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Patients with Anatomically "Simple" Renal Masses are More Likely to be Placed on Active Surveillance than those with Anatomically "Complex" Lesions

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Abstract

Objective—To determine if radiographically less complex renal lesions are deemed clinically less "worrisome" and therefore are more likely to be considered for active surveillance (AS).

Methods—We queried our prospective institutional database to identify and compare patients with localized RCC undergoing an initial period of AS or immediate surgery. Multivariate logistic regression was used to examine covariates associated with receipt of AS.

Results—Of 1059 patients with available anatomic complexity data, 195 underwent an initial period of AS (median duration of AS 25.6 months [IQR 11.8, 52.8 months]. Compared to patients undergoing immediate surgical treatment, patients selected for AS had lower overall Nephrometry scores, were smaller, further from the sinus or urothelium, more often polar and less often hilar ($p<0.0015$ all comparisons). After adjustment for age, largest tumor size, individual components of NS, total NS, and CCI, total NS (OR 1.9 [CI 1.4–2.5]), "R" score of 1 (OR 5.2 [CI 1.8–15.2]), "N" score of 1 (OR 2.3 [CI 1.5–3.6]), "L" score of 1 (OR 1.4 [CI 0.84–2.2]), and non-hilar tumor location (OR 2.7 [CI 1.2–5.8]) increased the probability of being selected for AS compared to immediate surgery. Findings remained significant in a sub-analysis of T1a renal masses.

Conclusions—Lower tumor anatomic complexity was strongly associated with the decision to proceed with AS in patients with Stage I renal mass. Not only may these data afford new insights into renal mass treatment trends, but the findings may also prove useful in development of objective protocols to most appropriately select patients for AS.

Keywords

Renal cell carcinoma; active surveillance; nephrometry score; radiographic imaging

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Introduction

Increased use of abdominal imaging over the last three decades has led to a rise in the incidental detection of asymptomatic small renal masses (SRMs), typically defined as tumors 4 cm or less in diameter.[1] In fact, SRMs now account for nearly 50% of all newly diagnosed kidney tumors with the greatest number of cases found in patients over 70 years of age. As such, increased detection at earlier stages in elderly patients has led to a significant stage migration with a concurrent increase in the median age at diagnosis of renal cell carcinoma (RCC).[2, 3]

While nephron-sparing surgery (NSS) is currently the reference standard treatment for healthy patients with clinically localized T1a renal tumors, meaningful impact of active treatment on overall survival in elderly patients with SRM is yet to be demonstrated.[1, 4, 5] For patient populations that are either unfit or unwilling to undergo surgery, including the elderly and infirmed, recent emphasis has been placed on the role of initial active surveillance (AS)[6] with delayed intervention as necessary in management of SRMs.[7]

The subjective nature of clinical decision-making for treatment of SRMs, which is likely influenced by surgeon and institutional biases, is recognized and thus reflected by the intentional ambiguity of international treatment guidelines.[8–12] In fact, the peer-reviewed literature regarding which masses are appropriate for AS nearly exclusively focuses on tumor size.[7, 10–12] We hypothesized that tumor characteristics beyond tumor size likely influence critical decision-making with regard to immediate intervention, since anatomically “simple” renal masses may be more likely to be deemed clinically less “worrisome”. To test the hypothesis, we compared patients who underwent an initial course of AS to those who proceeded to immediate surgery with regard to tumor anatomic complexity at diagnosis, as quantified by the R.E.N.A.L. nephrometry score, in our large prospectively-maintained institutional cohort adjusting for patient age and comorbidity.

Material and Methods

After institutional review board approval, our prospectively maintained kidney tumor database was queried to identify all patients undergoing AS, radical nephrectomy (RN) or PN for clinical stage I renal tumors from 2007–2012 with available nephrometry score data. Active surveillance or surgery was offered to patients at each surgeon’s (RGU, RV, DYC, REG, AK) discretion. Clinical variables evaluated included variables such as age, gender, Eastern Cooperative Oncology Group [ECOG] performance status and BMI. Disease-related variables included R.E.N.A.L. nephrometry scrore and its components including the hilar designation, solitary kidney status, tumor size, and laterality. For multifocal tumors, tumor size indicated diameter of the largest tumor. Treatment variables included utilization of AS and its duration, year of surgery, and surgery type. Co-morbidity status was quantified using the Charlson comorbidity index (CCI). Patients were stratified into low (NS 4–6), intermediate (NS 7–9), and high (NS 10–12) anatomic complexity groups. Tumor staging was designated according to the TNM classification based on the 2010 American Joint Committee on Cancer/International Union Against Cancer classification system.

Duration of AS was defined from the time of diagnosis to an outcome, or to last clinical examination for those who did not reach a specified outcome. Patients who withdrew or were lost to follow-up were censored at the time of their last visit, and those who died were censored at time of death. Active patients were censored at the time of their last surveillance visit. Patients undergoing an initial period of AS were compared to those who went directly to surgery using tumor anatomic attributes as quantified by nephrometry (size, endo/exophycity, nearness to sinus/urothelium, anterior/posterior, location relative to polar line, and hilar structures) total NS, age, largest tumor size, CCI, and modified total NS (removal of the "R" component to minimize the influence of tumor size on outcome). To avoid simultaneous inclusion of collinear variables, separate multivariable models including either individual NS components or total NS were created. A subgroup analysis of patients with T1a tumors was also performed. Patient and tumor characteristics were compared using Fisher's Exact and Wilcoxon Rank-Sum tests. The associations between AS and tumor anatomic characteristics were assessed using multivariate logistic regression models, using patients undergoing surgery as the reference group. Covariates meeting a P <0.10 level of significance were included for model development, and our final model was adjusted for age, tumor size, total NS, modified NS, individual NS components, and CCI. All analyses were performed using Stata, version 10 (StataCorp, College Station, TX), all hypothesis tests were 2-sided, and the criterion for statistical significance was P <0.05.

Results

A total of 1059 patients (mean age 65±13 years, 64.4% males, 81% white, and mean CCI 1.8±1.8) with clinical stage Ia (77.5%)) or Ib (22.5%)) renal tumors (mean tumor size 3.1±1.6cm, mean NS sum 6±1.8) met the final inclusion criteria. There were 30 (2.9%) patients who had a solitary kidney and 127 (12.0%)) patients with multifocal tumors. As quantified by NS, 30.6%, 49.5%, and 19.8% of patients had low-, medium-, and high-complexity lesions, respectively.

195 patients (mean age 75±13 years, 60% male, 79% white) underwent an initial period of AS (median duration of AS 25.6 months [IQR 11.8, 52.8 months]). NS was available in all patients included for final analysis. Comparing patients placed on initial AS and those who underwent immediate surgical treatment (n=864), significant differences in age (75±13 vs. 63±12 years; p<0.001), tumor diameter (2.5 ± 1.2 vs. 3.2 ± 1.7cm, p<0.001), modified NS (5.5±1.8 vs. 6.1±1.8), CCI (3.1 ± 1.5 vs. 1.4 ± 1.7; p<0.001), BMI and NS complexity grouping (44.1 vs. 50.9% intermediate complexity, p<0.001; 7.8 vs. 21.8% high complexity, p=0.013), were observed, while no differences were seen in gender, race, ECOG performance status, tumor location, and laterality. When compared to patients who underwent immediate surgical treatment, lesions undergoing AS were smaller, further from the sinus and/or urothelium, more often polar and less often hilar (p<0.0015 all comparisons) (Table 1). Among patients undergoing operative intervention, those with hilar tumor were less likely to undergo robotic assisted partial nephrectomy when compared to patients without hilar tumor (7.6 vs. 23.6%; p<0.01).

After adjustment for age, largest tumor size, solitary kidney, multifocal tumor, individual components of NS, modified total NS, and CCI, the modified total NS (OR 1.8 [CI 1.3–

2.4]), “N” score of 1 (OR 2.3 [CI 1.5–3.6]), “L” score of 1 (OR 1.4 [CI 0.8–2.2]), and non-hilar tumor location (OR 2.7 [CI 1.2–5.8]) increased the probability of being selected for AS compared to immediate surgery (Table 2). An additional subgroup analysis of patients with T1a tumors showed that patients placed on AS were older (74.1±13.4 vs. 62.5±12.3 yrs; p<0.001), had smaller (2.1±0.8 vs. 2.4±1.0cm; p<0.001) and less complex tumors as measured by NS (5.0±1.8 vs. 6.0±1.8; p=0.03), and had more comorbid conditions (CCI 3.1±1.4 vs. 1.4±1.7; p<0.001). Following multivariate adjustment for age, largest tumor size, solitary kidney, multifocal tumor, individual components of NS, total NS, and CCI, total NS (OR 1.8 [1.3–2.6]), CCI (OR 1.7 [1.5–1.9]), “N” score of 1 (OR 1.8 [1.1–3.1]), and “L” score of 1 (OR 1.1 [0.61–1.9]) were associated with being selected for AS among patients with T1a disease (Table 3).

Discussion

Critical clinical decision-making for patients with renal tumors is complex. A multitude of factors such as age, competing health risks, renal tumor anatomy, contralateral renal unit status, physician experience/comfort, and patient preference/perceptions affect treatment decisions.[6] Furthermore, the biological heterogeneity of SRMs presents significant clinical challenges. [13] A better understanding of physician and patient choices to pursue one treatment vs. another affords opportunities for more rational, personalized, and standardized management pathways for patients with SRM.

Indeed, how pretreatment variables affect treatment strategies is yet to be fully defined. Data from our large institutional cohort demonstrate that tumor anatomic complexity is strongly associated with selection of patients for active surveillance of renal mass. After adjusting for appropriate clinicopathologic variables such as comorbidity, patient age, and tumor size, renal masses selected for AS were less often central, large, hilar, or near the collecting system. Based on these data we hypothesize that less complex (smaller, exophytic, less central) tumors are subjectively deemed less biologically worrisome by physicians and therefore more likely to undergo a period of AS.

The significance of the relationship between renal mass anatomy and pathology has been described.[14–16] In fact, the RENAL Nephrometry scoring system[8] has been demonstrated to predict tumor histology and grade, with more complex tumors harboring a higher likelihood of malignant and high grade disease.[17–19] As such, our findings that clinicians select more anatomically complex tumors for immediate treatment, while masses that are smaller, less central, peripheral, polar and non-hilar are more often selected for AS may have a biological basis. In fact, the concept of harnessing tumor characteristics to assess oncogenic potential continues to grow. Pioneers in the field of radiogenomics have preliminarily identified predictable and systematic associations between imaging features and underlying molecular and genomic alterations in lung,[20] breast,[21] and RCC.[22, 23] An analysis of clear cell RCC imaging revealed associations between CT features such as tumor margin, nodular enhancement, intratumoral vascularity, and renal vein invasion and a number of underlying mutations including VHL, KDM5C, BAP1, or PBRM1.[23] Taken collectively, these data support the hypothesis that imaging characteristics may provide insight into tumor biology and may prove useful for development of AS selection criteria.

The association between tumor anatomic characteristics such as endophytic features,[24] high RENAL NS,[6, 25] and tumor size,[6, 24] with treatment choice has been previously reported. Nevertheless, the current data represent the first study to specifically address the effect of anatomic tumor complexity on selection for AS. Tumor size, independent of NS, was also associated with a decreased probability of being placed on AS (OR 0.77 [0.69–0.85]) in our study. To assess whether anatomic attributes beyond tumor size correlated to selection for AS, we assessed the relationship between “modified total NS” (R score eliminated) and treatment choice. Indeed, the “modified total NS” was strongly associated with the likelihood of a patient being placed on AS (OR 1.8 [1.3–2.4]). Sub-analysis limiting the cohort to patients with T1a tumors revealed similar results, albeit hilar tumor location was no longer a significant variable in this analysis, likely due to the fact that smaller tumors are unlikely to abut the main renal artery or vein (only 8.2% of T1a masses in our cohort).

One previous study had indicated a possible link between a tumor’s anatomic features and recommendations for AS. A survey of members of the American Urological Association suggested that respondents were more likely to treat polar than hilar masses; however, these data represented hypothetical scenarios presented in survey format with a response rate of only 19%.[26] In turn, results from our large clinical dataset may indicate that in a urologic oncology practice with significant focus and expertise on renal surgery, oncologic concerns for biological aggressiveness of more complex masses appear to override technical barriers to treatment. However, one could argue conversely that the reason for expectant management was the relative confidence that small peripheral tumors remain amenable to NSS even if they become larger. By contrast larger and centrally located tumors if left untreated and grow may require radical nephrectomy. Nevertheless, the data from the AUA respondents potentially suggest that different practitioners may possess unique biases which affect patient selection for AS. As such, we believe our manuscript unveils an important clinical research need.

In addition to tumor anatomy, appropriate patient selection for AS must consider patient age and competing risks of morbidity and mortality. Indeed, the associations between receipt of AS, comorbidity (OR 6.9 [2.5–18.9]),[6] and ECOG performance status[24] have been well-described. In our study, age and CCI were also strongly associated with an increased probability of being placed on AS. The presence of a solitary kidney and multifocal disease may also impact management decisions. However, following multivariate adjustment, tumor anatomic complexity remained associated with the decision to proceed with surveillance.

Despite its strengths, our single-center cohort study has important limitations, which include its retrospective nature and likely idiosyncratic selection bias inherent to institutional and physician preferences. Furthermore, we did not control for perceived feasibility of resection or surgeon, which may significantly influence treatment type. The infrequent use of focal therapy at our institution also may have affected our findings. Renal mass biopsy results may influence management, and that data was not included in the current study. While we controlled for comorbidities, current comorbidity metrics such as the CCI are imperfect and additional variables which influence competing risks to mortality (e.g. frailty) likely contributed to treatment selection. Despite these limitations, our data are novel, provide opportunities for new avenues of investigation, and deserve verification in other cohorts.

Conclusions

Our findings demonstrate that the anatomical features of renal masses are associated with patient selection for Active Surveillance. Recent data suggesting that worse tumor biology is associated with anatomic tumor complexity indicate there may be a biological basis for placing smaller, less central, peripheral, polar and non-hilar lesions on AS in the appropriate clinical circumstance.

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Table 1

Comparison of demographic details and R.E.N.A.L. Nephrometry Scores between patients placed on AS and those who underwent immediate surgery

	AS Patients (n=195)	Surgical Patients (n=864)	p-value
Age (yrs)	74.5±13.0	62.9±12.2	<0.001
Gender (% male)	60.0%	65.4%	0.112
Tumor size, cm (median±SD)	2.2±1.2	3.0±1.7	<0.001
CCI (median±SD)	3.1±1.5	1.4±1.7	<0.001
Modified NS (no “R” component) mean (median ± SD)	5.5 (6±1.8)	6.1 (6±1.8)	<0.001
(R)adius			0.001
1	168 (86.2%)	653 (75.6%)	
2	27 (13.9%)	211 (24.4%)	
(E)xo/Endophytic			0.209
1	57 (29.2%)	307 (35.5%)	
2	103 (52.8%)	427 (49.4%)	
3	35 (18.0%)	130 (15.1%)	
(N)earness of the tumor to the collecting system			<0.001
1	92 (47.2%)	260 (30.1%)	
2	40 (20.5%)	121 (14.0%)	
3	63 (33.3%)	483 (55.9%)	
(A)nt/Posterior			0.159
A	81 (41.5%)	418 (48.4%)	
P	83 (42.6%)	339 (39.3%)	
X	31 (15.9%)	106 (12.3%)	
(L)ocation relative to the polar lines			0.003
1	86 (44.1%)	286 (33.1%)	
2	63 (32.3%)	280 (32.4%)	
3	46 (23.6%)	298 (34.5%)	
“H”ilar location (abutting main artery or vein)	8 (4.1%)	136 (15.7%)	<0.001

Table 2

Multivariable logistic regression analysis demonstrating associations between tumor anatomic characteristics and the probability of being placed on AS.

Variable	OR	95% CI	p-value
Age	1.09	1.07–1.10	<0.001
Largest tumor size	0.77	0.69–0.85	<0.001
Charlson Comorbidity Index	1.66	1.5–1.84	<0.001
Nephrometry Score	1.85	1.37–2.5	<0.001
(R)adius (1 vs. 3)	5.2	1.78–15.2	0.003
(R)adius (2 vs. 3)	3.27	1.15–9.26	0.026
(N)earness (1 vs. 3)	2.3	1.5–3.6	<0.001
(N)earness (2 vs. 3)	2.5	1.5–4.2	<0.001
(L)ocation (1 vs. 3)	1.4	0.84–2.2	<0.001
(L)ocation (2 vs. 3)	1.3	0.8–2.1	0.274
Non-hilar	2.7	1.2–5.8	0.015
Solitary Kidney	1.4	0.6–3.4	0.394
Multifocal Tumor	1.8	0.96–3.4	0.068

Controlling for gender, race, Eastern Cooperative Oncology Group Score, tumor laterality, endo/exophycity, anterior/posterior, and location relative to polar line.

Table 3

Multivariable logistic regression analysis demonstrating associations between tumor anatomic characteristics and the probability of being placed on AS among patients with T1a disease.

Variable	OR	95% CI	p-value
Age	1.1	1.06–1.10	<0.001
Largest tumor size	0.70	0.55–0.88	0.002
Charlson Comorbidity Index	1.68	1.48–1.91	<0.001
Nephrometry Score	1.8	1.3–2.6	<0.001
(N)earness (1 vs. 3)	1.9	1.1–3.1	0.017
(N)earness (2 vs. 3)	1.8	0.96–3.3	0.050
(L)ocation (1 vs. 3)	1.1	0.61–1.9	0.002
(L)ocation (2 vs. 3)	0.97	0.54–1.7	0.922
Non-hilar	2.0	0.7–5.9	0.192
Solitary Kidney	1.7	0.67–4.6	0.259
Multifocal disease	2.4	1.2–4.9	0.016

Controlling for gender, race, Eastern Cooperative Oncology Group Score, tumor laterality, endo/exophycity, size, anterior/posterior, and location relative to polar line.