The Natural History of Observed Enhancing Renal Masses: Meta-Analysis and Review of the World Literature

Sam N. Chawla, Paul L. Crispen, Alexandra L. Hanlon, Richard E. Greenberg, David Y. T. Chen and Robert G. Uzzo*

From the Departments of Urologic Oncology and Biostatistics (ALH), Fox Chase Cancer Center, Temple University School of Medicine, Philadelphia, Pennsylvania

Purpose: Standard therapy for an enhancing renal mass is surgical. However, operative treatment may not be plausible in all clinical circumstances. Data on the natural history of untreated enhancing renal lesions is limited but could serve as a decision making resource for patients and physicians. We examined available data on the natural history of observed solid renal masses.

Materials and Methods: A Medline review of the literature was performed from 1966 to the present regarding untreated, observed, localized solid renal masses. To these data we added our institutional experience with a total of 61 lesions observed in 49 patients for a minimum of 1 year. Variables examined were initial lesion size at presentation, growth rate, duration of followup, pathological findings and progression to metastatic disease. Overall weighted mean estimates were calculated for lesion size at presentation, growth rate and followup based upon combining single institutional series with complete information.

Results: We identified 10 reports from 9 single institutional series in the world literature regarding the natural history of untreated solid localized renal lesions. The series included 6 to 40 patients (mean 25) with a mean followup of 30 months (range 25 to 39). When combined with our institutional data, a total of 286 lesions were analyzed, of which 234 could be included in the meta-analysis. Mean lesion size at presentation was 2.60 cm (median 2.48, range 1.73 to 4.08). Meta-analysis revealed a mean growth rate of 0.28 cm yearly (median 0.28, range 0.09 to 0.86) at a mean followup of 34 months (median 32, range 26 to 39) in all series combined. Pathological confirmation was available in 46% of the cases (131 of 286) and it confirmed 92% (120 of 131) as RCC variants. Evaluable data in this subset of confirmed RCC demonstrated a mean growth rate of 0.40 cm yearly (median 0.35, range 0.42 to 1.6). Lesion size at presentation did not predict the overall growth rate ($p = 0.46$). Progression to metastatic disease was identified in only 1% of lesions (3 of 286) during followup.

Conclusions: The majority of small enhancing renal masses grow at a slow rate when observed. Although metastatic and cancer specific death are low, serial radiographic data alone are insufficient to predict the true natural history of these lesions. Therefore, physicians and patients assume a calculated risk when following these tumors. Basic biological data are needed to assess the natural history of untreated renal masses.

Key Words: kidney, kidney neoplasms, natural history

The clinical diagnosis of RCC is based on radiographic findings. Effective imaging of the kidneys can be achieved by ultrasound, computerized tomography or magnetic resonance imaging.[1] Solid lesions on ultrasound as well as those that enhance on cross-sectional imaging are considered malignant until proven otherwise. Data on the usefulness of percutaneous biopsy of solid enhancing renal masses suggest that its role is limited in the diagnosis of RCC and its variants. Additionally, biopsy rarely changes clinical management.[2]

The detection of small incidental renal masses has increased in the last 2 decades due to the widespread use of body imaging modalities as generalized screening tests.[3–5] Alone they are often adequate to characterize the malignant potential of renal masses.[6–10] Given that the gold standard for treating enhancing masses is surgical and the relative resistance of advanced RCC to systemic therapies, data on the natural history of these lesions left untreated in situ are limited.[11] To date there are only 10 small series describing the outcomes of expectantly followed localized renal masses.[6,12–21] Collectively these studies account for only 225 lesions.

While surgical therapy remains the cornerstone of treatment, some patients may be poor candidates or unwilling to accept the risks of surgical therapy. Median age at RCC diagnosis is approximately 65 years.[22] These patients may have accrued an extensive list of comorbidities that may complicate recovery and/or result in a quality of life that they believe is unacceptable. The perioperative morbidity of nephrectomy has decreased as surgical techniques improve, although in some elderly populations it remains a relative risk.[3,23,24] Another subset of patients is simply unwilling to undergo treatment after a discussion regarding the potential morbidity of therapy and they elect to follow the renal mass. Furthermore, as patients age, competing health risks

Submitted for publication April 19, 2005.

* Correspondence: Department of Urologic Oncology, Fox Chase Cancer Center, 333 Cottman Ave., Philadelphia, Pennsylvania 19111 (telephone: 215-728-3501; FAX: 215-214-1734; e-mail: (R_Uzzo@fccc.edu).

Vol. 175, 425-431, February 2006
Printed in U.S.A.
DOI:10.1016/S0022-5347(05)00148-5

may affect overall longevity more significantly than a small or incidental untreated, enhancing renal lesion.

The practice of observing enhancing renal masses in the elderly or high risk surgical patient exists, although reports on the topic have been small and limited. Therefore, no guidelines for this situation have been established due to the lack of existing natural history data. When a physician and patient elect to observe a presumed malignant renal mass, each assumes a calculated risk, particularly in the absence of pathological confirmation. To better define this risk we reviewed the worldwide experience with enhancing renal masses for which therapy was delayed or has yet to be rendered. In addition, we examined the concurrent experience at our institution with the observation of enhancing renal lesions.

MATERIALS AND METHODS

Data sources. A MEDLINE search was preformed from 1966 through 2004 using the National Center for Biotechnology Information PubMed Internet site to review the world literature regarding the observation of suspected renal malignancies. Additionally, a previously unpublished series of patients undergoing observation of enhancing renal lesions at FCCC was included. A review of the FCCC computed database on patients undergoing observation of an enhancing renal lesion was performed from 2000 through 2004.

Study selection. This meta-analysis was limited to series analyzing tumors that were clinically localized at initial presentation. Therefore, series that included metastatic RCC and those that did not discriminate the growth rates of localized and metastatic disease were excluded from analysis. Prospective and retrospective series were included in the analysis. Case reports regarding the observation of single lesions were excluded.

After the initial MEDLINE search 13 potential studies of the growth rate of enhancing renal lesions were identified. Ten of these studies met our inclusion criteria, while 3 did not distinguish local growth rates between patients with metastatic disease and those with localized disease. The recent report of Volpe et al on 32 patients[17] included a prior series of 13 patients examined by Rendon et al.[6] Therefore, the series of Rendon et al was not considered in the meta-analysis since the data are accounted for by the series of Volpe et al.[17] This left 9 single previously published institutional series and our institutional series for inclusion in the analysis.

Analysis. The variables examined were the number of lesions, mean lesion size, mean lesion growth rate yearly and the duration of followup. Ideally individual renal lesion data would have been used for the meta-analysis. However, individual renal lesion data were not available in most series. After they were identified the data were collated and meta-analysis was performed. A meta-analytic approach was taken to combine available demographic data on the natural history of observed renal masses, where mean estimates were combined based on provided sample sizes. Overall weighted mean estimates were calculated for lesion size at presentation, growth rate and followup based on combining single institutional series with complete information. Only series for which patient data were presented as mean values and were representative of the entire patient population could be included in the meta-analysis evaluating the growth rate. An overall mean growth rate estimate was based on the assumption of independence.

Pathological findings presented in individual reports were pooled and analyzed for benign and malignant disease, and the prevalence of low and high nuclear grade lesions. The classification system used to determine nuclear grade varied among series and was not reported in 5. For this reason lesions were recategorized as low (1 or 2) or high (3 or 4) grade. Progression to metastatic disease was evaluated in all series. Correlation of lesion size at presentation with the growth rate was completed using series in which each individual lesion size and growth rate were presented. When using the lesions in the series of Volpe et al,[17] the assumption was made that all lesions were spherical when converting the change in tumor volume to the change in maximal diameter.

To evaluate the relationship between lesion growth parameters in confirmed RCC variants and benign tumors, further subset analysis was performed. Tumor size at presentation and the growth rate comparison between RCC variants and oncocytomas were evaluated using tumors with known individual growth rates and pathological findings. The series that contained evaluable data in this regard were those of Bosniak,[12,13] Kato,[16] Fujimoto[21] and Wehle[15] et al, and our current FCCC series.

Statistical analysis. Linear regression models were used to estimate the slope of individual lesion growth curves. For the FCCC institutional experience and meta-analyses involving individual lesions growth rate comparisons were accomplished under the assumption of independence among lesions using the parametric t test and nonparametric Wilcoxon statistics. To validate our findings in the FCCC group linear mixed effects modeling was used to incorporate the dependence of multiple lesions in a patient. Linear parameters were assumed to be random. SAS, version 8.2 (SAS Institute, Cary, North Carolina) was used for all statistical analyses.

RESULTS

FCCC institutional experience. We identified a total of 61 lesions in 49 patients that were followed at least 1 year. Average patient age was 71 years (median 73.0, range 42 to 85). The majority of patients were men (73% or 36 of 49). Average lesion size at presentation was 2.97 cm (median 2.30, range 1.0 to 12.0). The majority of lesions (79% or 48 of 61) were less than 4 cm in maximal diameter at presentation. Mean followup was 36.0 months (median 27.0, range 12 to 152). The reasons for patient observation were delay in referral in 22%, patient refusal to undergo surgery in 53% and extensive patient comorbidity in 25%. Lesions grew an average of 0.20 cm yearly (median 0.12, range to −1.64 to 1.80). This average was significantly different from the 0 slope ($p < 0.005$). The correlation of growth rates based on lesion size at presentation was not statistically significant ($p = 0.49$).

Of the 61 lesions 20 were treated with surgical intervention after an initial period of observation. Of these lesions 50% (10 of 20) had been observed prior to being referred to

TABLE 1. *Meta-analysis of available data on the natural history of observed masses*

References	Institution	No. Pts	Mean Lesion Size (cm)	Mean Growth Rate (cm/yr)	Mean Followup (mos)
Fujimoto et al[21]	Sendai Shakaihoken Hospital, Sendai, Japan	6	2.47	0.47	29
Bosniak et al[12,13]	New York University Medical Center, New York, NY	40	1.73	0.36	39
Kassouf et al[18]	McGill University Health Center, Montreal, Quebec, Canada	26	3.27	0.09	32
Volpe et al[17]	Princess Margaret Hospital, Toronto, Ontario, Canada	32	2.48	0.1	35
Wehle et al[15]	Mayo Clinic, Jacksonville, FL	29	1.83	0.12	32
Kato et al[16]	Tohoku School of Medicine, Sendai, Japan	18	1.98	0.42	27
Sowery and Siemens[20]	Kingston General Hospital, Kingston, Canada	22	4.08	0.86	26
Present series	FCCC, Philadelphia, PA	61	2.97	0.20	36
Totals (median)		234	2.60 (2.48)	0.28 (0.28)	34 (32)

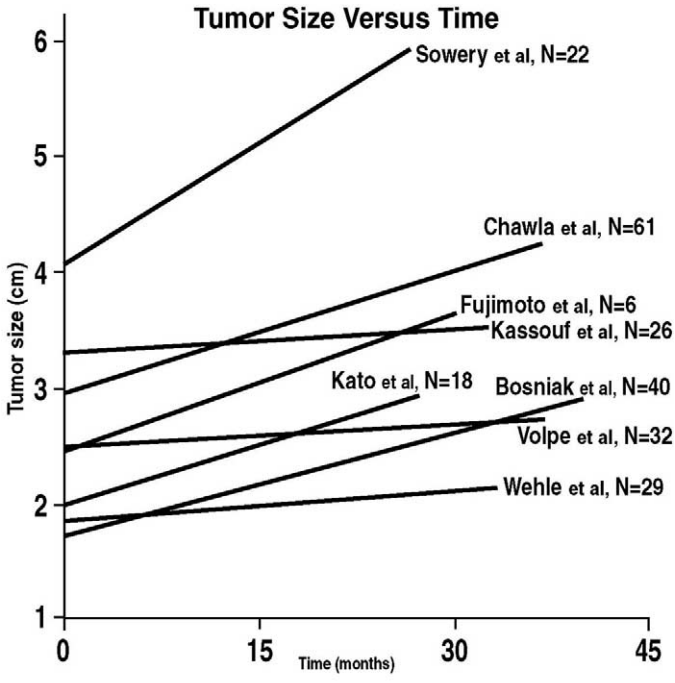
our institution for treatment. Additionally, biopsy data were available on 1 other lesion, which were consistent with papillary RCC. Therefore, pathological data were available on 34% of the lesions (21 of 61). Pathological evaluation confirmed RCC stage in 16 cases, including pT1a in 14, pT1b in 1 and pT2 in 1, and oncocytoma in 4. Only 1 RCC variant was high grade (Furman 3) and the remainder were low grade (Furman 1 to 2). Histological subtypes of RCC included clear cell, papillary and collecting duct in 9, 7 and 1 of the 17 cases, respectively.

Meta-analysis. A MEDLINE search from 1966 to the present revealed only 10 prior studies describing the outcome of expectantly followed, localized, enhancing renal masses. Most series were small with a mean of 25 lesions followed (median 26, range 6 to 40). Collectively these studies were reviewed and found to account for 225 analyzable lesions. These data were then combined with those on 61 observed lesions at our institution for a total of 286. The series of Oda et al of 16 lesions could not be evaluated in our meta-analysis, given that their data were reported as median values.[14] Data presented in the series of Lamb et al were excluded from growth rate analysis because not all patients included in their series were represented in the mean growth rate data given.[19] After excluding these 2 series 234 lesions remained for analysis. Overall mean initial lesion size at presentation was 2.60 cm (median 2.48, range 1.73 to 4.08). In series that contained evaluable data 86% of the lesions followed (178 of 208) were less than 4 cm in maximal diameter at presentation. Lesions were followed a mean of 34 months (median 32, range 26 to 39) and they grew at an mean rate of 0.28 cm yearly (median 0.28, range 0.09 to 0.86) (table 1). Individual series mean growth rates were plotted with respect to mean followup (see figure).

Of the 286 lesions reviewed 131 (46%) had pathological evaluation available (table 2). Of the lesions with available pathology 92% were malignant. The percent of malignant lesions in each series was 80% to 100%. Comparisons of renal lesion size at presentation and the growth rate were made among the 63 pathologically confirmed RCC variants and the 53 for which observational therapy was continued, with evaluable data available. Mean lesion size ± SD at presentation did not differ significantly among pathologically confirmed RCC variants and lesions for which observational therapy was continued (2.21 ± 1.54 vs 2.65 ± 1.77 cm, p = 0.34). The mean growth rate of pathologically confirmed RCC variants was significantly greater than lesions for which observational therapy was continued (0.40 ± 0.36 vs 0.21 ± 0.40 cm yearly, p = 0.0001).

Data on nuclear grade were presented in 74% of the pathologically confirmed RCC variants (89 of 120). The majority of lesions were low grade (89% or 79 of 89). The possible relationship between RCC nuclear grade and the growth rate could not be evaluated secondary to the limitations of the presented data.

Progression to metastatic disease was noted in 3 patients in the meta-analysis, representing 1.0% of the total number of lesions followed. Details on lesion size at presentation, followup and the growth rate were available for 2 of the 3 lesions that progressed to metastatic disease. One patient had metastatic disease in the FCCC series during followup.



Slope of lines represent mean growth rate of each individual series.
Length of each line represents mean duration of follow-up.
N=number of renal lesions followed in each series.

Tumor size vs time in series of Bosniak,[12,13] Wehle,[15] Kato,[16] Volpe,[17] Sowery[20] and Fujimoto[21] et al, and present series (*Chawla et al*). Line slope represents mean growth rate in each series. Line length represents mean followup.

TABLE 2. *Meta-Analysis of available pathological findings in renal masses that underwent observation*

References	No. Lesions	No. Pathological Findings Available (%)	No. RCC Pos (%)	No. Benign (%)	No. Progression to M+ (%)
Fujimoto et al[21]	6	6 (100)	6 (100)	0	0
Bosniak et al[12,13]	40	26 (65)	22 (85)	4 (15)	0
Oda et al[14]	16	16 (100)	16 (100)	0	0
Kassouf et al[18]	26	4 (15)	4 (100)	0	0
Volpe et al[17]	32	9 (28)	8 (89)	1 (11)	0
Wehle et al[15]	29	5 (17)	4 (80)	1 (20)	0
Kato et al[16]	18	18 (100)	18 (100)	0	0
Lamb et al[19]	36	24 (67)	23 (96)	1 (4)	1 (3)
Sowery and Siemens[20]	22	2 (9)	2 (100)	0	1 (5)
Present series	61	21 (34)	17 (81)	4 (19)	1 (2)
Totals	286	131 (46)	120 (92)	11 (8)	3 (1)

This patient presented initially at age 84 years with a 2.0 cm lesion and was followed elsewhere prior to referral. The tumor grew rapidly at a rate of 1.3 cm yearly to a final of diameter of 8 cm on last imaging. Multiple pulmonary lesions were noted at 54 months of followup. The patient with metastatic disease in the series of Sowery et al presented with an 8.8 cm mass, which was followed for 111 months with a growth rate of 0.2 cm yearly.[20] The patient with metastatic disease in the series of Lamb et al had metastasis at 132 months of followup.[19] Initial lesion size and the growth rate were not presented. All 3 patients with metastatic disease were symptomatic at the time of disease progression.

Subset analysis was performed to identify whether existing data support the notion that tumor size is an important predictor of the growth rate. In this regard, in addition to our series, 4 series had evaluable data relating tumor size to the growth rate in all patients. By combining the lesions in the experience of Fujimoto,[21] Volpe,[17] Bosniak[12,13]and Kato[16] et al, and our FCCC experience a total of 157 lesions were analyzed, representing 55% of all those observed in the literature. Mean lesion size was 2.42 cm (median 2.20, range 0.5 to 12.0). The majority of lesions (93% or 146 of 157) in this subset analysis were less than 4 cm in maximal diameter. Given these data, we could not identify a significant correlation between lesion size at presentation and the growth rate, when observed ($p = 0.46$).

On further analysis of these data we compared initial tumor size and the observed growth rate in pathologically benign (oncocytoma) and malignant (RCC variants) solid masses. A total of 76 tumors had the individual growth rate and pathological data available for comparison. Of these tumors 12% (9 of 76) were oncocytomas, while the remaining 88% (67 of 76) were RCC variants. Mean tumor size at presentation in oncocytomas and RCC variants was 2.00 ± 0.99 (median 1.50, range 1 to 3.9) and 2.21 ± 1.5 cm (median 2.0, range 0.20 to 12.0), respectively ($p = 0.59$). The mean growth rate of oncocytomas and RCC variants did not differ statistically (0.05 ± 0.67, median 0.16, range 1.6 to 0.62 and 0.35 ± 0.41 cm yearly, median 0.35, range 0.42 to 1.6, respectively, $p = 0.15$).

DISCUSSION

Observation of an enhancing renal mass is a calculated risk for the treating physician and the affected patient. Incidental renal masses that may require treatment are increasingly being detected, although to our knowledge the growth and metastatic potential of untreated lesions remains unquantified. It is now recognized that RCC is a heterogeneous disease from its inception. This heterogeneity is reflected in its clinical course. Forces arguing against observation are the relative low risk of anesthesia, expanding surgical options, including nephron sparing, ablative, laparoscopic and percutaneous approaches, the ineffectiveness of systemic therapy and the uncertain biological potential of untreated renal masses. Underlying an argument for observation, particularly in the elderly patient with comorbidities, is the indolent growth rate observed in small series and unreported clinical practice patterns.

Data on the observation of enhancing renal masses has been presented in several small series. The results of individual series are similar in regard to renal lesion size, the growth rate and progression to metastatic disease (tables 1 and 2). The conclusions and recommendations of the individual investigators are also similar. They advise that a period of observation, comprising routine followup and serial imaging, can be safely performed in patients who are medically unfit for surgery. However, given the limitations of individual series, we performed a meta-analysis including 286 patients, of whom 234 had sufficient mean growth rate data to be analyzed. The 234 lesions were followed a mean of 34 months (median 32, range 26 to 39) with a mean growth rate of 0.28 cm yearly (median 0.28, range 0.09 to 0.86) (table 1). The figure shows these results.

It is important to emphasize that in this study the majority of the lesions that were eventually removed were pathologically confirmed RCC (table 2). It would likely follow that a large proportion of the remaining lesions were also RCC, given that the same criteria were used for radiographic evaluation and subsequent inclusion in this study. However, we do not have pathological data on the remaining 155 lesions, which may limit interpretation. Furthermore, the growth rate of pathologically confirmed RCC variants was significantly greater than that of lesions for which observation was continued. This finding likely represents lesions being removed because of their rapid growth rates, while lesions demonstrating slow or no interval growth continued on observation. Another possibility is that a higher percent of lesions that underwent continued observation were benign. To evaluate this possibility tissue from the lesions on continuing observation would need to be evaluated. However, negative biopsy would not rule out RCC and experience has shown that a positive biopsy may significantly under stage or under grade the lesion.[2,25] A noninvasive test that simultaneously provides histological and prognostic information in RCC is currently lacking. There-

fore, we are left to follow enhancing renal masses without knowledge of the 3 main prognostic indicators in RCC, namely grade, histological subtype and pathological stage. This is clearly a limitation of any observational treatment plan. The majority of lesions followed were clinically and likely pathologically stage 1 but again pathological results are an unknown variable in most cases reported. Additionally, a positive overall mean growth rate was noted in each series analyzed. Therefore, it is important to emphasize that the majority of observed lesions in these series were not static.

We stratified the growth rate of lesions based on their size at initial presentation. When using the available pooled data, we found no correlation. Additionally, in some of the series mentioned the investigators examined the relationship between tumor grade and growth rate. However, it was not possible to analyze this in meta-analytical fashion because nuclear grading remains somewhat subjective and it is not applied or reported universally. In individual studies the results comparing grade and growth rates were equivocal. For example, Kato et al did not observe a significant growth rate difference between grades 1 and 2, and 1 and 3 tumors, although they noted a difference between grades 2 and 3 tumors.

Oncocytomas lack distinct radiographic findings on computerized tomography and they cannot be diagnosed accurately using imaging alone. No difference was noted in tumor size at presentation or the tumor growth rate between oncocytomas and RCCs in our review of the existing literature. This further supports the consideration of all enhancing lesions to be malignancies based on radiographic data alone.

Nonetheless, we recognize that some small observed lesions are not RCC. Recent data suggest that smaller lesions may have a greater chance of being benign than previously recognized. In a large series of Frank et al from the Mayo Clinic 2,935 solid renal tumors were treated in a 30-year period.[26] Of these lesions 12.8% were benign and the remainder were malignant. The investigators found that each 1 cm increase in tumor size increased the odds of malignancy by 17%. Of the lesions less than 1 cm 46.3% were benign compared to 53.8% that were malignant. However, limitations of these data exist since more sensitive imaging modalities have been developed in the last several decades, consistent criteria for true vs marginal enhancement are lacking and radiographic data must be subjectively interpreted. In another study of Gill et al 30% of the 100 tumors removed by laparoscopic partial nephrectomy were benign.[27] Mean tumor size in this cohort was 2.8 cm. While it appears that the risk of malignancy is less in smaller lesions, the majority of these lesions are malignant with growth potential. Thus, we cannot advocate observational therapy for all small lesions.

In our series only 1 patient had metastatic disease. An additional 2 patients were noted to have metastatic disease during observation in the other reviewed series. This represents 1.0% of patients (3 of 287) in the meta-analysis population with progression to metastatic disease. Although the possibility of progression to metastatic disease is low, it remains the most significant risk of observational therapy since there is no satisfactory treatment for metastatic RCC. Some investigators have suggested a safe cutoff of 3 cm, above which the danger of metastases increases. In a recent prospective study of hereditary renal cancer, Walther et al reported that none of 52 patients with von Hippel-Lindau disease and a tumor less than 3 cm had metastases.[28] However, in 11 of the 44 patients (25%) with tumors larger than 3 cm metastatic RCC developed or was already present. Although these investigators examined hereditary RCC, it is plausible to cautiously extend these findings to sporadic clear cell RCC, given the common association of the von Hippel-Lindau gene. However, an absolutely safe cutoff for observation may not exist because the metastatic potential of observed lesions is difficult to quantify and competing health risks exist.

No definitive protocol for radiographic followup of renal lesions exists since it is not the gold standard of therapy. However, several principles are apparent. The imaging modality used should be consistent and be performed with a contrast agent to evaluate enhancement characteristics. Furthermore, the radiologist should be informed of the clinical history and should have access to prior studies for direct comparison. The physician assuming responsibility for observing the lesion(s) should directly review and compare the studies. With regard to the interval of imaging we believe that it is prudent to have more frequent followup during the first 24 months. After the lesion has demonstrated radiographic stability the followup interval may be cautiously extended. Additionally, periodic reassessment for metastatic disease is important.

When observing enhancing renal lesions the physician and the patient assume risk. RCC is a radiological diagnosis and all lesions included in this study qualified as surgical lesions because of their radiographic characteristics. We believe that competing health risks are the only justification for observation, given the limitations of current data. Lesions that may be in difficult anatomical locations should not dictate observation. Similarly observational data such as ours should not take precedence over advancing newer techniques, such as cryoablation, radio frequency ablation or extracorporeal ablation technologies. However, caution should be used when interpreting data on these new technologies, since the data on observation without treatment appear to be encouraging. Parsons et al noted that the increased detection and treatment of renal tumors, particularly using newer technologies, has not been associated with a corresponding decrease in age specific renal cancer mortality rates in the United States.[29] Given data such as those presented in our study, they appropriately caution against over enthusiasm for noninvasive technologies, given the lack of evidence that treatment for small lesions is ultimately beneficial. We extend the same cautionary note when interpreting short-term treatment data on incidental RCC, while recognizing that the forces to do something rather than nothing are significant.

Overall our review of the available data demonstrate that, while no large-scale, prospective data on observation exist with which to counsel patients considering an observational approach, the results of our meta-analysis demonstrate that many small incidental tumors are associated with a slow natural growth rate and low metastatic risk. However, there are several limitations of our analysis. The weaknesses of meta-analysis are well recognized when evaluating clinical questions.[30] A prospective, randomized trial would likely provide a more accurate appraisal of the natural history of clinically localized, enhancing renal masses

but it would be difficult to justify, given the efficacy of surgical treatment. Furthermore, a certain degree of selection bias may be present in the reviewed series by inadvertently selecting patients who may have fared better during an initial period of observation. This is especially true of patients who were referred from elsewhere, where they had already undergone a period of initial observation without evidence of disease progression.

Clearly the biological potential of these lesions must be more fully elucidated through the study of RCC prognostic variables[31,32] and biomarkers.[33–36] We summarized the limited data on the natural growth history of enhancing renal masses, so that these data can be presented to patients in an informed discussion of risk. Only by extending studies such as these, correlated with translational research, will we 1 day be able to select patients with rapidly growing tumors who are at risk for progressive disease and, thereby, increase the safety of observational therapy when it is indicated.

CONCLUSIONS

The majority of small, incidentally discovered, enhancing renal masses are malignant. These lesions commonly grow at a slow but consistent mean rate of 0.28 cm yearly. Surgical therapy remains the standard of care. A course of observation should only be performed when patient and physician alike are willing to accept the calculated risks involved. It should be avoided in well patients simply because the lesion is anatomically challenging.

Although the metastatic potential of observed lesions remains, it appears low in the absence of significant interval growth. Additionally, size at presentation does not appear to be a reliable indicator of the growth rate. Long-term clinical and translational studies are required to identify markers of progression and select individuals most at risk who are, therefore, in need of early intervention.

Abbreviations and Acronyms

FCCC = Fox Chase Cancer Center
RCC = renal cell carcinoma

REFERENCES

1. Israel, G. M. and Bosniak, M. A.: Renal imaging for diagnosis and staging of renal cell carcinoma. Urol Clin North Am, **30:** 499, 2003
2. Campbell, S. C., Novick, A. C., Herts, B., Fischler, D. F., Meyer, J., Levin, H. S. et al: Prospective evaluation of fine needle aspiration on small, solid renal masses: accuracy and morbidity. Urology, **50:** 25, 1997
3. Derweesh, I. H. and Novick, A. C.: Small renal tumors: natural history, observation strategies and emerging modalities of energy based tumor ablation. Can J Urol, **10:** 1871, 2003
4. Smith, S. J., Bosniak, M. A., Megibow, A. J., Hulnick, D. H., Horii, S. C. and Raghavendra, B. N.: Renal cell carcinoma: earlier discovery and increased detection. Radiology, **170:** 699, 1989
5. Jayson, M. and Sanders, H.: Increased incidence of serendipitously discovered renal cell carcinoma. Urology, **51:** 203, 1998
6. Rendon, R. A., Stanietzky, N., Panzarella, T., Robinette, M., Klotz, L. H., Thurston, W. et al: The natural history of small renal masses. J Urol, **164:** 1143, 2000
7. Coll, D. M., Uzzo, R. G., Herts, B. R., Darvos, W. J., Wirth, S. L. and Novick, A. C.: 3-Dimensional volume rendered computerized tomography for preoperative evaluation and intraoperative treatment of patients undergoing nephron sparing surgery. J Urol, **161:** 1097, 1999
8. Novick, A. C.: Management of the incidentally detected solid renal mass. Semin Nephrol, **14:** 519, 1994
9. Rofsky, N. M. and Bosniak, M. A.: MR imaging in the evaluation of small (< or = 3.0 cm) renal masses. Magn Reson Imaging Clin North Am, **5:** 67, 1997
10. Szolar, D. H., Kammerhuber, F., Altziebler, S., Tillich, M., Breinl, E., Fotter, R. et al: Multiphasic helical CT of the kidney: increased conspicuity for detection and characterization of small (<3-cm) renal masses. Radiology, **202:** 211, 1997
11. Uzzo, R. G. and Novick, A. C.: Nephron sparing surgery for renal tumors: indications, techniques and outcomes. J Urol, **166:** 6, 2001
12. Bosniak, M. A.: Observation of small incidentally detected renal masses. Semin Urol Oncol, **13:** 267, 1995
13. Bosniak, M. A., Birnbaum, B. A., Krinsky, G. A. and Waisman, J.: Small renal parenchymal neoplasms: further observations on growth. Radiology, **197:** 589, 1995
14. Oda, T., Miyao, N., Takahashi, A., Yanase, M., Masumori, N., Itoh, N. et al: Growth rates of primary and metastatic lesions of renal cell carcinoma. Int J Urol, **8:** 473, 2001
15. Wehle, M. J., Thiel, D. D., Petrou, S. P., Young, P. R., Frank, I. and Karsteadt, N.: Conservative management of incidental contrast-enhancing renal masses as safe alternative to invasive therapy. Urology, **64:** 49, 2004
16. Kato, M., Suzuki, T., Suzuki, Y., Terasawa, Y., Sasano, H. and Arai, Y.: Natural history of small renal cell carcinoma: evaluation of growth rate, histological grade, cell proliferation and apoptosis. J Urol, **172:** 863, 2004
17. Volpe, A., Panzarella, T., Rendon, R. A., Haider, M. A., Kondylis, F. I. and Jewett, M. A.: The natural history of incidentally detected small renal masses. Cancer, **100:** 738, 2004
18. Kassouf, W., Aprikian, A. G., Laplante, M. and Tanguay, S.: Natural history of renal masses followed expectantly. J Urol, **171:** 111, 2004
19. Lamb, G. W., Bromwich, E. J., Vasey, P. and Aitchison, M.: Management of renal masses in patients medically unstable for nephrectomy—natural history, complications, and outcomes. Urology, **64:** 909, 2004
20. Sowery, R. D. and Siemens, D. R.: Growth characteristics of renal cortical tumors in patients managed by watchful waiting. Can J Urol, **11:** 2407, 2004
21. Fujimoto, N., Sugita, A., Terasawa, Y. and Kato, M.: Observations on the growth rate of renal carcinoma. Int J Urol, **2:** 71, 1995
22. Ries, L. A. G., Eisner, M. P., Kosary, C. L., Hankey, B. F., Miller, B. A., Clegg, L. et al: SEER Cancer Statistics Review, 1975-2002. National Cancer Institute. Bethesda, Maryland. Available at http://seer.cancer.gov/csr/1975_2002/. Accessed April 15, 2005
23. Pantuck, A. J., Zisman, A. and Belldegrun, A. S.: The changing natural history of renal cell carcinoma. J Urol, **166:** 1611, 2001
24. Lee, C. T., Katz, J., Shi, W., Thaler, H. T., Reuter, V. E. and Russo, P.: Surgical management of renal tumors 4 cm. or less in a contemporary cohort. J Urol, **163:** 730, 2000
25. Dechet, C. B., Zincke, H., Sebo, T. J., King, B. F., LeRay, A. J., Farrow, G. M. et al: Prospective analysis of computerized tomography and needle biopsy with permanent sectioning to determine the nature of solid renal masses in adults. J Urol, **169:** 71, 2003
26. Frank, I., Blute, M. L., Cheville, J. C., Lohse, C. M., Weaver, A. L. and Zincke, H.: Solid renal tumors: an analysis of pathological features related to tumor size. J Urol, **170:** 2217, 2003
27. Gill, I. S., Matin, S. F., Desai, M. M., Kaouk, J. H., Steinberg, A., Mascha, E. D. et al: Comparative analysis of laparoscopic versus open partial nephrectomy for renal tumors in 200 patients. J Urol, **170:** 64, 2003

28. Walther, M. M., Choyke, P. L., Glenn, G., Lyne, J. C., Rayford, W., Venzon, D. et al: Renal cancer in families with hereditary renal cancer: prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. J Urol, **161:** 1475, 1999
29. Parsons, J. K., Schoenberg, M. S. and Carter, H. B.: Incidental renal tumors casting doubt on the efficacy of early intervention. Urology, **57:** 1013, 2001
30. LeLorier, J., Gregoire, G., Benhaddad, A., Lapierrre, J. and Derderian, F.: Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med, **337:** 536, 1997
31. Patard, J. J., Kim, H. L., Lam, J. S., Dorey, F. J., Pantuck, A. J., Zisman, A. et al: Use of the University of California Los Angeles integrated staging system to predict survival in renal cell carcinoma: an international multicenter study. J Clin Oncol, **22:** 3316, 2004
32. Gettman, M. T. and Blute, M. L.: Update on pathologic staging of renal cell carcinoma. Urology, **60:** 209, 2002
33. Dulaimi, E., Ibanez de Caceres, I., Uzzo, R. G., Al-Saleem, T., Greenberg, R. E., Polascik, T. J. et al: Promoter hypermethylation profile of kidney cancer. Clin Cancer Res, **10:** 3972, 2004
34. Shvarts, O., Seligson, D., Lam, J., Shi, T., Horvath, S., Figlin, R. et al: p53 is an independent predictor of tumor recurrence and progression after radical nephrectomy in patients with localized renal cell carcinoma. Urology, **173:** 725, 2005
35. Mizutani, Y., Nakanishi, H., Yamamoto, K., Li, Y. N., Matsubara, H., Mikami, K. et al: Downregulation of smac/DIABLO expression in renal cell carcinoma and its prognostic significance. J Clin Oncol, **23:** 448, 2005
36. Skates, S. and Iliopoulos, O.: Molecular markers for early detection of renal carcinoma: investigative approach. Clin Cancer Res, **10:** 6296S, 2004