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Predicting Growth of Solid Renal Masses Under Active Surveillance

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Abstract

Objectives—The natural history and growth rates of untreated solid enhancing renal tumors is being defined through active surveillance series. Serial radiographic evaluation of patients who are not surgical candidates or refuse surgical treatment provides an opportunity to characterize the growth of untreated enhancing renal tumors. Here we evaluate factors which may help predict for radiographic growth during observation.

Methods and Materials—We reviewed our renal cancer database for enhancing renal masses that were radiographically observed for a period of at least 12 months. Variables examined included patient age, gender, lesion size on presentation, radiographic tumor characteristics, duration of active surveillance, linear growth rate, surgical pathology, development of new renal tumors, and stage progression.

Results—109 patients with 124 sporadic enhancing renal tumors were identified undergoing a period of active surveillance of at least 12 months. Median patient age was 73 years (mean 69.8, range 35–87). 72% (78/109) of patients were males. Median duration of active surveillance was 26 months (mean 33.4, range 12–156). Multifocal disease was present in 9% (10/109) patients on presentation, accounting for 20% (25/124) of all tumors. Tumor size on presentation was a median of 2.0 cm (mean 2.61, range 0.4 – 12.0). Overall median tumor growth rate was 0.21 cm/yr (mean 0.28, range –1.4 – 2.47). Observed linear growth rates were independent of patient age, gender, tumor size on presentation, multifocality, and radiographic characteristics (solid versus cystic), $p > 0.05$. Of the patients initiating a period of active surveillance 36% (39/109) eventually underwent definitive therapy. Malignant pathology was present in 90% (35/39) of patients undergoing treatment. In patients continuing active surveillance (64% (70/109)), 2.9% (2/70) developed de novo renal lesions and 1.4% (1/70) developed metastatic disease.

Conclusions—Currently, no clinical predictors of tumor growth or disease progression have been identified; although, the risk of developing progressive disease over the short term appears low. Clinical and molecular markers of disease progression are needed prior to offering active surveillance to otherwise acceptable surgical candidates.

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Keywords

Renal Tumors; Active Surveillance; Disease Progression

Introduction

The incidence renal cell carcinoma (RCC) has increased dramatically during the last three decades primarily as a result of incidental detection (1,2). There has been an increase in surgical treatments and the development of novel therapies coinciding with earlier detection and stage migration of small renal masses (SRM). (2). Prompt surgical excision remains the standard of care for localized enhancing renal tumors because of the limited efficacy of systemic therapies for advanced disease (3,4). However, recent data demonstrate that despite earlier diagnosis and treatment, there has been no significant decrease in cancer specific or overall mortality suggesting an over-treatment bias (2).

Currently, the natural history of untreated localized renal tumors is being defined through active surveillance series. A recent meta-analysis of active surveillance series revealed that the majority of renal tumors demonstrated slow interval growth with an average growth rate of 0.28cm/yr (5). Moreover, a subset of approximately 30% of renal tumors did not demonstrate any interval growth. Analysis of these “zero growth” tumors failed to demonstrate any difference in pathology between growing and non-growing tumors, and could not identify any predictive clinical or radiographic characteristics(6).

The ability to discriminate between tumors that will grow and those that will not would greatly facilitate treatment planning. In order to investigate and better define clinical predictors of future tumor growth we reviewed our experience with active surveillance of enhancing renal tumors.

Methods

We retrospectively analyzed the Fox Chase Cancer Center renal cancer database for enhancing renal masses which were radiographically observed from January 2000 through July of 2006. A total of 124 clinically localized lesions in 109 patients were identified which had been observed for at least 12 months. All lesions were presumed malignant and locally confined to the kidney based upon radiographic findings. Only solid renal masses and complex cystic lesions with clear radiographic enhancement were included. Patients with hereditary RCC were excluded from analysis. Patients were managed with active surveillance if they were medically unfit or unwilling to undergo surgical intervention.

Variables examined included patient age, gender, indication of active surveillance, lesion size on presentation, duration of active surveillance, radiographic tumor characteristics (solid versus cystic), presence of multifocal renal tumors, linear tumor growth rate, surgical pathology, development of new renal tumors, and progression to metastatic disease. Multifocal disease was defined as multiple tumors in one kidney or the presence of bilateral enhancing renal tumors. Indications for active surveillance were categorized as absolute, relative and elective. Absolute indications include patients who are not surgical candidates based upon significant medical co-morbidities which put them at excessive post-operative risk. Relative indications for active surveillance include the desire to avoid the potential need for renal replacement therapy following treatment of the suspected RCC. Elective indications for active surveillance include patients who refuse surgical intervention despite being of low operative and nephrologic risk.

Regular radiographic follow-up was performed at 3–6 month intervals and tumor size was measured as the maximal cross-sectional diameter. Lesion measurements were performed at consistent levels within the kidney by direct comparison to existing studies. Tumor growth rate was defined as net change in diameter per year over the course of observation. Surveillance for metastatic disease was performed at least yearly, and included chest x-ray, hepatic function tests, and a bone scan in symptomatic patients. Pathologic confirmation of metastatic disease was required when documenting progression to metastatic disease. Disease progression was defined as the development of previously undetected enhancing renal tumors in the ipsilateral or contralateral kidney. Surgical pathology was reviewed for all tumors undergoing definitive treatment.

Statistical analysis was performed using GraphPad InStat software, San Diego, Ca. Statistical significance was assigned to p values <0.05 using 2-tailed analysis.

Results

109 patients with 124 sporadic enhancing renal tumors were identified undergoing a period of active surveillance of at least 12 months. Median patient age was 73 years (mean 69.8, range 35–87). The majority, 72% (78/109), of patients were males. Median duration of active surveillance was 26 months (mean 33.4, range 12–156). Indications for active surveillance were absolute in 28% (31/109), relative in 12% (13/109) and elective in 60% (65/109) of patients.

Radiographically, 85% (106/124) of tumors were solid, with the remaining 15% (18/124) of tumors being Bosniak III ($n = 5$) and IV ($n = 13$) cysts. Multifocal disease was present in 9% (10/109) of patients at presentation, accounting for 20% (25/124) of all tumors. Tumor size on presentation was a median of 2.0 cm (mean 2.61, range 0.4 – 12.0). Overall median linear tumor growth rate was 0.21cm/yr (mean 0.28, range $-1.4 - 2.47$). 25% (31/124) of tumors undergoing active surveillance did not demonstrate interval growth.

Potential clinical and radiographic predictors of future tumor growth were investigated. The potential clinical predictors of tumor growth examined were gender and patient age on presentation. Tumor growth rate did not differ significantly between males (median 0.22 cm/yr, mean 0.28cm/yr) and females (median 0.19cm/yr, mean 0.28 cm/yr), $p > 0.05$ (Figure 1). Additionally, patient age on presentation was not predictive of future tumor growth rate, $p > 0.05$ (Figure 2). The potential radiographic predictors of tumor growth rate examined included: multifocal disease, cystic appearance on imaging, and tumor size on presentation. The observed growth rates of solitary (median 0.18 cm/yr, mean 0.29 cm/yr) and multifocal (median 0.27 cm/yr, mean 0.25cm/yr) tumors were not significantly different, $p > 0.05$. Additionally, no difference in growth rates was noted between solid tumors (median 0.22 cm/yr, mean 0.28 cm/yr) and complex enhancing cysts (median 0.16 cm/yr, mean 0.28 cm/yr), $p > 0.05$ (Figure 1). Lastly, tumor size on presentation did not correlate with future tumor growth rate, $p > 0.05$ (Figure 3).

Of the patients initiating a period of active surveillance 36% (39/109) eventually underwent definitive therapy. Malignant pathology was present in 90% (35/39) of patients undergoing treatment. Histologically, the majority of tumors were clear cell RCCs ($n=24$). The remainder of RCC histologic variants included: papillary ($n=9$), chromophobe ($n=1$), and collecting duct ($n=1$) variants. Accurate pathologic staging was available only on tumors managed with surgical excision. The majority of tumors undergoing extirpative therapy were T1a ($n=16$). The remaining tumors were T1b ($n=2$), T2 ($n=1$), and T3b ($n=1$). All tumors with benign pathology were oncocytomas ($n=4$).

Of the 64% (70/109) of patients continuing active surveillance, 2.9% (2/70) developed de novo renal lesions and 1.4% (1/70) developed metastatic disease. Both patients developing de novo renal lesions presented with multifocal disease, representing 20% (2/10) of patients with multifocal disease on presentation. de novo lesions were noted at 27 and 35 months of initial patient presentation. Of the patients developing de novo lesions only one has undergone surgical intervention. Pathologic evaluation revealed papillary RCC. The remaining patient developing de novo renal tumors continues to refuse surgical intervention. No patient with de novo renal lesions during active surveillance developed extra-renal disease.

The single patient who developed metastatic disease initially presented at 84 years of age with a 2.0 cm lesion and was followed at an outside institution prior to referral to our institution. The tumor grew rapidly at a rate of 1.3 cm/yr to a final of diameter of 8 cm on last imaging. Multiple pulmonary lesions were noted at 54 month follow up. At the time of detection of metastatic disease, the patient had developed hematuria and tumor related flank pain.

Discussion

These data demonstrate that although most untreated localized enhancing renal tumors under slow interval growth during active surveillance, some exhibit “zero growth”. With the observed heterogeneous behavior of renal masses, it would be helpful to establish clinical and pathologic predictors of future tumor growth and/or progression to metastatic disease. Potential predictors of future tumor growth include gender, patient age on presentation and radiographic tumor characteristics. As described above, neither gender nor patient age predicted future tumor growth in our series. A recent report by Kouba et al noted a significant correlation between patient age on presentation and linear tumor growth rates (7). Their data suggests that tumors detected in younger patients exhibit increased linear growth compared to older patients. As the authors suggested this data must be interpreted with caution due to their small sample size.

Potential radiographic predictors of renal lesion growth investigated included lesion size on presentation, presence of cystic components, and the presence of multifocal disease on presentation. Consistent with our findings here, others have demonstrated that lesion size at presentation does not correlate with growth potential (8–11). This finding is evident when reviewing the observations of Lamb et al. The mean lesion size in their series was 7.2 cm (range 3.5 – 20.0) with a mean growth rate of 0.39 cm/yr (12). This observed growth rate was similar to those of other series with smaller mean lesion sizes. Additionally, the presence of cystic components did not predict future tumor growth when compared to solid lesions despite their potentially improved prognosis (10,13–17).

This is the first report to our knowledge that compares the growth rates of multifocal and solitary renal lesions under surveillance. Multifocal disease is present in 5 – 21% of patients presenting with RCC in current series(18–20). The presence of multifocal disease on presentation does not impact survival in patients undergoing nephrectomy(19,20). Our data did suggest that clinically localized multifocal and solitary tumors have similar growth rates. However, this finding must be viewed with caution given the small sample size of multifocal tumors (n=10) in the current series.

The ability to identify tumors which are destined to grow and/or metastasize would be of great benefit when designing and implementing treatment plans for patients presenting with enhancing renal tumors. As clinical and radiographic characteristics on patient presentation are poor predictors of future growth rate, alternative measures are needed. Individual tumor growth kinetics and molecular markers may provide a means of identifying which tumors may exhibit an aggressive phenotype. Developing a dynamic model which relates a tumor’s growth kinetics to its metastatic potential may allow for delayed management following active

surveillance. A recent review of current active surveillance series demonstrated that 26% to 33% of tumors do not demonstrate interval growth during observation (median follow up 29 months) and that no patient with a zero growth tumor developed metastatic disease. Importantly, there was no difference noted in the incidence of malignant disease comparing zero growth tumors to those that showed radiographic growth(6). While this implies that tumors which do not demonstrate interval growth have a low metastatic potential, this biological assumption remains unproven.

Although the rate of disease progression (2.9%) and development of metastatic disease (1.4%) was relatively low in our series, they are the primary deterrents from electing active surveillance or delayed management in acceptable surgical candidates. This practice is strongly supported by the poor prognosis of metastatic RCC(3,4). We defined disease progression as the development of previously undetected enhancing renal tumors in the ipsilateral or contralateral kidney. Although no difference was noted in the observed growth rate between multifocal and solitary renal tumors, multifocal tumors were associated with both cases of de novo renal tumors in our series. The occurrence of de novo lesions is not widely reported in other active surveillance series. Volpe et al noted de novo lesions developing in 10% (3/29) of patients in their series at 1, 10 and 30 months follow up (13). The overall development of de novo lesions in our series was 1.8% (2/109), and 10% (2/10) in patients presenting with multifocal disease. Disease progression in terms of pathologic upstaging is difficult to establish secondary to the known poor correlation between clinical and pathologic stage in small renal tumors that are treated promptly (21,22). This makes it difficult to determine if pathologic upstaging can be attributed to delayed intervention in patients undergoing active surveillance.

The development of metastatic disease in our current series (1.4 % (1/70)) is similar to the observed rate of 1% (3/286) in our previously published meta-analysis. With only three cases of patients progressing to metastatic disease in the current active surveillance series, it is difficult to define predictors of metastatic potential. Of the three patients developing metastatic disease, all tumors demonstrated interval growth and 2 of the patients became symptomatic (hematuria) during their progression. Regardless of the patient's observed tumor growth kinetics or the absence of tumor related symptoms, we recommend at least annual evaluation for metastatic disease to include imaging of the thorax (chest X-ray or CT scan) and other radiographic testing as clinically appropriate. During active surveillance, abdominal imaging with CT or MRI will screen for local progression. Although the rate of progression to metastatic disease appears to low in patients undergoing active surveillance, the true rate of metastatic disease may be higher due to several factors. First, pathology is not available on all tumors undergoing observation. This means that benign disease is also included when calculating rates of progression to metastatic disease. Additionally, tumors which demonstrate increased growth kinetics are selectively undergoing intervention, which if left untreated may metastasize. Lastly, the current active surveillance series have a relatively short duration of follow up (median 34months). This relatively short duration of follow up may not reflect the intermediate or long term biology of these tumors.

Conclusions

The majority of enhancing renal tumors undergoing active surveillance demonstrate slow interval growth. The risk of developing metastatic disease is the primary deterrent for initiating active surveillance of enhancing renal tumors. As such, surgical excision remains the standard of care. Tumor growth kinetics may provide a means of identifying aggressive tumors that warrant expedient intervention. However, currently no clinical predictors of future tumor growth or progression have been identified. For this reason we advocate prompt surgical intervention for patients presenting with enhancing renal tumors who are acceptable surgical candidates. Future investigation and development of molecular and histologic markers of

disease progression are needed as well as randomized clinical trials investigating the efficacy of active surveillance and delayed management.

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Figure 1.
Observed tumor growth rate comparing male versus females, solid versus cystic tumors, and multifocal versus solitary tumors. $p > 0.05$ for all comparisons.

Figure 2.
Observed tumor growth rate versus patient age on presentation, $p > 0.05$.

Figure 3.
Observed tumor growth rate versus tumor size on presentation, $p > 0.05$.