Clinical and radiographic characteristics governing the selection of therapy of small renal masses

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Introduction: *Renal masses are commonly managed by partial nephrectomy (PN) or active surveillance (AS). We assessed the impact of patient demographics and clinical indices in determining treatment decisions of renal masses between these two options.*

Materials and methods: *We retrospectively reviewed our renal mass database to retrieve demographic and clinical records of patients who underwent immediate PN or entered a ≥ 12 month period of AS during February 1999 to May 2014. Age, gender, body mass index (BMI), Charlson Comorbidity Index (CCI) score, follow up time, tumor size, tumor location, renal invasion, creatinine, and estimated glomerular filtration rate (eGFR) were assessed as predictors of the selected treatment option.*

Results: *Seven hundred thirty-five patients with 744 renal masses underwent immediate PN, while 123 patients with 140 renal masses entered active surveillance. PN patients were predominantly male, younger, had elevated BMI, lower CCI scores, elevated eGFR and had larger tumors that invaded further into the renal collecting system. Renal masses in men were more likely to be treated by PN, while patients categorized as overweight or obese were 2-3 fold more likely to have their renal mass being manage by PN (versus patients with BMI in the normal range). Higher CCI scores were associated with a renal mass being more likely to be treated by AS, while increased renal mass size was associated with decisions to treat with PN. Compared to cortical location, renal masses abutting the renal collecting system were more likely to be treated by PN.*

Conclusions: *Gender, BMI, CCI, tumor size, and tumor invasion into the renal system are useful predictors of renal mass treatment.*

Key Words: active surveillance, delayed intervention, renal mass, prognosis, partial nephrectomy

Introduction

Despite an increase in the rate of detection and treatment of localized renal masses, parallel improvements in disease-specific survival have not been observed.[1] Since most small renal cell carcinomas (RCCs) have a low metastatic potential, surgical intervention may be unnecessary in the short term. A desire to conserve renal function, if intervention becomes necessary, has elevated partial nephrectomy (PN) as the gold standard treatment for RCCs.[2-4] Since 80% of renal masses are benign or indolent, delaying surgical intervention or enrolling in active surveillance (AS) may also be a reasonable and viable paradigm for selected patient groups.[5,6] Other treatment options for localized, small renal masses include excision and ablation, with each having intermediate cancer-specific outcomes.

The majority of renal masses that are monitored under AS grow relatively slowly, with a low rate of metastatic progression. However, a subset of AS patients ultimately opts out of surveillance and undergoes definitive treatment (e.g. PN, nephrectomy, ablation). It is not uncommon that surgical treatment may be delayed or postponed due to radiographic uncertainties, a desire to acquire a second opinion, medical insurance clearance, and scheduling.[7] These

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delays are likely underreported, and consequently the effect of delaying intervention on stage migration and whether it limits treatment options remains unknown.

One criticism of AS is that tumor growth rate is often used as an indicator of malignancy potential. Paradoxically, growth rate and malignancy are only weakly correlated, and tumors with zero growth rates have been subsequently proven to be malignant.[4,8] Patients considered candidates for AS as a treatment option typically have a limited life expectancy, significant comorbidities or have consciously opted out of interventional approaches.[4] However, defining which patients do not qualify for surgery is challenging, as the Charlson Comorbidity Index (CCI) does not necessarily accurately define patient comorbidity and frailty.[3]

Previous studies have described outcomes of AS[5] and nephron-sparing surgery (NSS).[2] However, the demographics of patient populations best suited to each treatment have not been thoroughly investigated. In the current study, we assessed whether demographics and clinical indices are useful diagnostic tools to guide in deciding whether immediate PN or AS is the appropriate renal mass treatment regime.

Materials and methods

Institutional review board approval

The study was reviewed and approved by the Hartford Hospital Institutional Review Board (IRB).

Study design

We retrospectively reviewed our prospectively maintained, IRB-approved renal mass database and retrieved demographic, clinical, radiological and pathology data from patients who underwent either immediate PN or entered a period of AS of their renal mass during February 1999 to May 2014. PNs included both open and minimally-invasive surgeries (laparoscopic and robot-assisted). Patients included in the AS group had either a solid mass or ≥ Bosniak IIF cyst that was followed for ≥ 1 year. Some AS patients subsequently underwent an interventional procedure (PN or cryoablation) to treat their renal mass. As such, some renal masses are included in both the PN and AS groups.

Patients presented incidentally or following ultrasonagraphy (US), computerized tomography (CT), or magnetic resonance imaging (MRI). While there were no prospectively defined criteria for selecting a particular treatment regiment, the physician informed patients of all available treatment options and informed consent was obtained for the selected treatment. AS patients were proactively counseled that an interventional procedure could be required if it was determined at follow up that the size of their renal mass had significantly increased.

Clinical features at diagnosis and intervention (age, sex, BMI, CCI Index, follow up period, tumor size, creatinine, tumor location, degree of tumor invasion into the renal collecting system and estimated glomerular filtration rate) were assessed as predictors of small renal mass treatment options in the PN and AS. eGFR values were calculated using both the MDRD and CKD-EPI algorithms.[9,10] Renal mass biopsies were only performed when clinically indicated (e.g. tumor size, comorbidities). The majority of the renal masses exhibited low malignancy potential and biopsies were performed in only seven cases.

Statistical analyses

Statistical analyses were conducted to compare clinical decisions to treat patients with either immediate partial nephrectomy or to begin a period of active surveillance. The sample sizes for the two groups comprise all the patient/mass/decisions at the time the immediate treatment decision was made. Thus, some patients accounted for more than one case if there were subsequent decisions made, or if a patient had multiple masses.

Where appropriate, univariate analyses included chi-square tests of proportion for all categorical variables (e.g. gender or BMI category, location of mass). For continuous variables, independent group t-tests were used when the underlying distribution of the variable conformed to assumptions of normality (e.g. age at treatment decision time). The majority of the continuous variables, however, had sufficient outliers or variation and did not meet the normality assumptions. These are described by median and interquartile range and were compared using Wilcoxon Ranked Sum test.

A multivariate logistic regression was performed to assess the role of demographic and clinical factors in influencing whether patients proceeded with immediate PN or entered a period of AS. Demographic and clinical indices that were significantly different in univariate analyses between PN and AS groups were included as potential predictors using simultaneous entry. Predictors that were significant independent factors were described with odds ratio (OR), 95% confidence intervals (CI) for that OR and the related p value. There were a few modifications to the potential predictor list based on avoidance of redundancy. Since age is a component of both CCI and eGFR values, it was not included as a separate predictor. Similarly, since the MDRD and CKD-EPI algorithms to calculate eGFR, are similar (Spearman correlation of 0.973), including both of them in multivariate analyses would have resulted in high co-linearity. Two separate logistic regression analyses were run using one of the measures each time.

Data were compiled in an Excel spreadsheet and imported into SPSS v 21 for analyses. The significance threshold was set at $p < 0.05$.

Results

Renal masses treated by PN immediately after diagnosis

We identified 735 patients with 744 renal masses who underwent PN immediately after diagnosis. PNs were performed utilizing both open and minimally invasive techniques. The breakdown of PN surgical procedures used to treat renal masses was 404 (54.3%) robot-assisted laparoscopic PN, 136 (18.3%) open PN, 113 (15.2%) laparoscopic PN, 78 (10.5%) laparoscopic-assisted open PN and 13 (1.8%) hand-assisted laparoscopic PN.

The mean age at presentation of patients who underwent immediate PN was 60.5 ± 12.5 years, and median tumor size and BMI were 2.9 (IQR: 2.1-4.0) cm and 28.6 (IQR: 25.5-33.0) kg/m^2, respectively. Initial plasma creatinine and CCI scores were 1.0 (IQR: 0.8-1.1) mg/mL, and 3 (IQR: 2-4), respectively. eGFR was calculated using both the MDRD and CKD-EPI algorithms, and was 74.3 (IQR: 61.3-87.4) and 79.3 (IQR: 62.9-92.1) mL/kg/1.73 m^2, respectively.

A total of 451 (64%) of tumors undergoing PN were exophytic while 254 (36%) were endophytic. The location of these tumors was split relatively evenly between upper, mid and lower poles, Table 1. The majority of tumors invading the collecting system were found to be abutting, rather than cortical or invading.

TABLE 1. **Demographics and clinical indices of patients undergoing immediate partial nephrectomy or active surveillance**

	Renal mass treatment paradigm		
	Partial nephrectomy	**Active surveillance**	**p value**
Number of patients in which renal masses were treated/total number of renal masses	735/744	123/140	-
Gender of patients in which a renal mass was treated (n; %) (males)	454 (61)	68 (48.6)	0.007
Age at diagnosis (mean ± SD) (years)	60.5 ± 12.5	66.3 ± 14.2	0.021
Body mass index (median; IQR) (kg/m^2)	28.6 (25.5-33.0)	26.6 (23.8-30.3)	< 0.001
Charlson Comorbidity Index score (median; IQR)	3 (2-4)	6 (4-7)	< 0.001
Initial tumor size (median; IQR) (cm)	2.9 (2.1-4)	1.7 (1.2-2.5)	< 0.001
Tumor type (n; %)			0.295
Exophytic	451 (64)	96 (68.6)	
Endophytic	254 (36)	44 (31.4)	
Tumor location (pole) (n; %)			0.177
Upper	207 (30.4)	37 (26.4)	
Mid	254 (37.3)	64 (45.7)	
Lower	220 (32.3)	39 (27.9)	
Tumor invasion of collecting system (n; %)			< 0.001
Cortical	192 (31.9)	99 (70.7)	
Abutting	313 (52.1)	39 (27.9)	
Invading	98 (13.2)	2 (1.4)	
Initial serum creatinine (median; IQR) (mg/mL)	1 (0.8-1.1)	1 (0.8-1.2)	0.18
eGFR (median; IQR) (mL/kg/1.73 m^2)			
MDRD algorithm	74.3 (61.3-87.4)	68.1 (52.9-82)	0.001
CKD-EPI algorithm	79.3 (62.9-92.1)	69.2 (50.9-84.4)	< 0.001

Renal masses treated under an AS program

In contrast to undergoing PN immediately after diagnosis, 123 patients with 140 masses (solid or ≥ Bosniak IIF) were identified who entered a ≥ 12 month period of AS to manage their renal mass. The mean age of AS patients at diagnosis was 66.3 ± 14.2 years, with a median BMI and CCI score of 26.6 (IQR: 23.8-30.3) and 6 (IQR: 4-7), respectively. A total of 68 (48.6%) of these patients were male. Demographics and clinical indices of AS patients are shown in Table 1. None of these patients underwent an interventional procedure during the first 12 months of surveillance. At a follow up consultation ≥ 12 months after initial diagnosis, a decision to continue with AS of their renal mass, or to opt out of surveillance and undergo interventional treatment (PN or cryoablation) was made. The mean follow up time of AS patients was 3.8 ± 2.3 years.

Renal masses receiving interventional therapy after a period of AS

Based upon CT and MRI imaging at follow up, a subgroup of AS patients (12 patients with 17 renal masses) subsequently underwent an interventional procedure (PN or cryoablation) after ≥ 12 months active surveillance, Table 2. The clinical history and treatment of these renal masses are detailed in Table 2. The average time between diagnosis and interventional treatment was 4.3 ± 2.0 years. The remaining 111 patients (with 123 renal masses) continued on an AS treatment regime, with serial imaging every 6 or 12 months.

Comparison of demographics and clinical indices of patients with renal masses managed with PN or an AS program

Statistical comparisons of PN and AS patient demographics and clinical indices are detailed in

TABLE 2. **Renal masses initially managed under active surveillance that subsequently underwent an interventional therapy**

Patient	Age (yrs)	Prior history	Renal mass location	Follow up (yrs)	Post-AS intervention
1	36.7	T3a RCC, PN	Mid-medial	5.4	OPN
			Upper pole	5.4	OPN
			Mid-pole	5.4	OPN
2	38.8	None	Anterior mid-pole	5.4	OPN
	40.3	Bilateral cysts	Posterior mid-pole	5.44	OPN
3	45.4	Ureteral stones	Medial lower pole	8.54	CRYO
4	68.5	None	Endophytic, posterior lateral at junction of upper pole and interpolar	1.74	CRYO
5	72.0	None	Projecting from posterior aspect of mid portion, partially endo and exophytic	4.3	CRYO
6	80.6	None	Most cephalad aspect	2.1	CRYO
7	70.8	CRI, RF, CHF	Upper pole	2.9	CRYO
			Upper pole	2.9	CRYO
			Exophytic mid to lower pole lateral cortex	3.7	RPN
8	74.1	None	Endophytic midpole	2.4	RPN
9	74.7	Hemorrhagic cyst	Partially exophytic, posterior inferior aspect	4.2	CRYO
10	65.0	None	Partially endophytic	2.6	RPN
11	61.8	None	ND	2.8	RPN
12	44.3	None	ND	8.5	RPN

AS = active surveillance; CRI = chronic renal insufficiency; RF = renal failure; CHF = chronic heart failure; OPN = open partial nephrectomy; RPN = robotic partial nephrectomy; CRYO = cryoablation; ND = no data

Table 1. Patients undergoing PN at diagnosis were significantly younger than their counterparts who elected to undergo AS (p = 0.007). In addition, a significantly greater proportion of renal masses initially managed by PN were in males (p = 0.021; Table 2). Renal masses initially managed by PN were in patients with significantly higher BMI compared to AS patients. These renal masses were also significantly larger in size at diagnosis compared to those managed under an AS program, Table 2. Renal masses that were initially managed by AS were in patients with significantly elevated CCI scores compared to their PN counterparts (p < 0.001; Table 2). While serum creatinine levels were not significantly different between PN and AS patients, eGFR at diagnosis (calculated by the MDRD or CKD-EPI algorithms) was significantly higher in patients whose renal mass was initially managed with PN (p < 0.001).

There was no significant difference in the type of renal mass (exophytic versus endophytic) that was treated by PN or AS (p = 0.295). Furthermore, the location of the renal mass (upper, mid or lower pole) was not significantly different between the PN and AS groups (p = 0.177). However, more invasive tumors were managed by PN rather than by AS (p < 0.001; Table 1).

Multivariate analysis of the predictive impact of clinical indices in decisions regarding initial treatment of renal masses by PN or AS

We performed multivariate logistic regression to assess the impact of demographic and clinical factors in guiding the treatment decision of a renal mass between PN or AS, Table 3. Renal masses in men were significantly more likely to be treated by PN (OR: 3.1; Table 3). In addition, patients categorized according to their BMI as overweight or obese had a 2-3 fold greater likelihood of their renal mass being managed by PN compared to patients who had BMI values in the normal range, Table 3. Conversely, incremental increases in CCI score were associated with a patient's renal mass being more likely to be treated by AS (OR: 0.27).

Incremental increases in tumor size were more likely to be associated with a decision to treat a renal mass with immediate PN rather than manage it with AS (OR: 1.74 for each incremental increase in CCI score). Incremental increases in eGFR, however, were only weakly associated with a decision to treat a renal mass by AS (OR: 0.98 for each incremental increase in eGFR). Only one of the renal mass location factors had a significant association with the treatment decision. Compared to cortical location, masses that were abutting the renal collecting system were significantly more likely to be treated by PN. Similarly, there was a trend towards renal masses that infiltrated the renal collection system being even more likely to be managed by PN. However, this association was not statistically significant (p = 0.084; Table 3).

Discussion

The rate of renal mass detection continues to rise, particularly in elderly patients with significant comorbidities.[11] This phenomenon has, at least in part, been facilitated by an enhanced ability to detect

TABLE 3. **Multivariate analyses of the predictive impact of patient indices on clinical decisions to treat renal masses**

Variable	p value	Odds ratio (95% CI)
Patient gender (male)	0.001	3.10 (1.59-6.04)
Patient body mass index (kg/m^2)		
†Overweight (25-29.99)	0.037	2.25 (1.05-4.80)
†Obese (30-34.99)	0.032	2.93 (1.09-7.82)
†Morbidly obese (≥ 35)	0.030	3.25 (1.12-9.41)
Patient CCI score	< 0.001	0.27 (0.21-0.35)
eGFR using CKD-EPI algorithm (mL/kg/1.73 m^2)	0.014	0.98 (0.96-0.99)
Initial tumor size (cm)	< 0.001	1.74 (1.31-2.33)
Severity of tumor invasion into renal collecting system		
§Abutting	< 0.001	4.10 (2.07-8.11)
§Invaded	0.084	6.39 (0.78-53.30)

†relative to normal body mass index; §relative to cortical

smaller masses.[12,13] While NSS has become increasingly utilized to conserve renal function,[3] the utility of various demographic and clinical indices to effectively select patients for the most appropriate treatment regime has not been thoroughly investigated (particularly for patients who may be poor surgical candidates).[3,14] In the present study we assessed whether patient demographics and clinical indices of renal function are effective predictors in guiding decisions regarding the choice of treatment plan for a patient's renal mass.

AS is often cited as a preferred renal mass treatment option for elderly patients with associated comorbidities and limited life expectancy.[4] Our data revealed the patients undergoing AS were significantly older than those electing to undergo PN and had higher CCI scores. This may not be surprising since age is an integral component of the CCI scoring algorithm.[15]

Elevated BMI is often associated with an increased burden of chronic diseases,[16] and the clinical liabilities associated with these comorbidities are often cited as key criteria supporting the selection of patients for AS of their renal mass, rather than undergo PN.[14] Data from our current study indicate that categorical increases in BMI classification (i.e. normal versus overweight versus morbidly obese) were associated with decisions at our clinical center to manage renal masses with immediate PN rather than AS. Treatment decisions regarding the management of a renal mass are typically multifactorial and tailored towards the individual characteristics of a patient. Roscigno et al[17] reported that elevated CCI scores were associated with up to a three-fold increase in the risk of postoperative complications. Similarly, patients with CCI ≥ 3 are more likely to die of competing comorbidities than as a direct consequence of their renal mass.[17,18] Our multivariate analyses point strongly towards elevated CCI having a strong influence on decisions to treat a renal mass with AS ($p < 0.001$; OR: 0.27; 95% CI: 0.21-0.35). As such, advanced age and an associated burden of preexisting comorbidities may have a stronger influence on the selection of AS, compared to the influence of elevated BMI on the selection of PN in our patient cohort.

Multivariate analyses of our dataset allowed us to statistically assess the impact of various demographic and clinical factors on decisions to treat a renal mass by PN or a program of AS. Male gender, elevated BMI, larger initial tumor size and increased severity of tumor invasion into the renal collecting system were all associated with decisions to clinically manage a renal mass with immediate PN.

The relationship between tumor size and RCC subtype has been previously examined,[19] with increases in tumor diameter associated with an increased likelihood of tumor malignancy (OR 1.17; 95% CI 1.08-1.26), clear cell type (OR 1.17; 95% CI 1.11-1.23), and high-grade nuclear features (OR 1.32; 95% CI 1.27-1.37).[19] For these more aggressive, high-grade tumors surgical excision is the treatment of choice, as supported by our data illustrating larger tumors being selected for PN.

The severity of degree of invasion into the renal collecting system has been shown to have a profound impact on the prognosis of low stage tumors, with highly invasive tumors associated with a significant increase in mortality.[20] T1 renal cell carcinomas exhibit invasion into the renal collecting system in less than 10% of cases.[21] Data from our study cohort indicate that larger, and more invasive renal masses were more likely to be treated by PN.

In our study, a greater proportion of females were selected for AS compared to immediate PN. This may be related to concerns about female patients undergoing unnecessary surgery for benign AMLs that can be treated effectively using minimally invasive selective embolization.[22]

Limitations of this study include that our study may experience the same selection bias associated with other retrospective studies. However, physicians at our clinical center follow a prospective treatment paradigm to treat patients. In addition, we did not directly assess the potential interplay between patient demographics and clinical indices in influencing treatment decisions.

Conclusions

Gender, BMI, CCI score, initial tumor size, and the invasive nature of the tumor into the renal collecting system significantly influence the decision between immediate PN and AS as treatment for a renal mass. These data may help to better define and refine renal mass treatment nomograms. ☐

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