ( $P < 0.0001$ ). Currently available data suggest that cryoablation results in lower retreatments ( $P < 0.0001$ ), less local tumor progressions ( $P < 0.0001$ ) and may be associated with a decreased risk of metastatic progression compared with RFA. It is unclear whether these differences are a function of the technologies or their application. Given the excellent results reported for active surveillance of the SRM in selected patients, the extent to which focal ablation alters the natural history of SRMs has not yet been established.

**Summary**—Currently, data on the ability of interventions for SRMs to affect the natural history of these masses is lacking. Prospective randomized evaluations of available clinical approaches to SRMs are needed.

### Keywords

active surveillance; cryoablation; partial nephrectomy; radiofrequency ablation; renal cell carcinoma

### Introduction

Excision of localized renal cell carcinoma (RCC) is the current standard of care. Surgical series for small renal masses (SRMs) demonstrate excellent outcomes with 5-year survival approaching 97% [1]. Minimally invasive ablative technologies such as cryotherapy and radiofrequency ablation have entered the therapeutic arena with similar short and intermediate oncologic results [2]. Recently, data on active surveillance of SRMs have also emerged and demonstrate equivalent CSS rates to ablation in selected patient populations [3]. Here, we present an analysis of the currently available data specifically evaluating focal ablative therapies for the SRM and review these data in the context of natural history (active surveillance) data in an effort to guide clinicians who manage incidental SRMs.

### Overview

More than 54,000 individuals in the United States will be diagnosed with renal malignancy in 2008 and over 13,000 (24%) will die from the disease, making RCC the most lethal of all

genitourinary cancers [4]. Incidental discovery of renal malignancy has been on the rise for nearly two decades [5]. As more localized RCC is diagnosed, the rate of renal surgery has also increased [6,7]. Nevertheless, despite early detection and aggressive treatment approaches, death rates from RCC continue an upward trend. When all-cause mortality of patients diagnosed with RCC is examined in the United States, there is a rise from 1.5 deaths per 100,000 individuals in 1983 to 6.5 in 2002 [6]. These data suggest that a significant portion of localized RCC may be over-treated because early and effective treatments have not impacted RCC-related mortality. As such, it appears that renal masses differ in their inherent biology, and not all lesions are destined to progress, metastasize and threaten the life of the host.

Surgical resection, especially in young healthy patients with localized lesions continues to be standard management because these individuals have a long life expectancy and salvage therapies for advanced RCC are noncurative [8]. Indeed, surgical series have demonstrated remarkable 5-year cancer-specific survival rates in excess of 95% [1,9,10]. However, elderly patients with RCC present the urologist a unique set of challenges because comorbidities of these individuals compete with RCC for life expectancy. Minimally invasive ablative techniques such as cryoablation and radiofrequency ablation provide a less invasive, less morbid treatment option. Treatment patterns for anatomically uncomplicated SRMs have preferentially shifted toward these ablative technologies at some institutions [11]. Renal tumor ablation can be performed via an open, laparoscopic or percutaneous route using either cryo or radiofrequency ablative approach. Data have emerged, which suggest that these technologies may have equivalent short and intermediate term outcomes to surgical excision with less morbidity. What remains unanswered is whether focal ablation actually impacts the natural history of the SRM or whether the excellent metastasis-free survival of patients undergoing these treatments is simply a function of the indolent nature of their tumors. In recent years, data on the growth kinetics and metastatic potential of the SRM under active surveillance in selected patients have emerged [3]. Here, we review recent data examining the effects of ablative technologies for the SRM and utilize the active surveillance literature to provide a context for the interpretation of these data.

## Cryoablation

Cryoablation generates tumor destruction by controlled freezing of tissues [2,12]. A probe is placed under direct vision or image guidance into the renal mass and cooling is achieved using liquid argon or nitrogen. The ice ball that results produces protein denaturation and destroys cellular membranes [12]. Furthermore, disruption of the microvasculature sustains cell death due to local tissue ischemia [12]. Temperatures less than  $-20^{\circ}\text{C}$  are required for appropriate treatment, and such conditions are experimentally observed 3.1mm inside the boundary of the cryotherapy ice ball [13]. Hence, in clinical practice tissues are generally cooled to  $-40^{\circ}\text{C}$ , and the ice ball is propagated 1cm beyond the tumor's edge [2]. Thermocouple or ultrasound can be used to monitor progress of the cryotherapy procedure, and two freeze-thaw cycles appear to achieve the best tissue ablation [2,14]. A recent report demonstrated excellent correlation between postcryo radiographic findings and subsequent percutaneous biopsy of treated lesions. Weight *et al.* [15] demonstrated that no lesion that failed to enhance on posttreatment imaging revealed evidence of viable tumor. Although cryotherapy probes can be placed via open exploration, in practice laparoscopic and percutaneous techniques are overwhelmingly used [16,17]. Objective comparisons between the laparoscopic and percutaneous approaches are only recently emerging. Finley *et al.* [18] reported on 18 patients (19 masses) who underwent percutaneous cryoablation and 19 individuals (24 masses) who had laparoscopic cryosurgery at the University of California, Irvine. Mean tumor size was 2.9cm (range 1.1–5.4). Procedure times, narcotic requirements, and hospital stays were significantly greater with the laparoscopic approach. In another recent comparison between percutaneous and laparoscopic cryoablation, Bandi *et al.* [19] also demonstrated earlier convalescence for the percutaneous approach, but

did not find a difference in postprocedure opioid requirement nor patient satisfaction. Similarly, Badwan *et al.* [20] reported a comparative cost analysis of laparoscopic versus percutaneous cryoablation demonstrating that the percutaneous approach (median \$6861) was considerably more cost effective than laparoscopic cryoablation (median \$29,617). Nevertheless, long-term cancer control is yet to be proven equivalent between the percutaneous versus laparoscopic approach. Indeed, some authors believe that percutaneous approach is associated with higher tumor recurrence rates compared with laparoscopic cryoablation [21]. Finally, some anterior tumors are not amenable to a percutaneous approach; although, in clinical practice, this is rather uncommon [18•].

## Radiofrequency ablation

Radiofrequency ablation (RFA) harnesses a high-frequency alternating current to produce rapid heating of tissues. Denaturation of proteins and destruction of cell membranes results when the tissue temperature rises above 50°C. Temperature elevation above 105°C is avoided because resulting vaporization renders ablation nonuniform and ineffective. Clinically, temperatures between 50 and 100°C are employed [22]. Stern *et al.* [23] recently reported that at intermediate follow-up (mean 30 months) RFA was oncologically comparable with partial nephrectomy for T1a lesions with a disease-specific survival of 93.4%. A multiinstitutional long-term (at least 40 months) follow-up data also was recently published. Levinson *et al.* [24••] describe a 90.3% long-term recurrence-free survival in 31 individuals with solitary kidney who underwent RFA for SRM. In these and in most other studies, tumor recurrence was defined as a lack of radiographic contrast enhancement and absence of tumor growth [23,24••]. Recent concerns regarding reliability of imaging to assess RFA efficacy have been raised in the literature. For instance, Weight *et al.* [15••] reported that over 45% of renal tumors that fail to show enhancement following RFA, demonstrate viable tumor at a 6-month posttreatment biopsy. Nevertheless, others contend that these findings are explained by the fact that RFA heat fixation preserves tumor architecture and that a biopsy at 6 months is unreliable [25]. Indeed, a recent report by these authors suggests that lack of radiographic enhancement is in fact a reliable marker of cell-kill when a biopsy of RFA-treated masses is performed after 1 year. Raman *et al.* [26••] describe at least 4 biopsies per lesion no sooner than 1 year following treatment of 20 tumors that did not enhance on cross-sectional imaging following RFA. None of these lesion demonstrated viable tumor remnants on posttreatment biopsies. The authors conclude that a biopsy before 1 year following RFA is unreliable. Despite this data, a recent meta-analysis of available data indicates that RFA may have oncological outcomes, which are inferior to cryoablation [27].

## Comparison of cryoablation and radiofrequency ablation

We recently reported the results of a meta-analysis of the available literature comparing RFA with cryoablation [27]. Case reports, studies that included patients with hereditary or metastatic RCC, and publications that did not include outcome data were all excluded. We analyzed 46 studies from 44 institutions that characterized 1234 localized renal lesions, treated with either open, laparoscopic, or percutaneous cryoablation or RFA. When compared with lesions treated with cryoablation, lesions treated with RFA statistically did not differ in size (2.53 versus 2.67cm), patient age (64.5 versus 66.0 years), or follow-up interval (19.3 versus 15.5 months). Pretreatment biopsy was performed more often for lesions treated by cryoablation (82.3%) than RFA (62.2%) ( $P<0.0001$ ). Moreover, there was a significantly higher rate of indeterminate or unknown pathology for SRMs undergoing RFA (40.4%) versus cryoablation (24.5%) ( $P<0.0001$ ). Repeat ablation was performed more often following RFA (8.5%) than cryoablation (1.3%) ( $P<0.0001$ ).

The meta-analysis revealed that lesions treated with RFA exhibited a highly significant higher rate of local tumor progression than those lesions that were treated with cryoablation (4.7 versus 12.3%,  $P < 0.0001$ ). For both cryoablation and RFA, local tumor progression was defined as radiographic or pathologic evidence of residual disease following initial treatment, regardless of time to recurrence in accordance with the recommendations of the Working Group on Image-Guided Tumor Ablation [28]. Moreover, progression to metastatic disease was documented in 1.9% (23 of 1234) of the masses in the analysis. A greater number of lesions progressed to metastasis following RFA (6/577, 1%) than following cryoablation (17/657, 2.6%) – a difference that approached statistical significance ( $P = 0.06$ ). Univariate and multivariate regression analyses confirmed that the risk of tumor progression correlated with ablation modality, but not with incidence of malignant pathology nor incidence of unknown pathology in the series that were examined [27]. Although heterogeneous multiinstitutional retrospective data are insufficient to make hard recommendations against a given modality, such as RFA in clinical practice, such findings are provocative and should promote prospective evaluations.

## Active surveillance

Data regarding the natural history of untreated localized renal lesions have been limited [3]. In a recent large series of patients with renal masses under observation, Abouassaly *et al.* [29••] described 110 elderly patients (median age 81 years, range 76 to 95) with enhancing renal lesions (median size 2.5cm) who enrolled into an active surveillance protocol at the Cleveland Clinic. The strength of this study is the documentation of the Charlson comorbidity index for each patient (median 2, range 0–7) – data that is not available from other active surveillance series. Nearly one third (31%) of patients expired during the median follow-up time of 24 months (range 1–90) with no deaths being attributed to RCC. The authors do not report whether or not any lesion progressed to metastatic disease, but do document a median renal mass growth rate of 0.26cm per year [29••]. This growth velocity is very similar to the 0.28cm per year rate noted in a 2006 meta-analysis of 234 reported lesions [30]. Abouassaly *et al.* also documented that 43% of lesions failed to demonstrate growth during the time of follow-up. We have previously reported that between 26 and 33% of SRMs under surveillance fail to demonstrate any radiographic growth when observed for a median of 29 months. Unfortunately, no clinical predictors of this behavior could be identified in our analysis [31•]. As in the report by Abouassaly *et al.*, [29••] there was no significant correlation of growth rate with lesion size at the start of surveillance [31•]. Similarly, neither patient's age at diagnoses, solid versus cystic appearance, nor the number of imaging studies performed were found to be related to the growth rate. Interestingly, rate of malignancy for masses for which pathological data were available did not differ between lesions that remained stable (83% malignant) and those that exhibited growth (89% malignant). Although lack of growth did not correlate with lack of malignancy, no clinically available variable predicted whether a mass would exhibit radiographic growth on surveillance (Table 1 Table 1). Nevertheless, none of the zero growth lesions and only one lesion with radiographic growth demonstrated clinical progression. This lesion grew from 2 to 8cm over 54 months and progressed to metastatic disease [31•]. Indeed, only 8 examples of progression to metastatic disease are available in the current literature and to our knowledge only one case has been confirmed pathologically. To date, all lesions that progressed to metastatic disease were preceded by rapid radiographic growth (A Kutikov, Kunkle DA, Chen C, *et al.* Clinical features of small renal masses (SRMs) with documented metastatic progression on active surveillance (AS) protocols. In preparation).

Therefore, a new paradigm may be emerging; namely active surveillance of SRMs with delayed intervention in appropriately selected patients. We recently reviewed our experience with this practice. In 82 patients who underwent at least a 6-month delay (median 14) in intervention for an enhancing renal mass measuring 4cm or less (69% of patients having at least a 12-month delay), only three were upstaged at resection, and no patient progressed to metastatic disease.

Estimated 1 and 3-year cancer recurrence-free survival rates were 100 and 99%, respectively [32•]. Reasons for delay were multifactorial and were categorized as absolute (24%), relative (21%), or elective (55%). These data suggest that an initial interval of active surveillance is a low-risk approach for management of SRMs. Similarly, Stec *et al.* [33] recently showed that a surgical delay did not affect patient outcomes in a large cohort of patients ( $n=235$  for patients who had a surgical delay of greater than 1 month). In this study, treatment was delayed more than 6 months for 20 lesions without any apparent deleterious outcomes on cancer-free survival.

## Comparison of excision, ablation, and active surveillance

Given the data, selecting optimal management for the SRM, particularly in the elderly and infirmed has become a clinical dilemma. We recently completed a meta-analysis comparing excision to ablation, and active surveillance [34••]. All published series that reported management of SRMs with open or laparoscopic partial nephrectomy, cryoablation, RFA, or observation were included in the study. Case reports, series that treated patients with hereditary or metastatic RCC were excluded. If redundant data was published, only the most recent report was included. A total of 99 studies encompassing 6471 renal masses comprised the meta-analysis. Data for 5037 (77.8%) distinct masses treated with partial nephrectomy were available in the literature. Outcomes were reported for 496 (7.7%) and 607 (9.4%) masses that were treated with cryoablation and RFA, respectively. A total of 331 (5.1%) reported masses were managed with active surveillance. Patients treated with partial nephrectomy were statistically significantly younger (60.1 years) than patients treated with ablative technologies (cryo=65.7, RFA=67.2) or active surveillance (68.7). Masses managed with surgery tended to be larger (3.26cm) than those treated with cryoablation (2.56cm,  $P<0.001$ ) or RFA (2.69,  $P<0.001$ ), but were similar to those treated by active surveillance (3.04cm,  $P=0.54$ ) [34••].

Mean weighted follow-up was longest for the cohort of patients treated with partial nephrectomy (54 months), followed by patients managed with active surveillance (33.3 months). Reported follow-up was shortest for ablation technologies with cryoablation posting a follow-up of 18.3 months and RFA 16.4 months. Differences in follow-up between surgery, active surveillance, and ablation technologies were statistically significant. Local recurrence was reported in 2.6% of masses treated with partial nephrectomy, 4.6% of cases treated with cryoablation, and in 11.7% of masses treated with RFA. Despite shorter follow-up, multivariate analysis revealed a statistically significant higher risk of developing recurrence following cryoablation (RR=7.45) and RFA (RR=18.23) when compared with partial nephrectomy (Table 2 Table 2) [34••]. Importantly, the data confirmed that CSS rates were very high and similar across all modalities.

## Conclusion

Prospective data are limited regarding the optimal management of the SRM. Given the definitive nature of excision and the longest follow-up, surgery remains the standard of care for small and localized RCC. Although cancer specific metrics for ablation appear promising, the impact of these modalities on the natural history of many SRMs 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. Before ablation technologies are adopted as the standard treatment for SRMs in the frail, elderly or comorbid or both, their effect must be measured against the null hypothesis (surveillance). This proof must be sought despite the medical, legal, social and financial disincentives toward active surveillance. Currently, longer follow-up is available for observation than for cryotherapy or RFA with very few patients demonstrating disease progression while on active surveillance. Delayed intervention for SRMs likewise appears to be a safe management strategy. Although patient selection biases are inherent to all retrospective analyses, prospective randomized

comparisons are both time-consuming and costly. Systematic management of localized RCC based on clinical and pathologic predictors of disease progression must be the long-term goal. Identification of such predictors should be the short-term objective.

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## References and recommended reading

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- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000–000).

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**Table 1**

Comparison of characteristics between lesions that grew and failed to grow on active surveillance

Characteristic	Zero growth lesions	Lesions that grew on active surveillance	P-value
Number (%)	35(33)	71(67)	–
Median pt age	71	73	0.96
Median initial size (cm)	2	2	0.5
Median follow-up (mo)	25	30	0.066
Median growth (cm/yr)	0	0.31	<0.00001
Median imaging studies	5	6	0.76
No. cystic lesions (%)	4 (11)	9 (13)	1
No. malignant pathology/total no. (%)	5/6 (83%)	32/36(89)	0.56
No. metastatic progression (%)	0	1	1

Adapted from [31•].

**Table 2**

Relative risk of local recurrence or metastatic disease as derived from a meta-analysis of available literature

SRM management strategy	n	Relative risk of local recurrence	Relative risk of metastatic progression
Partial nephrectomy	5037	1.00	1.00
Cryoablation	496	7.45	1.24
RFA	607	18.23	3.21
Active surveillance	331	–	0.11

Local recurrence was defined as radiographic or pathological evidence of residual disease or recurrent disease (adjacent to previous tumor bed in the case of partial nephrectomy) regardless of time to recurrence. Adapted from [34••].