Original Article

Impact of diabetes and chronic kidney disease on active surveillance outcomes for small renal masses: A cohort study

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ABSTRACT

Introduction: The American Cancer Society estimates 79,000 individuals will be diagnosed with kidney cancer in 2022, most of which are initially found as small renal masses (SRMs). Proper management of SRM patients includes careful evaluation of risk factors such as medical comorbidities and renal function. To investigate the importance of these risk factors, we examined their effect on crossover to delayed intervention (DI) and overall survival (OS) in patients undergoing active surveillance (AS) for SRMs.

Methods: This is an Institutional Review Board-approved retrospective analysis of AS patients presented at kidney tumor conferences with SRMs between 2007 and 2017. Univariable and multivariable logistic regression analyses were performed to determine how factors including estimated glomerular filtration rate (eGFR), diabetes, and chronic kidney disease are associated with DI and OS.

Results: A total of 111 cases were reviewed. In general, AS patients were elderly and had significant comorbidities. On univariate analysis, intervention was more likely to occur in patients with a younger age (P = 0.01), better kidney function (P = 0.01), and higher tumor growth rates (GRs) (P = 0.02). Higher eGFR was associated with better survival (P = 0.03), while higher tumor GRs (P = 0.014), greater Charlson Comorbidity Index (P = 0.01), and larger tumors (P = 0.01) were associated with worse OS. Of the comorbidities, diabetes was found to be an independent predictor of worse OS (P = 0.01).

Conclusions: Patient-level factors – such as diabetes and eGFR – are associated with the rate of DI and OS among SRM patients. Consideration of these factors may facilitate better AS protocols and improve patient outcomes for those with SRMs.

INTRODUCTION

Active surveillance (AS) of suspicious renal masses <4.0 cm in size – known as small renal masses (SRMs) – has a growing body of literature supporting its practice.[1-3] Typically consisting of serial monitoring of tumor size through abdominal imaging, AS has been shown to have survival outcomes similar to interventions such as partial nephrectomy (PN) and radical nephrectomy (RN) and percutaneous ablation in well-selected patients.[2] Although >80% of these masses have malignant potential,[4] <2.0% of SRMs progress to metastatic disease.[5] Therefore, urologists must consider additional factors such as patient

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comorbidities before recommending surgery or other interventions.

Largely consisting of an elderly population, patients undergoing AS have an increased number of comorbidities such as diabetes mellitus (DM) and chronic kidney disease (CKD).[2,6,7] Despite the elevated surgical risk associated with comorbid patients, there are times when surgical or other potentially curative intervention is undertaken. Previous studies are controversial regarding the importance of these comorbidities on oncologic outcomes of patients on AS;[2,3] however, no studies have looked specifically at this relationship. As DM and other comorbidities may be associated with the development of renal cell carcinoma (RCC),[8] understanding the clinical impact of these comorbidities on patients undergoing AS for SRMs is essential.

In this retrospective analysis of AS for patients with SRMs, we investigate the relationship between DM, CKD, and other risk factors affecting the rate of progression to delayed intervention (DI) and overall survival (OS).

METHODS

Patient population and study design

This study is an Institutional Review Board (IRB) approved retrospective analysis of a prospectively managed small kidney tumor database (IRB # IRB00084391, approved on February 5, 2022). The authors confirm the availability of, and access to, all original data reported in this study. A waiver of consent was obtained before study start. The procedures adhered to the ethical guidelines of Declaration of Helsinki and its amendments.

Patient data were collected from those on AS for small kidney tumors at Atrium Health, in Charlotte, North Carolina between January 2007 and December 2017. At our institution, patients are denoted to be on AS if they were designated AS candidates at our small kidney tumor conference if they did not receive intervention within the first 6 months of diagnosis, and if the patient agreed to regular imaging and follow-up.

Patients were 18-years-old or older with a clinically localized, solid, contrast-enhancing SRM incidentally found on axial imaging (computed tomography or magnetic resonance imaging). Patients are followed prospectively from the time of study entry until death or loss to follow-up. Exclusion criteria included inability to undergo intervention, a prior RCC history, and/or a familial RCC syndrome. All patients meeting the inclusion criteria met with their urologist and were counseled regarding AS and primary intervention (PI).

Active surveillance protocol

To be considered for AS, patients must be able to undergo surgical or percutaneous intervention if indicated. AS consisted of cross-sectional imaging every 6–12 months following initial diagnosis with subsequent annual history and physical, chest imaging, and appropriate investigations. Intervention was generally recommended for renal masses with a linear growth rate (GR) that exceeded 0.5 cm/year or if the greatest tumor diameter became larger than 4.0 cm. Patients may also choose DI at any time or continue on AS. Patients choosing DI are followed at the discretion of the attending urologist.

Data collection, analysis, and outcomes

The data were stored and managed in a secure REDCap database. The following variables were either collected directly from electronic medical records, or calculated from information provided by electronic medical records: age, gender, race, body mass index (BMI), Charlson Comorbidity Index (CCI), estimated glomerular filtration rate (eGFR), diabetes status, metastasis status, final tumor size, tumor GR, time since starting surveillance, types and dates of imaging, types, and dates of surgical interventions, and time to surgical intervention since starting surveillance. Tumor size was measured by maximal axial diameter. The tumor GR was calculated as the final maximum axial diameter minus the initial maximum axial diameter as a function of time (years).

Univariable logistic regression models were fit for all independent variables to assess association with progression to DI and OS. Variables that had a $P < 0.15$ were included in a multivariable logistic regression model. A backward elimination method was utilized in which the independent variables were entered into the regression before being removed one at a time to obtain a parsimonious model. Statistical significance was defined as $P < 0.05$, and all analyses were completed with SAS 9.4 (Cary, NC). The primary outcome was an odds ratio (OR) determining the risk of DI and OS.

RESULTS

Patient characteristics

Our study identified 111 patients on AS protocols for SRMs within the small kidney tumor database who met the inclusion/exclusion criteria. Patient characteristics are presented in Table 1. Gender was closely distributed with 60 male patients (54.1%) and 51 (45.9%) female. The patient population consisted of 24 (22.6%) black patients and 82 (77.4%) white. In general, the median age of AS patients was 75 with a mean CCI of 4.77 (standard deviation [SD] 2.36). There were 12 patients less than age 60 years who opted for AS versus initial surgical intervention. DM was present in 37 (33.3%) of the patients. Following placement on AS, 16 (14.4%) patients died and 2 (1.8%) patients developed metastatic disease. Patients had a median follow-up of 3.56 years, with deceased patients having a median survival of 3.42 years.

Table 1: Patient and disease characteristics

Demographics	Total, *n* (%)
Total patients	111
Age (years)	
Mean (SD)	75.08 (11.36)
0–59	12 (10.8)
60–69	20 (18)
70–79	33 (29.7)
80+	46 (41.4)
Gender	
Male	60 (54.1)
Female	51 (45.9)
Race	
White	82 (77.4)
Black	24 (22.6)
Other	4 (3.6)
CCI	
Mean (SD)	4.77 (2.36)
Median (IQR)	5 (0–11)
BMI	
Mean (SD)	29.98 (6.61)
Median (IQR)	28.8 (17.3–52.8)
Diabetes	
Yes	37 (33.3)
No	74 (66.7)
Final tumour size (cm)	
Mean (SD)	2.46 (1.57)
Median (IQR)	2 (0–9.5)
Mean growth rate (cm/year) (SD)	0.122 (0.32)
Crossover	
Intervention	27 (24.3)
No intervention	84 (75.7)
Pathology	
Clear cell	11 (64.7)
Papillary	3 (17.7)
Oncocytoma	2 (11.8)
Chromophobe	1 (5.9)
Overall survival	
Deceased	16 (14.4)
Not deceased	95 (85.6)

BMI=Body mass index, IQR=Interquartile range, SD=Standard deviation, CCI=Charlson comorbidity index

Tumor characteristics

Table 1 shows the overall disease characteristics of the 111 patients in our study. The mean final tumor size was 2.46 cm (SD 1.57) with a mean GR of 0.122 cm/year (SD 0.32). Overall GRs among diabetics trended higher than nondiabetics (0.26 cm/year vs. 0.15 cm/year, P = 0.24), although not statistically significant. Of the 24 tumors with pathologic data, the majority were clear cell RCC (45.8%) followed by papillary RCC (12.5%).

Predictors of delayed intervention

Table 2 shows the characteristics of patients who crossed over to DI and those who remained on AS. In total, 27 (24.3%) patients crossed over to DI. Of these patients, 50% underwent PN, 12.5% underwent RN, and 37.5% underwent percutaneous cryoablation. On average, DI patients were significantly younger at 69.5 years old as compared to 76.6 among noncrossover patients (P = 0.01). DI patients had a faster tumor GR of 0.44 cm/year (SD 0.35) as compared to 0.11 cm/year (SD 0.10; P = 0.01). DI patients had a higher mean eGFR at 78.3 mL/min/1.73 m^2 (SD 22.44) as compared to 63.8 mL/min/1.73 m^2 (SD 22.6) among non-DI patients (P = 0.01). There was a trend toward larger tumors and the likelihood of intervention in cross-over patients (mean size = 2.55 cm, P > 0.05) compared to non-DI patients, although this was not statistically significant. BMI was not a significant predictor of conversion to DI, although both groups had a mean BMI > 29. Of note, there was no difference in the rate of DM in DI patients versus long-term AS patients (P = 0.84).

Table 2 shows the univariable and multivariable analyses of factors associated with DI. On univariable analysis, the main predictors of DI were kidney function (OR 1.03, 95% confidence interval [CI] 1.00–1.05, P = 0.02) and faster GR (OR 6.2, 95% CI 1.36–28.1, P = 0.02). Older patients were less likely to crossover to DI (OR 0.95, 95% CI 0.91–0.99, P = 0.02). On multivariable analysis, older age was associated with decreased rates of DI (OR 0.95, 95% CI 0.91–0.99, P = 0.015) while higher GR was associated with increased probability of DI (OR 5.49, 95% CI 1.13–26.58, P = 0.03). eGFR was not an independent predictor of DI on multivariable analysis (P > 0.05).

Predictors of overall survival

Table 3 displays the characteristics and univariable and multivariable analyses of factors associated with OS for all patients included in this study. Of the 16 deceased patients, 11 (69%) were diabetic (P = 0.0004). Diabetes was significantly associated with worse OS [P < 0.05, Figure 1]. The following factors correlate with decreased OS on univariable analysis: diabetes (OR 5.84, 95% CI 1.84–18.42, P = 0.01), CCI (OR 1.38, 95% CI 1.08–1.76, P = 0.01), tumor size (OR 1.56, 95% CI 1.14–2.11, P = 0.01), and tumor GRs (OR 8.24, 95% CI 1.52–44.5, P = 0.01). Higher eGFR was correlated with improved mortality (OR 0.97, 95% CI 0.95–0.99, P = 0.03). On multivariable analysis, diabetes (OR 5.09, 95% CI 1.50–17.2, P = 0.01) and higher GR (OR 9.50, 95% CI 1.42–63.3, P = 0.02) were independently associated with mortality while higher eGFR was inversely associated with mortality (OR 0.97, 95% CI 0.95-1.00, P = 0.05). Female gender and mean BMI were not significantly different among the two groups.

DISCUSSION

The present study identifies factors associated with the rate of DI and survival among 111 patients on AS for SRMs at our institution. To summarize, patients were more likely to crossover to DI if they were younger, had better kidney function, and had a higher tumor GR. Patients had worse all-cause mortality if they had diabetes, lower eGFR, and a faster GR. To the best of our knowledge, this is the first study looking specifically at DM and CKD and their impact on AS outcomes in this unique patient population.

Table 2: Factors associated with delayed intervention

Variable	No intervention	Delayed intervention	Univariable, OR (95% CI) *P*	Multivariable, OR (95% CI) *P*
Total patients, *n* (%)	84 (75.7)	27 (24.3)	-	-
Female, *n* (%)	40 (46.0)	11 (45.8)	0.99 (0.40–2.46) 0.99	-
Diabetic, *n* (%)	27 (32.1)	10 (37.0)	1.59 (0.62–4.02) 0.33	-
Mean age (SD)	76.6 (10.7)	69.5 (12.1)	0. 946 (0.90–0.98) 0.02	0.95 (0.91–0.99) 0.02
Mean BMI (SD)	29.6 (6.40)	31.4 (7.25)	1.05 (0.97–1.11) 0.19	-
Mean CCI (SD)	4.87 (2.46)	4.38 (1.95)	0.91 (0.74–1.11) 0.36	-
Mean eGFR (SD)	63.8 (22.6)	78.3 (22.4)	1.03 (1.00–1.05) 0.02	>0.05
Mean final tumour size (SD)	2.42 (1.62)	2.58 (1.40)	1.07 (0.80–1.40) 0.66	-
Mean growth rate (SD)	0.11 (0.10)	0.44 (0.35)	6.20 (1.36–28.1) 0.02	5.49 (1.13–26.58) 0.03

BMI=Body mass index, SD=Standard deviation, CCI=Charlson comorbidity index, eGFR=Estimated glomerular filtration rate

Table 3: Factors influencing overall survival

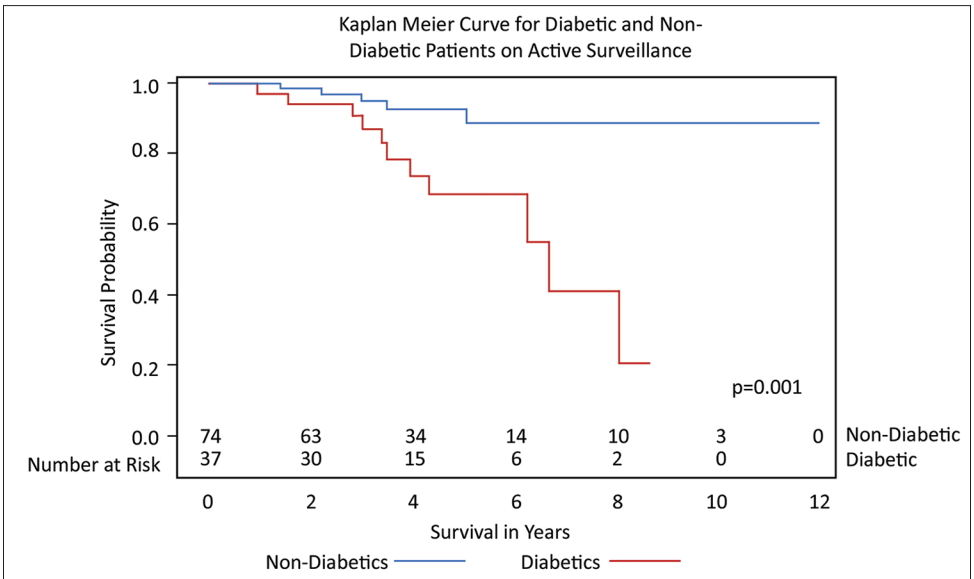
Variable	Alive	Deceased	Univariable, OR (95% CI) *P*	Multivariable, OR (95% CI) *P*
Total patients, *n* (%)	95 (85.6)	16 (14.4)	-	-
Female, *n* (%)	43 (45.3)	8 (50.0)	1.21 (0.41–3.49) 0.73	-
Diabetic, *n* (%)	26 (27.4)	11 (68.8)	5.84 (1.84–18.42) 0.01	5.09 (1.50–17.2) 0.01
Mean age (SD)	74.6 (11.9)	78.1 (7.25)	1.03 (0.97–1.08) 0.26	-
Mean BMI (SD)	30.0 (6.97)	29.6 (3.96)	0.99 (0.91–1.07) 0.80	-
Mean CCI (SD)	4.52 (2.29)	6.25 (2.29)	1.38 (1.08–1.76) 0.01	>0.05
Mean eGFR (SD)	69.0 (21.7)	55.0 (28.55)	0.97 (0.95–0.99) 0.03	0.97 (0.95–1.00) 0.05
Mean final tumor size (SD)	2.26 (1.35)	3.61 (2.25)	1.56 (1.14–2.11) 0.01	>0.05
Mean growth rate (SD)	0.09 (0.29)	0.31 (0.40)	8.24 (1.52–44.5) 0.01	9.50 (1.42–63.3) 0.02

BMI=Body mass index, SD=Standard deviation, CCI=Charlson comorbidity index, eGFR=Estimated glomerular filtration rate

Diabetic patients in our study had significantly worse survival (OR 5.09, 95% CI 1.50–17.2, $P = 0.01$) than their nondiabetic counterparts, with 69% of all deceased patients having comorbid DM. Among our deceased diabetic AS patients, two (18%) died of metastatic RCC; however, the remaining 82% died of unrelated cancers (36%), vascular causes (27%), and nonvascular causes (18%). Prior studies analyzing diabetics in the general US population have cited an increased risk of mortality (HR 1.93, CI 1.94–2.03) among diabetics as compared to nondiabetics, with an estimated 11.5% of overall deaths in the US attributable to the disease.[9] Psutka *et al.* have previously published worsened OS and cause-specific survival (CSS) among diabetic patients treated surgically for RCC – a trend that is seen across a broad range of malignancies including hepatocellular, pancreatic, ovarian, colorectal, lung, bladder, and breast cancer.[8,10] This high rate of non-RCC-related mortality suggests that OS may play a larger role than CSS when considering the clinical management of diabetic AS patients. Specifically, the high prevalence of vascular and nonvascular causes of mortality emphasizes the importance of a multi-disciplinary approach involving urology, endocrinology, cardiology, and primary care when managing diabetic AS patients.

Outside of diabetic patients, our findings related to tumor size and GR concurs with previously reported data and suggest that larger tumors and faster GRs are associated with worse survival.[6] In addition, higher GRs (mean 0.262 cm/year; OR 5.49, 95% CI 1.13–26.58, $P = 0.03$) and younger age were predictive of crossover, again concurring with previously published studies.[3] While the rate of crossover to DI was not significantly affected by diabetes (OR 1.05, 95% CI 0.62–4.02, $P = 0.33$) it was associated with CKD status, with higher eGFRs more often proceeding to DI on univariable analysis, though this was not an independent predictor of DI. The increased crossover rate among patients with higher eGFR could be reflective of surgical risk, as patients with CKD have been shown to have significantly higher rates of intra- and post-operative complications, in-hospital mortality, and longer hospital stays[11,12] It is also possible that younger age was confounding with kidney function as kidney function declines with age. This may be especially relevant to our study as eGFR declines more rapidly among AS patients compared to age-matched, healthy counterparts.[7] Most importantly, survival was shown to be correlated with CKD status, with survivors having a mean eGFR of 69 (CKD Stage II) versus 55 among the deceased (CKD Stage IIIa) ($P = 0.05$). This finding underscores the importance of considering kidney function when counseling patients on AS or DI, as the higher CKD stage was predictive of mortality.

Although further research is needed to better understand the relationship between kidney function, diabetes, and survival among AS patients, these findings make it clear that oncologic management and OS are impacted by these comorbid conditions. As management of these conditions often falls outside of the scope of urologic practice, it may be beneficial to incorporate a multi-disciplinary approach to AS patients. Recent studies have shown a significant mismatch between guideline recommendations regarding the multi-disciplinary management of renal cancer patients and real-life urologic practice.[13,14] Although multidisciplinary tumor boards have been shown to improve survival across a range of different cancers, there are limited



Diabetes	No. of Subjects	Deceased	Censored	Median Survival (95% CI)	2 Year Survival	5 Year Survival	10 Year Survival
No	74	5 (7%)	69 (93%)	NA (NA,NA)	98.5% (89.9%, 99.8%)	92.5% (81.0%, 97.2%)	88.7% (73.4%, 95.5%)
Yes	37	11 (30%)	26 (70%)	6.6 (4.3,NA)	94.1% (78.5%, 98.5%)	68.6% (46.1%, 83.3%)	NA (NA, NA)

Figure 1: Diabetic patients on AS for SRMs had significantly worsened OS as compared to nondiabetic patients. SRMs = Small renal masses, OS = Overall survival, AS = Active surveillance

studies looking at their use in small kidney tumors.[15,16] At our institution, entry into AS is dictated by the small kidney tumor program – a multi-disciplinary tumor board made up of urologists, oncologists, nephrologists, pathologists, and radiologists. Importantly, decisions regarding patient management should ideally also include the referring physician, all informed by the patient's priorities and input. Conclusions of this tumor board often drive decisions on PI versus AS and contribute to the oncologic and survival outcomes seen in our study.

Our study has several limitations. First, this study is a retrospective review and therefore subject to an inherent selection bias among patients undergoing AS and DI. Furthermore, all patients in the study were vetted by a multidisciplinary tumor board which may not be feasible in many healthcare environments. Due to the limited sample size of our study at a single institution, the results of our regression may be underpowered and nongeneralizable. As we continue to enroll patients into our AS protocol for SRMs, we hope to further expand the database and better power our future results. Nevertheless, this study provides valuable insight into several patient-level factors predicting the oncologic outcomes of patients on AS for SRMs.

CONCLUSIONS

Our data show that comorbidities such as diabetes and CKD may be associated with worse survival among AS patients with SRMs. In addition, the presence of DM, specifically, did not affect the rate of crossover to DI. Conversely, patients with better kidney function were more likely to crossover to DI emphasizing how these patients may be good surgical candidates. This study highlights how consideration of patient-level factors, such as DM and CKD, and a multidisciplinary approach are essential for the optimal management of this unique patient population on AS.

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