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The Natural History of Large Renal Masses Followed on Observation

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Abstract

Purpose—The safety and feasibility of active surveillance in comorbid patients with renal masses ≥ 4.0 cm is uncertain. The aim of this study is to describe our institutional experience with the observation of large renal masses.

Materials and Methods—One hundred patients were identified with renal masses ≥ 4.0 cm that were followed on observation for at least 6 months without surgical intervention between 1994 and 2016. Linear regression was conducted to determine predictors for renal mass growth and competing risk methods were used to estimate the probability of progression in the setting of death from other causes.

Results—Median age at diagnosis was 73 years and 73% of patients had a Charlson Comorbidity Index ≥ 4 . At presentation, the median mass size was 4.9 cm. The median growth rate was 0.4 cm/year and there were no significant predictors of growth. Surveillance was discontinued in 34 patients who underwent delayed intervention. Median follow up for metastasis-free survivors was 4 years. In total, 10 patients developed metastatic disease, 3 died from kidney cancer and 30 patients died from other causes. The 5-year probability of other cause mortality was 22% (95% CI 14%, 32%) compared to 6% (95% CI 2%, 13%) for metastatic progression of kidney cancer.

Conclusion—In highly comorbid patients, the observation of large renal masses has low likelihood for metastatic progression relative to the risk of non-kidney cancer related death. This data supports the use of surveillance as an acceptable strategy for highly selected patients with competing risks from other serious illnesses.

Keywords

large renal mass; observation; surveillance; growth rate; renal cell carcinoma

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Introduction

Over 67,000 new cases of kidney cancer are diagnosed each year in the United States, with the greatest incidence in men and women over the age of 70.¹ The majority are incidental small renal masses; although large renal masses (LRM) ≥ 4 cm make up a significant portion of cases and can present unique challenges in elderly and highly-comorbid populations. Historical data indicate an increased risk of high-grade malignancy and potential for disease progression with each 1cm increase in tumor size,² supporting the use of surgical extirpation as the standard treatment for LRM. Despite these oncologic concerns, many patients with competing risks from multiple comorbidities may not be suitable candidates for immediate operative intervention. Previous works assessing overall survival in patients with localized renal cell carcinoma (RCC) have questioned the benefits of surgery in individuals with multiple comorbidities.^{3–5}

Active surveillance (AS) is an acceptable alternative to surgery for selected patients whose medical comorbidities increase the risk associated with intervention. The American Society of Clinical Oncology has endorsed the practice of AS for kidney tumors, linking slow tumor growth rates with low potential for progression, albeit limited to patients with small renal masses < 4 cm.⁶ No guidelines or management recommendations exist for the observation of LRM in patients with poor performance status. The safety and feasibility of AS for LRM in this population is therefore unclear with a paucity of data on the natural history of these untreated tumors. The aim of this study is to describe a single institutional experience with the observation and expectant management of renal masses ≥ 4cm including the growth rate of LRM under surveillance, factors associated with growth rate, and overall outcomes.

Materials and Methods

Study Cohort

Following Institutional Review Board approval, the Memorial Sloan Kettering Cancer Center patient registry was used to identify patients with LRM undergoing surveillance from 1994 until 2016. Surveillance initiation date was defined as the first diagnostic image identifying the renal mass. Patients were included with renal masses ≥ 4 cm and if they had been followed with serial imaging for at least 6 months without surgical intervention. The date of surveillance discontinuation was defined as the first event of surgical intervention (partial or radical nephrectomy) or the diagnosis of RCC metastasis. Imaging was conducted by surgeon discretion at 3 to 6 month intervals after the initial diagnosis. Patients were excluded from analysis if they had Bosniak class 1 and 2 renal cysts, clinically benign renal masses such as angiomyolipomas, upper tract urothelial cell carcinoma, or evidence of RCC metastases at the time of diagnosis.

Outcome measurement

The maximal cross-sectional diameter for each mass was obtained from imaging studies interpreted and measured by a radiologist at the time of the original study. All measurements from serial imaging were utilized to determine the annual growth rate of the LRMs, expressed as centimeters per year. Computerized tomography (CT), magnetic resonance

imaging (MRI) and ultrasonography were used interchangeably for follow-up. The development of RCC metastasis during the surveillance period was identified from clinical records that indicated the histologic confirmation of RCC metastasis or radiographic evidence of distant metastatic disease. Clinical endpoints such as RCC related mortality and all cause mortality were also captured from institutional records.

Statistical Analysis

Linear regression was used to calculate LRM growth rate (cm/year) for each patient based on maximal diameter. Univariate linear regression was used to assess whether growth rate was associated with factors such as initial renal mass size, cystic renal mass versus solid, tumor location, age, Body Mass Index (BMI), Charlson Comorbidity Index (CCI), smoking status, history of another malignancy, gender, and race. Univariate Cox regression was used to assess whether any clinical or renal mass characteristics were associated with the time until surgical intervention in our cohort. Additionally, competing risk methods were used to estimate the probability of developing RCC metastasis in the setting of death from other causes. All statistical analyses were completed with Stata version 13.0 (StataCorp, College Station, TX).

Results

Patient Population

A total of 401 patients with renal masses managed by AS were identified, 100 met the study inclusion criteria. Eighty-one patients were initially diagnosed with LRM ≥ 4 cm while an additional 19 patients on AS were identified that had been initially diagnosed with renal masses smaller than 4cm, but had progressed to ≥ 4.0 cm or greater within a 12-month time frame. These patients were also included as part of the analysis and the duration of surveillance was defined from the date of initial renal mass diagnosis. As it could be argued that there may be a potential lead time bias in patients with renal masses smaller than 4cm, we ran a sensitivity analysis defining surveillance from the date in which the renal mass were ≥ 4 cm. One patient was excluded from the sensitivity analysis as there was no additional scans following the date in which the renal mass was ≥ 4 cm. Overall, the results from the sensitivity analyses were nearly identical to the results reported below, therefore all patients were included in the final analysis using data from the time of initial diagnosis. The overall median renal mass size at time of discovery was approximately 4.9cm (IQR 4.0, 6.6). Median size at diagnosis for masses initially less than 4.0 cm was 3.3cm (IQR 2.8, 3.5) and 5.2cm (IQR 4.3, 7.1) for masses greater than 4cm at diagnosis. Only 18% had Bosniak class 3 & 4 lesions (Table 1). The median age at diagnosis was 73 years (IQR 64, 80) and 73% of patients had a Charlson Comorbidity Index ≤ 4 immediately prior to the diagnosis of the renal mass. At the time of LRM diagnosis, 32% of patients had a history of another non-renal malignancy. In total, 19% of the cohort was diagnosed with non-RCC metastatic disease from another malignancy during the surveillance period.

Growth Rate

The median renal mass growth rate was 0.4 (IQR 0.1, 0.8) cm/year (Figure 1). Seventeen patients (17%) were found to have renal masses with stable or negative growth throughout

the follow up period. There were no significant associations between growth rate and any of the clinical variables tested (Supplemental Table 1).

Delayed Intervention and Outcomes

Surveillance was discontinued for 34 patients who underwent delayed surgical intervention (Table 2). The estimated probability of undergoing surgical intervention was 21% during the first 2 years of surveillance, and 41% by 5 years. Two distinct groups were identified among patients undergoing delayed surgical intervention. The first was an elective active surveillance group (n=17). Patients in this category selected active surveillance as an initial management strategy. Eventually, all 17 of these patients underwent surgery for various reasons such as changes on imaging, renal mass growth, or symptoms from hematuria and flank pain; 5 of whom underwent surgery within two years of diagnosis. The second group consisted of patients with serious underlying comorbidities that precluded them from surgical intervention upon the diagnosis of renal cancer (n=17). Ten patients underwent surgical intervention after successful oncologic management of other non-RCC malignancies, and seven after undergoing other interventions for underlying cardiovascular and medical diseases. Among this comorbid group, 14 of 17 underwent surgical intervention within two years of their renal mass diagnosis.

Among all patients that underwent surgical intervention, 17 (50%) had documented complications after surgery. The majority of complications were low grade; however, two patients suffered grade 3 complications and one patient required admission to the intensive care unit for ventilatory support and management of hemodynamic instability following surgery (grade 4). There were no peri-operative mortalities in any patient who underwent delayed surgical intervention.

A univariate Cox regression model used to assess factors associated with surgical intervention. We were unable to identify any clinical or renal mass characteristics that were significantly associated with delayed surgical intervention (Supplementary Table 2).

Histology was available for 56 patients (56%) who underwent surgery or biopsy during surveillance (Table 1). Eighty-two percent had RCC, with clear cell RCC being the most common histologic pattern. Median follow up for patients who did not undergo surgery was 3.5 years (IQR 1.9, 5.0). In total, 10 patients progressed to metastatic RCC and 3 of these patients died from their disease (table 3). Overall, 30 patients from the entire cohort died from other causes, 12 of which occurred in patients with metastatic disease from other malignancies.

There were 36 patients who did not undergo surgery and did not have any recorded events of RCC metastasis or death from any cause; their median follow up was 3.8 years (IQR 1.6, 4.9). The median follow up for all patients that remained metastasis free was 4.0 years (IQR 2.2, 6.8). Twenty patients were followed without any events at 5 years and six patients were followed without any events in 10 years. The estimated probability of developing metastasis from RCC during the first 2 years of surveillance was 1% (95% CI 0.1%, 5%), and 6% (95% CI 2%, 13%) after 5 years of surveillance. The 2 and 5-year probability of non-RCC related death was 7% (95% CI 3%, 13%) and 22% (95% CI 14%, 32%), respectively (Figure 2).

Discussion

In this study we have reported our institutional experience with the observation and expectant management of large renal masses in a group of highly comorbid patients. Despite oncologic concerns of LRMs harboring more aggressive disease,² we have demonstrated in this select population that the risk of non-RCC death outweighs progression to metastatic disease. Greater than 70% of individuals had a Charlson Comorbidity Index score of 4 or greater, and 30% with a history of another underlying non-renal malignancy. As such, any risk of RCC progression to metastasis after observation was greatly overshadowed by the probability of non-RCC related death, which was identified as 22% at 5 years. Additionally, we identified 36 patients that did not undergo any intervention and were alive with no evidence of metastatic progression after a median follow up of 4 years. These findings add further insight into the natural history of large renal masses and provide support for an initial strategy of observation in patients that are very poor surgical candidates.

Previous works have questioned the benefits of elective surgical intervention for localized RCC in highly comorbid patients.^{4,5} Use of the Charlson Comorbidity Index to define “fitness” for surgery has lead to suggestions that individuals with high CCI scores (3) maybe poor candidates for elective intervention with reduced overall survival relative to less co-morbid patients with localized RCC.^{3,7} Although there are no established CCI cutoff used to define surgical candidates at our institution, it was observed that patients undergoing surgery had similar CCI scores relative to those continuing on observation. Additionally we noted a relatively low number of high grade post-operative complications in our study. It is plausible, however, that if all patients in this study had undergone surgery as an initial management strategy, a larger number of high grade complications and potentially peri-operative mortalities may have been seen.

In the assessment of LRM growth kinetics, the calculated linear growth rate of 0.4 cm/year in our cohort is similar to that of previous reports of larger renal masses undergoing surveillance.^{8–11} Ultimately, this is comparable to the median growth rate of small renal masses on active surveillance, which is estimated to be between 0.1–0.3cm/year.^{12–14} In our cohort we were unable to identify any significant predictors of renal mass growth, which is consistent with other publications of AS in small renal masses.^{15,12,16} However, others have found that growth rate is associated with sizes of renal masses on diagnosis and imaging features assessing tumor complexity.^{17,18} The growth rate of renal masses followed on AS can be established from the assessment of serial imaging, which can provide valuable clinical information in a simple and non-invasive manner. Tumors exhibiting growth faster than expected may provide indications for underlying aggressive disease.¹⁴ In our cohort, persistent growth and changes in imaging were the most common reasons for triggering intervention in patients followed on elective active surveillance. Interestingly, 17% of LRM in this study demonstrated zero or negative net growth throughout the duration of follow up. These findings are not unique given that 15% of LRMs in a surveillance series reported by Mehrazin exhibited no measurable evidence of growth on serial imaging.¹⁰ Although there has been evidence indicating that tumors with no growth may portend similar histology to lesions exhibiting positive growth on AS¹⁶, the implications of slow or negative net growth on overall patient outcomes are unknown. In this study, 9 patients with slow or negative net

growth were discovered to have RCC upon surgery or renal mass biopsy, suggesting that slow growth may not be a reliable indicator of underlying tumor histology. Further prospective studies are needed to assess the potential impact of growth rate on overall outcomes in patients with LRM.

This study has several strengths given its longer duration of follow-up and consideration of competing comorbidities. The median follow-up of metastasis-free patients was 4 years and 20 patients were event free at 5 years. To our knowledge, this is the longest reported follow-up in any series that has examined surveillance in patients with large renal masses.^{9–11} Given the longer duration of surveillance, this study allowed for a more accurate depiction of the natural history of LRMs in a highly comorbid group of patients. This is in contrast to other reports of surveillance in LRM that have either underreported the progression to metastatic disease, or failed to identify any cases of RCC metastasis altogether.^{9,10} However, despite these advantages there are some notable limitations. The majority of patients that were followed with continued surveillance were highly co-morbid and not considered operative candidates. As such, deductions regarding the natural history and growth kinetics of LRMs from this study may not be directly generalizable, even to a population of the same age distribution. Approximately 73% of the cohort had CCI scores ≥ 4 , 32% had another non-renal malignancy and 19% with established metastasis from malignancies other than kidney cancer. This represents an extremely high-risk group for intervention, therefore validating the logic behind expectant management. In our study, the probability of non-RCC mortality heavily outweighed the risk of RCC progression at 5 years; this may not be the case for a younger and less co-morbid group of patients. Close follow-up and caution is required when recommending observation for patients with LRM, as only those with significant competing risks may benefit from delaying intervention.

Conclusion

Large renal masses followed by observation exhibit modest annual growth. There are no obvious predictors of tumor growth. In highly comorbid patients such as those with other advanced malignancies, the observation and expectant management of LRMs demonstrate a low likelihood for metastatic progression of RCC, which is greatly overshadowed by the risk of non-RCC related death. This data supports the observation of LRM as an acceptable strategy in highly select patients with competing risks from other serious illnesses.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

List of abbreviations

LRM	Large Renal Masses
RCC	Renal Cell Carcinoma
AS	Active Surveillance
CCI	Charlson Comorbidity Index

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Figure 1.
Histogram of renal mass growth rate (cm/yr) (N=100)

Figure 2.
Cumulative incidence of developing RCC metastasis (solid black line) and death from other causes (dashed gray line)

Table 1.

Patient and Renal Mass Characteristics (N = 100) All values are median (IQR) or frequency (proportion)

Age at diagnosis (years)	73 (64, 80)
Male	67 (67%)
Charlson Comorbidity Index	
0	3 (3.0%)
1–3	24 (24%)
4	73 (73%)
Other Malignancy History	32 (32%)
Non RCC mets from other malignancy	19 (19%)
Race	
White	86 (86%)
Black	7 (7.0%)
Asian	2 (2.0%)
Other	1 (1.0%)
Unknown	4 (4.0%)
Body Mass Index (N=74)	29 (26, 33)
Smoking Status	
Never	35 (35%)
Former	39 (39%)
Current	9 (9.0%)
Unknown	17 (17%)
Diagnostic Renal Mass Size (cm)	4.9 (4.0, 6.6)
Left Renal Mass	49 (49%)
Tumor Pole	
Lower	30 (30%)
Mid	32 (32%)
Upper	38 (38%)
Bosniak 3 & 4 lesions (vs Solid Mass)	18 (18%)
Histology[*] (N=56)	
Benign	10 (18%)
Clear Cell	31 (55%)
Papillary	4 (7.1%)
Chromophobe	5 (8.9%)
Other RCC	6 (11%)

* Histology is provided for patients who underwent biopsy or surgery

Table 2.

Delayed surgical intervention (N=34)

Estimated probability of surgical intervention over time	
2 years from renal mass diagnosis	21%
5 years from renal mass diagnosis	41%
Surgery type	
Radical nephrectomy	24 (71%)
Partial nephrectomy	10 (29%)
Elective surveillance discontinued	17 (50%)
Changes on imaging or growth	8 (24%)
Symptoms (hematuria & flank pain)	3 (8.8%)
Patient preference	6 (18%)
Surgical candidates pending treatment of other disease	17 (50%)
Medical and Cardiovascular	7 (21%)
Other (non-RCC) malignancy	10 (29%)

Table 3.

Characteristics of patients that progressed to metastatic disease (N=10) All values are median (IQR) or frequency (proportion)

Age	70 (61, 77)
CCI	10 (8,12)
History of another malignancy	3 (30%)
Diagnostic Renal Mass Size (cm)	5.3 (IQR 4.0, 6.7)
Annual Tumor Growth (cm/year)	0.6 (0.1, 0.7)
Death from any cause	4 (40%)
Death from Kidney Cancer	3 (30%)
Progression after delayed intervention	N=4
Progression after continued observation	N=6
Estimated probability of metastatic progression over time	
2 years from renal mass diagnosis	1%
5 years from renal mass diagnosis	6%