# Excise, Ablate or Observe: The Small Renal Mass Dilemma—A Meta-Analysis and Review

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**Purpose:** The incidence of renal cell carcinoma is increasing due to the incidental detection of small renal masses. Resection, predominantly by nephron sparing surgery, remains the standard of care due to its durable oncological outcomes. Active surveillance and ablative technologies have emerged as alternatives to surgery in select patients. We performed a meta-analysis of published data evaluating nephron sparing surgery, cryoablation, radio frequency ablation and observation for small renal masses to define the current data.

**Materials and Methods:** A MEDLINE® search was performed for clinically localized sporadic renal masses. Patient age, tumor size, duration of followup, available pathological data and oncological outcomes were evaluated.

**Results:** A total of 99 studies representing 6,471 lesions were analyzed. Significant differences in mean patient age ($p < 0.001$), tumor size ($p < 0.001$) and followup duration ($p < 0.001$) were detected among treatment modalities. The incidence of unknown/indeterminate pathological findings was significantly different among cryoablation, radio frequency ablation and observation ($p = 0.003$), and a significant difference in the rates of malignancy among lesions with known pathological results was detected ($p = 0.001$). Compared to nephron sparing surgery significantly increased local progression rates were calculated for cryoablation (RR = 7.45) and radio frequency ablation (RR = 18.23). However, no statistical differences were detected in the incidence of metastatic progression regardless of whether lesions were excised, ablated or observed.

**Conclusions:** Nephron sparing surgery, ablation and surveillance are viable strategies for small renal masses based on short-term and intermediate term oncological outcomes. However, a significant selection bias exists in the application of these techniques. While long-term data have demonstrated durable outcomes for nephron sparing surgery, extended oncological efficacy is lacking for ablation and surveillance strategies. The extent to which treatment alters the natural history of small renal masses is not yet established.

*Key Words: kidney; kidney neoplasms; carcinoma, renal cell; natural history; nephrectomy*

Cancer of the kidney accounts for approximately 3.5% of all malignancies and it is the third most common cancer of the urinary tract.[1] With an estimated 51,190 new cases occurring in 2007 and 12,890 deaths attributable to the disease RCC is the most lethal of all genitourinary tumors.[1]

The clinical diagnosis of RCC is radiographic and effective imaging of the kidneys can be achieved by ultrasound, CT or MRI.[2] Solid lesions detected by ultrasound and those showing enhancement on cross-sectional imaging are considered malignant until proven otherwise. Due to the increased use of diagnostic imaging for evaluating patients with abdominal symptomatology incidentally discovered SRMs are being diagnosed with greater frequency[3] and they now account for 48% to 66% of RCC diagnoses.[4] This has resulted in an increased incidence of RCC during the last 3 decades with an associated stage migration[3] and a concurrent increase in the rates of surgical intervention.[5] Unfortunately despite earlier diagnosis and treatment there has not been a significant increase in CSS or overall survival.[5]

The standard of care for clinically localized RCC remains surgical resection due to the favorable prognosis associated with surgery and the relative ineffectiveness of systemic therapy. Patients undergoing radical or partial nephrectomy for pT1a (4 cm or less) tumors have demonstrated 5-year CSS rates in excess of 95%.[6,7] Laparoscopic approaches to NSS have shown similarly favorable early results.[8]

Recently minimally invasive ablative technologies have emerged as potential treatment options for clinically localized RCC. Effective renal cryoablation has been achieved by open and laparoscopic approaches as well as by percutaneous image guided techniques.[9] Percutaneous RFA has been successfully performed under ultrasound, CT or MRI guidance.[10] While these newer nephron sparing techniques appear promising, data on their long-term effectiveness are lacking.

A small but emerging body of data exists regarding observation or active surveillance of selected SRMs in elderly populations. A meta-analysis of clinically localized tumors determined an overall median growth rate of 0.28 cm per

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year for observed lesions across multiple series.[2] While growth rates vary considerably among reports, only 1% of observed lesions in this meta-analysis progressed to metastatic disease after a median followup of almost 3 years.[2]

While treatment options for low stage RCC have expanded in recent years, to our knowledge their proper application and effect on the biology of SRMs is yet to be defined. We analyzed the combined published data on the management of SRMs. We reviewed the published literature and performed a meta-analysis for evaluating NSS, cryoablation, RFA and active surveillance for localized RCC.

## MATERIALS AND METHODS

### Data Sources

A MEDLINE search was performed from 1980 through 2006 using the National Center for Biotechnology Information PubMed® Internet site to review the world literature on the treatment of suspected renal malignancies. Additionally, an updated series of patients undergoing active surveillance of enhancing renal lesions at our institution was included.[11]

### Study Selection

This meta-analysis was limited to series analyzing clinically localized sporadic renal tumors that were managed by open/laparoscopic partial nephrectomy, cryoablation, RFA or observation. Series consisting of patients with hereditary or metastatic RCC were excluded. Additionally, series that did not assess tumor recurrence or oncological outcomes were excluded. Prospective and retrospective series were included in the study, although case reports were excluded. Multiinstitutional series as well as single institution experiences were analyzed, provided that other inclusion criteria were met. In the case of multiple series from an institution or overlapping patient cohorts with redundant data the most updated or inclusive series was selected. A total of 99 studies met inclusion criteria and were analyzed.

### Analysis

Mean data on patient age, tumor size and followup duration were extracted from published series. Pathological data were categorized as histologically confirmed RCC, benign lesions or unknown/indeterminate histology. The oncological outcomes evaluated included local recurrence or distant metastases. For cryoablation and RFA local recurrence was defined as radiographic or pathological evidence of residual disease following initial treatment regardless of time to recurrence. For lesions treated with partial nephrectomy local recurrence was considered to have occurred if there was radiographic or pathological evidence of tumor in the ipsilateral kidney adjacent to the site of previous resection. Ipsilateral tumor recurrence distant from the site of resection was not considered to represent locally recurrent disease for the purpose of this analysis. Masses undergoing observation were not included in the analysis of local recurrence since these lesions had not undergone primary local intervention.

Differences in mean patient age, tumor size and followup were weighted by differences in study sample size and analyzed using weighted linear regressions. Hypothesis tests were done using the Wald test of regression coefficients with robust SEs. Data on each series could not be weighted by inverse SEs, which might have increased the efficiency of estimators since more than 40% of the studies did not include variances or SEs with their descriptive statistics. Many groups reported ranges instead of variances as a measure of variability.

Differences in malignancy rates and pathological reporting across modalities were investigated using linear models of the logit of the expectation of the percents. We used estimating equations and derived SEs using sandwich estimators[12] to account for the nonnormal distribution of percent data. Significance was determined using the Wald test.

Finally, we investigated multivariate models of recurrence and metastatic progression using Bayesian Poisson models, including treatment modality, mean age, mean tumor size and mean followup as covariates. We included a random intercept in the model for each study and an offset term to account for differing aggregate followup intervals. Aggregate followup was calculated using the reported mean followup multiplied by the number of tumors in the study. The random intercept was included to allow for different study specific baseline rates of metastasis beyond that which would be accounted for through the variables in the model. The model for local recurrence was similar to that for metastasis except observation data were omitted from analysis due to the lack of local treatment.

We used a Bayesian model to account for the fact that overall rates of metastasis and recurrence were low with many studies indicating no occurrences of metastasis. Bayesian models were estimated using WinBUGS, version 1.4 statistical software and the priors were parameterized as specified in the documentation. We used normally distributed priors for the coefficients with a mean of 0 and a precision of $10^{-7}$. For the variance of the random intercepts we used a gamma distributed prior with the 2 parameters set to $10^{-7}$. We believe that the posterior estimates of the incidence rates are more realistic estimates of the study specific incidence rates rather than the raw estimates since many studies had a small sample size with no events and, hence, had a raw incidence estimate of zero. Therefore, the Bayesian random effects model uses prior and pooled information across studies to bound the incidence estimates slightly away from zero. Random effects models and Bayesian approaches to meta-analysis were performed as described by Smith[13] and Berkey[14] et al.

## RESULTS

A total of 99 series representing 6,471 renal tumors met inclusion criteria and were analyzed. Table 1 lists the char-

TABLE 1. *Studies, institutions and lesions in meta-analysis by treatment modality*

| Treatment Modality | No. Studies | No. Institutions | No. Tumors (%) |
|---|---|---|---|
| Partial nephrectomy | 50 | 50 | 5,037 (77.8) |
| Cryoablation | 19 | 19 | 496 (7.7) |
| RFA | 21 | 21 | 607 (9.4) |
| Active surveillance | 10 | 10 | 331 (5.1) |
| Totals | 99* | 87 | 6,471 (100) |

* Data from 1 series are included for partial nephrectomy and cryoablation.

TABLE 2. *Weighted age of patients treated for enhancing SRMs*

| | All Lesions | Partial Nephrectomy | Cryoablation | RFA | Active Surveillance |
|---|---|---|---|---|---|
| No. series | 82 | 41 | 16 | 18 | 7 |
| No. lesions | 5,864 | 4,667 | 372 | 564 | 261 |
| Mean age | 61.6 | 60.1 | 65.7 | 67.2 | 68.7 |
| p Value vs partial nephrectomy | — | | <0.001 | <0.001 | <0.001 |
| p Value vs cryoablation | — | | | 0.31 | 0.12 |
| p Value vs RFA | — | | | | 0.45 |

acteristics of the included series. Institutions contributing published data are listed in the Appendix.

### Patient Age

A total of 82 studies provided data on the age of patients undergoing treatment (table 2). These studies accounted for 5,864 renal tumors. Mean age weighted by sample size for these studies was 61.6 years. Mean age by treatment modality was 60.1 years for NSS, 65.7 years for cryoablation, 67.2 years for RFA and 68.7 years for active surveillance. These differences were statistically significant when analyzed by weighted multiple linear regression (overall $p < 0.001$). Pairwise analyses revealed significant differences in published mean patient ages for cryoablation, RFA and active surveillance (each $p < 0.001$) compared to the standard of partial nephrectomy.

### Tumor Size

Data on mean kidney tumor size were provided in 88 studies, accounting for 5,999 lesions (table 3). Overall mean weighted tumor size was 3.26 cm. For each treatment modality mean tumor size was 3.40, 2.56, 2.69 and 3.04 cm for NSS, cryoablation, RFA and active surveillance, respectively. Weighted multiple linear regression analyses demonstrated that these overall differences were statistically significant (overall $p < 0.001$). Compared to lesions treated with partial nephrectomy, tumors managed by cryoablation and RFA were significantly smaller (each $p < 0.001$). However, those undergoing active surveillance were also smaller but the difference was not statistically significant ($p = 0.54$).

### Followup

As described in 84 studies, the mean followup for 5,825 renal lesions was 47.1 months (table 4). Mean weighted followup was 54.0, 18.3, 16.4 and 33.3 months after partial nephrectomy, cryoablation, RFA and active surveillance, respectively. Overall differences in reported followup intervals were statistically significant (overall $p < 0.001$). In pairwise analyses cryoablation, RFA and active surveillance (each $p < 0.001$) were shown to have included significantly shorter duration of followup compared to NSS. Additionally, observation series included longer followup than cryoablation and RFA series ($p = 0.001$ and $< 0.001$, respectively).

### Pathological Findings

Pathological data from 99 series on a total of 6,471 renal tumors were classified according to malignant, benign and unknown/indeterminate histology for each treatment modality (see figure). Overall 79.7% of lesions were pathologically confirmed RCC, while 12.2% were benign lesions and 8.1% had unknown or indeterminate pathological findings. While all lesions undergoing partial nephrectomy had confirmed pathological results, unknown or indeterminate pathological findings occurred for 17.7%, 42.8% and 54.1% of lesions managed by cryoablation, RFA and observation, respectively (overall $p = 0.003$). The increased incidence of unknown pathological results compared to cryoablation was statistically significant for RFA and surveillance ($p = 0.04$ and $< 0.001$, respectively).

The incidence of malignancy among only reported lesions with known histology was determined to be 87.6% for partial nephrectomy, 75.8% for cryoablation, 88.3% for RFA and 91.0% for active surveillance (overall differences $p = 0.001$). Significant differences in the incidence of malignancy were reported for cryoablation compared to partial nephrectomy ($p = 0.02$) and surveillance ($p < 0.001$), and marginally for RFA ($p < 0.07$). However, no significant differences were detectable in comparisons between partial nephrectomy-RFA ($p = 0.91$), partial nephrectomy-surveillance ($p = 0.34$) and RFA-surveillance ($p = 0.55$).

### Local Recurrence and Metastatic Progression

Local recurrence was reported in 2.6% of cases (132 of 5,037) following NSS, in 4.6% (23 of 496) after cryoablation and in 11.7% (71 of 607) after RFA. Lesions managed by active surveillance were excluded from this analysis due to the lack of primary local treatment. Overall local recurrence developed in 3.7% of treated renal tumors (226 of 6,140). Progression to metastatic disease was described in 5.6% of lesions (281 of 5,037) undergoing NSS, 1.2% (6 of 496) undergoing cryoablation, 2.3% (14 of 607) undergoing RFA and 0.9% (3 of 331) undergoing active surveillance. Overall metastasis developed in 4.7% of the patients analyzed (304 of 6,471).

Multivariate models analyzing local recurrence and metastatic disease were performed using Bayesian Poisson models. Models constructed to account for time interactions did not show any significant association with followup, as pro-

TABLE 3. *Weighted tumor size in patients treated for enhancing SRMs*

| | All Lesions | Partial Nephrectomy | Cryoablation | RFA | Active Surveillance |
|---|---|---|---|---|---|
| No. series | 88 | 42 | 16 | 21 | 9 |
| No. lesions | 5,999 | 4,723 | 354 | 607 | 315 |
| Mean tumor size (cm) | 3.26 | 3.40 | 2.56 | 2.69 | 3.04 |
| p Value vs partial nephrectomy | — | | <0.001 | <0.001 | 0.54 |
| p Value vs cryoablation | — | | | 0.40 | 0.41 |
| p Value vs vs RFA | — | | | | 0.56 |

TABLE 4. *Weighted followup in patients treated for enhancing SRMs*

| | All Lesions | Partial Nephrectomy | Cryoablation | RFA | Active Surveillance |
|---|---|---|---|---|---|
| No. series | 84 | 40 | 16 | 19 | 9 |
| No. lesions | 5,825 | 4,583 | 406 | 521 | 315 |
| Mean followup (mos) | 47.1 | 54.0 | 18.3 | 16.4 | 33.3 |
| p Value vs partial nephrectomy | — | | <0.001 | <0.001 | <0.001 |
| p Value vs cryoablation | — | | | 0.63 | 0.001 |
| p Value vs RFA | — | | | | <0.001 |

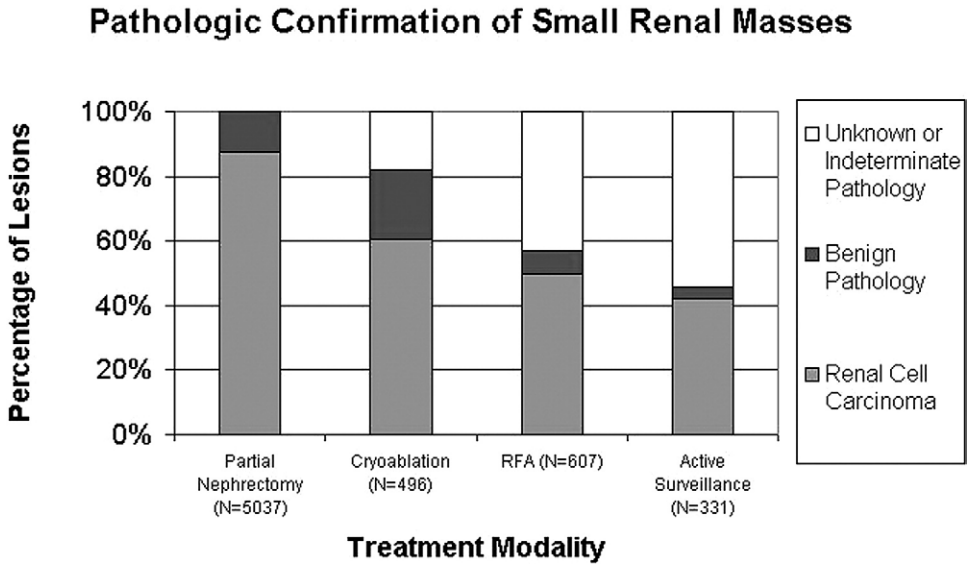
vided in the studies. Due to this lack of a time trend, trend lines were not fitted to the data. A significantly higher incidence of recurrence was demonstrated on multivariate analysis for lesions treated with cryoablation (RR = 7.45) and RFA (RR = 18.23) compared to those undergoing partial nephrectomy (table 5). While mean age (RR = 1.06) and mean followup (RR = 0.99) were not associated with local recurrence on multivariate analysis, a statistically significant relationship was seen between mean tumor size and the incidence of local recurrence (RR = 2.13). When the recurrence model was performed to evaluate the development of metastases, no significant differences were seen for lesions regardless of treatment modality (NSS or ablative technologies) or lack of treatment (observation). In fact, the incidence of metastases was only significantly associated with mean tumor size in the adjusted analyses (RR 2.74, table 5).

## DISCUSSION

Surgical resection is considered the standard of care for clinically localized RCC due to the favorable prognosis associated with surgery and the relative ineffectiveness of systemic therapy. The 5-year CSS for patients after nephrectomy ranges from 97% and 87% for pT1a and pT1b tumors, respectively, to only 20% for pT4 disease.[6] Similarly series of patients undergoing NSS showed a 5 and 10-year CSS of 92% and 80% across all pathological stages, and 96% and 90%, respectively, for tumors less than 4 cm.[7] Early data on laparoscopic partial nephrectomy is similarly favorable with 100% CSS at 3-year median followup.[8] The importance of treatment for localized RCC is accentuated by the fact that systemic treatments have demonstrated limited success as therapy for metastatic disease as well as in an adjuvant setting.[15,16]

In 1995 cryoablation was first applied to SRMs.[17] It involves rapid freeze and thaw cycles to produce tumor destruction.[9] Extracellular ice formation causes the movement of intracellular water, alterations in intracellular pH and protein denaturation.[18] Ice formation also results in the mechanical disruption of cell membranes.[18] Hours and days after cryoablation delayed tissue necrosis occurs as injury to the local microvasculature causes decreased tissue perfusion and delayed cell death.[18,19] Effective renal cryoablation has been achieved by open, laparoscopic and percutaneous image guided techniques.[9] The procedure can be monitored by a thermocouple or by ultrasound to confirm extension of the ice ball beyond the tumor margins.[9,20]

In 1997 RFA for an exophytic renal mass before open radical nephrectomy was first described.[21] In 1999 the first report of RFA as the only treatment for a renal tumor was published.[22] RFA may be applied using an open, laparoscopic or percutaneous approach under ultrasound, CT or MRI guidance.[9,10] Tumor coagulation by RFA occurs as radio frequency waves are converted to heat, resulting in thermal tissue damage.[9] High frequency current applied to target tissues results in ionic agitation, thereby heating the tissues, resulting in the denaturation of proteins and disintegration of cell membranes.[23] This process occurs during 4 to 6 minutes at temperatures above 50C and almost immediately above 60C.[23] Since temperatures greater than 105C result in tissue vaporization and ineffective ablation, opti-




Pathological data on renal lesions treated with partial nephrectomy, cryoablation, RFA and active surveillance

TABLE 5. *Bayesian Poisson model parameter estimates for risk of local recurrence or metastatic disease*

| | Local Recurrence | | Metastatic Disease | |
|---|---|---|---|---|
| | RR | 95% CI | RR | 95% CI |
| Intercept (log scale) | −7.76 | (−8.94, −7.73) | −8.84 | (−11.0, −7.19) |
| Random intercept SD (log scale) | 0.68 | (0.40, 1.04) | 1.36 | (0.85, 2.06) |
| Partial nephrectomy | 1.00 | — | 1.00 | — |
| Cryoablation | 7.45 | (2.24, 6.92) | 1.24 | (0.10, 12.60) |
| RFA | 18.23 | (6.08, 60.64) | 3.21 | (0.39, 8.19) |
| Observation | — | — | 0.11 | (0.00, .14) |
| Mean age | 1.06 | (0.98, 1.14) | 1.00 | (0.86, 1.16) |
| Mean tumor size | 2.13 | (1.39, 3.35) | 2.74 | (1.53, 5.21) |
| Mean followup | 0.99 | (0.97, 1.01) | 1.01 | (0.99, 1.05) |

RR with a 95% CI that does not cross 1 represents statistical significance and 70 studies had complete information available for multivariate analysis.

mal RFA is performed at temperatures of 50C to 100C throughout the tumor.[23] Vascular parenchyma may act as a heat sink during RFA and, therefore, exophytic tumors may be better ablated than central tumors in close proximity to the renal vasculature.[24]

Radiographic followup after cryoablation or RFA is the primary means of assessing the treatment effect.[25] Enhancement on post-contrast imaging is considered evidence of incompletely treated disease.[26] Groups at some centers have performed biopsy following ablation to assess for viable disease, while others have relied only on radiographic evaluation.[25,27] Evidence of disease recurrence at the ablation site indicates incomplete treatment of the renal tumor. While grossly viable disease may be detectable on followup imaging immediately following ablation, microscopic disease may require a longer duration of surveillance to become apparent. This may explain recent data suggesting that viable tumor may be present on post-ablation biopsy despite a lack of radiographic enhancement.[28] The Working Group on Image-Guided Tumor Ablation uses the term local tumor progression to indicate incomplete tumor treatment regardless of when enduring disease becomes evident.[25] Therefore, in our meta-analysis we considered all lesions with evidence of local disease persistence following ablation as locally recurrent disease regardless of time to reappearance. However, it should be noted that many local recurrences after ablation have been successfully re-treated with subsequent ablation. Thus, the ultimate rate of treatment failure after salvage ablation may remain to be fully defined.

When comparing rates of local recurrence among treatment modalities, it is important to consider that dissimilar criteria may be used to define recurrence for lesions treated with excision vs those undergoing ablation. To create a similar means of comparison in this study local recurrence after partial nephrectomy was considered to have developed if there was tumor recurrence in the ipsilateral kidney near the site of previous resection. However, these data may be subject to reporting bias and to the manner in which investigators describe ipsilateral tumor recurrence as local or distant from the previous resection. In addition, the definition of ablative success has been called into question by studies demonstrating viable tumor on post-ablation biopsy despite a lack of enhancement on imaging.[9,28] Perhaps the true rate of local recurrence may be more accurately determined if biopsy were routinely included, as in post-ablation surveillance protocols.

A small but emerging body of data exists regarding the observation or active surveillance of selected SRMs in elderly or infirm populations. Published series of the natural history of small renal tumors under active surveillance indicate some variability in the clinical behavior of observed SRMs. A recent meta-analysis of clinically localized tumors determined an overall median growth rate of 0.28 cm per year for lesions under active surveillance across multiple series, although growth rates varied considerably among reports (0.09 to 0.86 cm per year).[2] Moreover, 26% to 33% of incidental masses demonstrate zero net growth when observed for a median of 29 months.[11] With only 3 cases (1%) of progression to metastatic disease reported in the active surveillance literature,[2] it is difficult to accurately establish the rate at which sporadic, clinically localized RCC progresses to metastatic disease while under observation.

In this meta-analysis we noted that partial nephrectomy, cryoablation, RFA and active surveillance are oncologically viable approaches to the management of SRMs. While lesions treated with cryoablation or RFA are significantly more likely to experience residual disease following initial treatment, the incidence of progression to metastatic disease does not differ significantly among lesions treated with each modality. Moreover, lesions undergoing active surveillance demonstrate rates of metastatic progression that do not differ from those treated with NSS, cryoablation or RFA. In fact, the only factor significantly associated with the development of metastatic disease in our meta-analysis was tumor size. This raises the possibility of an overtreatment bias and suggests that treatment may not impact the biological potential of many indolent SRMs.

While rates of disease progression are similar for SRMs regardless of treatment modality or observation, our meta-analysis demonstrates that significant differences exist in the clinical application of these techniques. The current literature includes significant differences among lesions selected for each treatment with regard to tumor size and patient age. These differences reflect a selection bias in the use of available treatments. Less invasive treatment options have been selectively performed in older patients with smaller tumors, whereas data on partial nephrectomy generally describe younger patients with larger lesions. In addition, we noted that lesions treated with NSS as well as those in surveillance series have shown results with significantly longer posttreatment followup compared to ablative technologies. Furthermore, while lesions with known pathological results generally demonstrate similar rates of malignancy regardless of treatment modality, a significant number of tumors treated with ablative technologies or active surveillance have unknown or indeterminate pathological findings. Therefore, this absence of known pathological results is a confounding factor when attempting to compare oncological outcomes. The category of tumors with unknown pathological results certainly includes a number of histologically benign lesions and, thus, measures of treatment efficacy may be overestimated.[9] Therefore, our meta-analysis demonstrates the selection bias that exists in the current literature for the treatment of SRMs and emphasizes the need to develop more biologically relevant end points when measuring the outcomes of the therapies rendered. While the weaknesses of meta-analyses are well recognized,[29] these data underscore the need for long-term, prospective, randomized trials to determine the proper application and

biological implications for the treatment and surveillance of SRMs.

## CONCLUSIONS

The current data illustrate that NSS, ablation and surveillance are viable strategies for SRMs based on short-term and intermediate term oncological outcomes. However, a significant selection bias currently exists in the clinical application of these techniques with regard to patient age and tumor size. Although long-term data have demonstrated excellent outcomes for NSS, extended oncological efficacy remains to be established for ablation and surveillance strategies. While current data demonstrate a significantly higher incidence of local tumor progression following cryoablation and RFA, no significant differences in progression to metastatic RCC were seen for lesions regardless of treatment modality (NSS or ablation) or lack of treatment (observation). These data suggest an overtreatment bias for SRMs.

## APPENDIX

### Partial Nephrectomy

Beth Israel Hospital, Boston, Massachusetts; Case Western Reserve and Cleveland Clinic, Cleveland, Ohio; Chaim Sheba Medical Center, Ramat-Gan, Israel; Churchill Hospital, Oxford, and Guy's Hospital and St. Peter's Hospitals, London, United Kingdom; Columbia University, Memorial-Sloan Kettering Cancer Center and New York University, New York, New York; Duke University, Durham, North Carolina; Elisabethinen Hospital, Linz, General Hospital Klagenfurt, Klagenfurt and Rudolfstiftung, Vienna, Austria; General University Hospital of Heraklion, Crete and University of Patras, Patras, Greece; Henry Ford Hospital, Detroit and University of Michigan, Ann Arbor, Michigan; Hôpital Henri Mondor, Créteil, and Institut Mutualiste Montsouris and Hôpital Necker-Enfants Malades, Paris, France; Humboldt University, Berlin, Johannes Gutenberg University and Universitatskliniken Mainz, Mainz, University Hospital, Mannheim and University of Saarland Medical Center, Homburg/Saar, Germany; International Medical Center, Sendai, Kobe University School of Medicine, Kobe and Nagoya University, Nagoya City, Aichi, Japan; Istituto Clinico Humanitas, Milan, Marche Region Medical School, Ancona, National Institute for Cancer Research, Genoa, Universita degli Studi and University of Florence, Florence, University of Turin-San Luigi Hospital, Orbassano and University of Perugia, Perugia, Italy; Johns Hopkins University, Baltimore, Maryland; Kobenhavens Amts Sygehus Herlev, Herlev, Denmark; Mayo Clinic, Rochester, Minnesota; Medical College of Wisconsin, Milwaukee, Wisconsin; Sahlgrenska Sjukhuset, Gothenburg, Sweden; Thomas Jefferson University and University of Pennsylvania, Philadelphia, Pennsylvania; University Hospital Gasthuisberg and Katholieke Universiteit, Leuven, Belgium; University of Alabama, Birmingham, Alabama; University of California-Los Angeles, Los Angeles, California; University of Western Ontario, London, Ontario, Canada; Vanderbilt University, Nashville, Tennessee; and Washington University, St. Louis, Missouri.

### Cryoablation

Brigham and Women's Hospital, Boston and University of Massachusetts, Amherst, Massachusetts; Cedars-Sinai Medical Center and University of California-Los Angeles, Los Angeles, California; Cleveland Clinic, Cleveland, Ohio; Columbia University and New York University, New York, New York; Geisinger Medical Center, Danville, and MCP-Hahneman and Thomas Jefferson University, Philadelphia, Pennsylvania; Johns Hopkins University, Baltimore, Maryland; Northwestern University, Chicago and Southern Illinois University, Springfield, Illinois; San Raffaele Hospital, Milan, Italy; Jikei University School of Medicine, Tokyo, Japan; University Hospital, Basel, Switzerland; University of Mississippi, Jackson, Missouri; University of Virginia, Charlottesville, Virginia; and University of Wisconsin, Madison, Wisconsin.

### Radio Frequency Ablation

Aachen University of Technology, Aachen and Eberhard-Karls University, Tübingen, Germany; Brown University, Providence, Rhode Island; Case Western Reserve and Cleveland Clinic, Cleveland, Ohio; Duke University, Durham and Wake Forest University, Winston-Salem, North Carolina; Hull and East Yorkshire Hospitals, Kingston Upon Hull, United Kingdom; Institut Gustave Roussy, Villejuif, France; Johns Hopkins University, Baltimore, Maryland; Kochi University, Kochi and Kyoto Prefectural University of Medicine, Kyoto, Japan; Massachusetts General Hospital, Boston, Massachusetts; Mayo Clinic, Rochester, Minnesota; M. D. Anderson Cancer Center, Houston and University of Texas Southwestern, Dallas, Texas; Medical University of Lodz, Lodz, Poland; Taipei Veterans General Hospital, Taipei, Taiwan, Republic of China; University of Pennsylvania, Philadelphia, Pennsylvania; University of Turin, Turin, Italy; and Westmead Hospital, Westmead, New South Wales, Australia.

*(appendix continued)*

## APPENDIX continued

### Active Surveillance

Fox Chase Cancer Center, Philadelphia, Pennsylvania; Gartnavel General Hospital, Glasgow, United Kingdom; Kingston General Hospital, Queen's University, Kingston and University of Toronto, Toronto, Ontario and McGill University, Montreal, Quebec, Canada; Mayo Clinic, Jacksonville, Florida; New York University, New York, New York; and Sapporo Medical University, Sapporo, Tohoku University, Tohoku and University of Occupational and Environmental Health, Kitakyushu, Japan.

### Abbreviations and Acronyms

| | | |
|---|---|---|
| CSS | = | cancer specific survival |
| CT | = | computerized tomography |
| MRI | = | magnetic resonance imaging |
| NSS | = | nephron sparing surgery |
| RCC | = | renal cell carcinoma |
| RFA | = | radio frequency ablation |
| SRM | = | small renal mass |

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## EDITORIAL COMMENT

This timely review article on the management of SRMs highlights many of the deficiencies in the current literature that make comparison of the various modalities difficult at this time. Most notably the authors demonstrate a strong selection bias in this field. On average, patients undergoing surgical excision tended to have larger tumors, which correlated with high nuclear grade, invasive phenotype and other adverse features.[1] Patient selection also likely has an important role in active surveillance. Small tumor size and favorable radiographic appearance (homogeneous and well marginated) undoubtedly influence decision making in many cases.

The thermal ablation literature remains difficult to interpret due to limited followup in the majority of studies, considerable variability in technique (particularly for RFA), lack of pathological confirmation of cancer in a substantial proportion of patients and common acceptance of success criteria that may be flawed. Our recent experience suggests that lack of enhancement after RFA does not exclude the presence of viable cancer, emphasizing the need for post-treatment biopsy and extended clinical followup to define the true recurrence rates with these newer modalities.[2] Another important bias in this field is the use of different definitions of local recurrence, which for partial nephrectomy has traditionally comprised any ipsilateral tumor occurrence, even though it has long been recognized that most of these occur distant from the resection bed. In contrast, many thermal ablation studies have only counted recurrences at the original tumor site, which is better defined as treatment failure. I would propose that the more general definition should be used in the future, so that we will not still be comparing apples and oranges at our collective retirement.

While systemic recurrences have been uncommon with all of these modalities, and many are related to occult micrometastasis rather than local treatment failure, we must remember that even in the era of targeted molecular therapeutics most such recurrences are lethal. All current modalities ranging from surgical excision to active surveillance are viable. The Holy Grail for the future will be to match to the biological aggressive nature of the tumor, but at present this is best characterized as an educated guess. Given this element of uncertainty and the current status of the literature, which is well summarized by the authors, surgical excision is still the standard of care for most patients with SRMs. Renal mass biopsy enhanced by molecular profiling is the prime candidate for moving this field forward to a more enlightened state, so that these modalities can be used in a rational manner.[3]

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## REPLY BY AUTHORS

Optimal management of the SRM remains a clinical dilemma. The intention of our study was to provide a snapshot in time as to the current status of the world literature regarding biases, practice patterns and reported outcomes for management of the SRM. While there have been few (2)

prospective studies on the management of localized presumed renal carcinomas, we have still learned a great deal. As indicated in the publications summarized in our Bayesian hierarchical model, practice patterns have in fact changed in the management of the SRM during the last 3 decades in that we have become less radical and less invasive. These changes have been the result of single and multi-institutional studies documenting the efficacy of treatment with various modalities which have benefited patients. Therefore, despite the obvious shortcomings and limitations of these retrospective, highly selected reports, the published data have served to push the field slowly foward. However, these data have also reminded us that overtreatment and, less often, undertreatment of SRMs are common, and that our measured end points are imperfect.

A new era is dawning in medicine. Call it molecular, personalized or even targeted medicine, the goal is to match the treatment to the tumor biology. In 2008 market forces, technologies and outside influences will continue to force us all to be more critical of our collective published data sets. In this regard this article points out the limitations and biases of the data we rely on to counsel patients. It is our hope that the readers of this meta-analysis will discover the opportunities these limitations present, and participate in the necessary clinical and translational work required to uncover the answer to the small renal mass dilemma.