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Renal Hilar Lesions: Biological Implications for Complex Partial Nephrectomy

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Introduction:

Renal parenchymal tumors involving the hilum can present a considerable surgical challenge¹. As with most anatomic considerations, “hilar” lesions must be considered in the context of the tumor’s size, location within the sinus, extent, and location of contact surface area (CSA) and its relationship to the vascular anatomy, collecting system, and perinephric fat. Most tumor complexity scoring systems reflect the fact that hilar tumors pose an increased surgical risk. The RENAL Nephrometry score (NS) specifically requires that an “h” suffix be affixed to the score to recognize the juxtaposition of the tumor to the main or first-order renal vascular branches². The ABC score (Arterial Based Complexity) includes a category “3h” to reflect the same notion³.

The recent AUA guidelines recommend a risk-adapted approach to surgical decision making⁴. Specifically, they recommend that surgeons consider radical nephrectomy when an increased oncologic potential is suggested by “tumor size, biopsy, and/or imaging characteristics”⁴. Previous reports have suggested that hilar masses tend to be of higher grade⁵⁻⁷ and are more likely to be upstaged given their proximity to the renal sinus fat and vasculature^{8,9}. Moreover, hilar lesions are less amenable to percutaneous tissue sampling, which is increasingly performed for tumor risk stratification⁴. The decision to pursue active surveillance or complex partial nephrectomy¹ for hilar lesions is therefore hampered by the relative lack of information needed to evaluate complex surgical and oncologic tradeoffs. Ultimately many patients are recommended to undergo radical nephrectomy given the location and the concern that these lesions are biologically more aggressive.

The data regarding biological differences of hilar lesions is scarce, limited by small sample sizes, and inconsistencies^{5-8,10,11}. To date, most of the available data is inferred from analyses aimed at a model development^{5,6}, which included renal masses of all sizes and seldom discussion of the histopathological differences between hilar and non-hilar masses. Recent reports have had a more focused analysis on small hilar masses^{8,9}, but these have been limited to patients undergoing robotic partial nephrectomy which limits the generalizability of the results. In this analysis, we compare the pathological characteristics and recurrence risks of matched patients undergoing resection of localized, solitary, non-hereditary renal masses (cT1N0M0) with and without radiographic hilum involvement as determined on preoperative imaging by the R.E.N.A.L. nephrometry scoring system.

Methods:

After institutional review board approval, our prospectively maintained kidney tumor database was queried to identify all patients undergoing renal mass excision (radical or partial nephrectomy) for clinical stage I renal tumors from 2007–2017 with available nephrometry score (NS) data.

Clinical variables evaluated included patient (age, gender and race), tumor (size, NS and hilar designation, and laterality), use of active surveillance (only patients with at least 3 months on surveillance were considered), pathologic (histology, grade and size) and operative (estimated blood loss, operative time, partial vs radical, open vs. Laparoscopic/ Robotic, and length of hospital stay) characteristics. Tumor anatomic characteristics were assessed on pre-operative cross-sectional imaging (CT & MRI) using the R.E.N.A.L. nephrometry scoring system (NS)². Hilar masses, designated as “h” in NS, were defined as tumors that abut the first order renal vessels (renal artery or vein). Patients were stratified into low (NS 4–6), intermediate (NS 7–9), and high (NS 10–12) anatomic complexity groups. As part of our prospectively maintained kidney cancer database, NS is calculated and recorded for each renal mass at surgery and verified by two physicians familiar with the R.E.N.A.L. nephrometry scoring system. Tumor stage was designated according to the 2010 American Joint Committee on Cancer/International Union Against Cancer classification system. Renal mass upstaging was defined as cT1 renal masses which on pathological review were noted to have pT3a characteristics (extra-capsular extension, sinus fat invasion, and histological vascular invasion into segmental vessels). Disease recurrence was defined as any distant or local recurrence that occurred following treatment of the index lesion.

Management options including the role of biopsy, surveillance, surgical technique, and approach (robotic vs. open) were at the discretion of the primary surgeon and determined on a case-by-case basis. Robotic procedures typically employed a three-arm technique with port location tailored to the location of the renal tumor and hilum¹². Open approaches were generally performed via an extraperitoneal flank incision as previously described¹³.

Demographic, procedural, and pathologic characteristics were compared between hilar and non-hilar tumors. Associations were tested using Wilcoxon sum rank, chi-square, and Fisher’s exact tests. Logistic regression and Cox proportional hazards models were performed to test for predictors of renal mass upstaging (cT1 → pT3a) and disease recurrence, respectively. All analyses were performed using SAS 9.3 with p-values < 0.05 considered statistically significant.

Results:

A total of 1324 patients with clinical stage 1 (cT1NoMo) renal masses and nephrometry scores were identified as eligible for analysis. The cohort consisted predominantly of Caucasian (86.2%) men (63.8%) with a median age of 60 (20–89) (Table 1). Active surveillance (AS) rates between the two cohorts were equivalent (hilar: 6.2% vs. non-hilar: 7.0%, p=0.516), with non-hilar masses having a non-significantly longer mean-time on AS than hilar lesions (hilar: 8.8 ± 7.6 months vs. non-hilar: 15.2 ± 19.6 months, p=0.507). The

majority of patients underwent a nephron-sparing procedure (83.2%) via laparoscopic/robotic approach (70%). Mean pathologic tumor size was 3.5 ± 1.6 cm, with the majority of masses being of moderate (53.5%) nephrometry complexity. 226 (17%) patients were noted to have a hilar lesion based on NS classification. Mass size ($p < 0.01$) and complexity ($p < 0.01$) were notably different between hilar and non-hilar masses (Table 1). Nephron-sparing procedures were also less likely to occur in hilar masses (73.0 % vs. 85.3%, $p < 0.01$). Regarding perioperative factors, only operative time was significantly different between hilar and non-hilar masses (192 min vs. 177 min, $p < 0.01$); with a comparable mean estimated blood loss (177cc vs. 178cc, $p = 0.697$) and median length of hospital stay (3 days for each, $p = 0.756$).

The histopathological distribution of the cohort is shown in Table 2. On histopathological assessment, there was no significant difference in the rate of malignancy between anatomically designated hilar and non-hilar masses (87.2% vs. 82.6%, $p = 0.09$). The incidence of clear cell RCC was significantly higher in hilar masses (69.5% vs. 57.4%, $p < 0.01$); however, when renal masses were stratified into cT1a and cT1b the trend was only seen in masses > 4 cm in size (cT1a: 61.7% vs. 54.5%, $p = 0.123$; cT1b: 80.6% vs. 66.1%, $p = 0.01$). In contrast, angiomyolipoma (AML) histology was more common in non-hilar masses (4.3% vs. 0.9%, $p = 0.014$). This trend was maintained in cT1a masses ($p = 0.03$), but not in cT1b masses ($p = 0.105$).

The incidence of high grade histology (Fuhrman grade 3&4) in the cohort was 35.2%. There was no significant difference in the incidence of high grade histology between hilar and non-hilar masses (39.8% vs. 34.3%, $p = 0.116$), and this trend remained following stratification of masses into cT1a ($p = 0.235$) and cT1b ($p = 0.791$) sub-categories (Table 2). Furthermore, the risk of upstaging on pathologic examination (ie cT1 \rightarrow pT3a) was equivalent for hilar and non-hilar masses ($p = 0.09$) (Table 2). Extra-capsular extension was more commonly seen in non-hilar masses ($p = 0.018$); whereas, no difference was seen in regards to renal sinus fat invasion or vascular invasion ($p = 0.269$ and $p = 0.236$) (Supplementary Table 1). On regression analysis (Table 3), predictors of upstaging were increasing age (OR 1.02 [CI 1.00–1.04], $p = 0.037$), Caucasian race (OR 2.52 [CI 1.04–6.09], $p = 0.04$), high complexity per NS (OR 2.40 [CI 1.12–5.11], $p = 0.024$), and increasing mass size (OR 1.46 [CI 1.21–1.76], $p < 0.001$). Hilar location was not associated with renal mass upstaging (OR 1.02 [CI 0.59–1.76], $p = 0.955$).

Thirty-Seven (3.9%) patients developed a recurrence following resection at a median follow-up of 39 months. Of these, the majority (92%) were distant recurrences, with only three patients presenting with local recurrences (2 renal fossa and 1 partial nephrectomy bed). On multivariate regression analysis (Table 3), predictors of disease recurrence were increasing age (HR 1.04 [CI 1.00–1.07], $p = 0.028$), pT3a or greater pathology (HR 2.77 [CI 1.18–6.465], $p = 0.019$) and high grade disease (3.46 [CI 1.55–7.72], $p = 0.002$). Hilar location was not associated with disease recurrence (HR 1.87 [CI 0.88–4.01], $p = 0.106$).

Discussion:

The recent recommendation from the AUA guidelines⁴ for a risk-adapted approach for the treatment of localized renal masses places special emphasis on the pre-operative evaluation, which includes a detailed review of the patient's health status, diagnostic imaging, biopsy pathology if feasible and clinically meaningful, and the patient's support network. Renal mass characterization^{2, 3, 14, 15} on imaging has been the most widely used and validated method to predict treatment outcomes such as renal mass histology^{5, 6, 8}, post-treatment complications^{16–19}, and oncological outcomes^{5, 8, 19}. Hilar tumor location has been suggested as a key radiological finding associated with increased risk of high-grade pathology^{5–7}, upstaging^{8, 9} and more complex surgical decision making; yet, a detailed histopathological review of hilar masses remains lacking.

We aimed to analyze the histopathological characteristics of hilar lesions compared to non-hilar lesion classified per the R.E.N.A.L. Nephrometry score². In our analysis, we noted no difference in the incidence of malignancy (hilar: 87.2% vs. non-hilar: 82.6%, $p=0.612$), or high grade disease (hilar: 39.8% vs. non-hilar: 34.3 %, $p= 0.116$). The above findings are contrary to prior published reports and current conceptions on the histopathological make-up of hilar masses. Kutikov and colleagues⁵ were the first to report on the association between hilar location and high-risk pathology when the R.E.N.A.L nephrometry scoring system was modeled to predict renal mass histology and grade. Although comparative analysis and univariate modeling suggested that hilar masses may be biologically aggressive; multivariate analysis failed to show that a hilar location was predictive high-grade disease (OR 1.16 [CI 0.69–1.95], $p = 0.583$). In fact, that analysis primarily noted that increasing mass size was the overriding factor in determining high-grade pathology and no explicit comparison of histology was made based on hilar location alone.

On review of histological subtypes clear cell RCC was more common in hilar masses (69.5% vs. 57.4%, $p< 0.01$), but the difference was only significant for larger cT1b lesions ($p=0.01$). In contrast, AML histology (predominantly lipid-poor) was more common in non-hilar masses (4.3% vs. 0.9%, $p=0.014$). Several reports^{10, 11, 20} correlating renal mass location with histological subtypes have been published, with none of them reporting consistent results. One must wonder if the results obtain here and elsewhere are the result of selection bias or limited sampling rather than a true biological phenomenon.

Clinicians may believe that there is a higher risk of upstaging of renal hilar lesions based on their juxtaposition to sinus structures such as renal vessels and peri-sinus fat. This is sometimes used as a soft justification for radical nephrectomy. Importantly, hilar masses have been identified in two separate studies as a risk factor for upstaging^{8, 9} (cT1 → pT3a), prompting caution when considering a nephron-sparing approach. In this, the largest review on the topic, the risk of upstaging was similar between hilar and non-hilar masses (9.7 vs. 6.6%, $p=0.09$), a trend which was consistent when lesions were stratified by size into cT1a ($p=0.149$) and cT1b ($p=0.951$) renal masses. On regression analysis factors associated with upstaging were age, Caucasian race, high tumor complexity, and tumor size, which are consistent with previous reports^{8, 9}. On review of up-staging characteristics, invasion into the perinephric fat was significantly higher in non-hilar masses; whereas, vascular and sinus

fat invasion was comparable between the two locations (Supplementary Table 1). This finding is of great importance given the perceived risk of invasion into juxtaposed vascular and sinus structures that some associate with hilar masses, prompting clinicians to select radical nephrectomy over a nephron-sparing procedure. The contradictory findings noted in the present study are likely related to the more comprehensive nature of the analysis. In contrast to prior reports, our analysis includes patients managed with both radical and partial nephrectomy which limits the selection bias seen in prior studies^{8, 9} which focused on patients undergoing a robotic partial nephrectomy only.

Disease recurrence occurred in approximately 3% of the cohort. The majority of the recurrences were distant with only three recurrences occurring locally. All local recurrences occurred in patients with non-hilar masses, and two of these occurred following radical nephrectomy. On multivariate modeling, only age and pathological factors (pT3a stage, and high-grade disease), not hilar location, were associated with recurrence consistent with previous published reports^{21, 22}.

The current study is limited by its retrospective design as well as lack of an external pathological validation. The retrospective nature of the study inherently adds selection bias to the findings. Nonetheless, the non-significant difference in the use of active surveillance between hilar and non-hilar lesions allows for a reasonable comparison between the groups. A second limitation is the limited sample size, though our cohort represents the largest published analysis of strictly-defined hilar masses using a nephrometry scoring system to date. Lastly, the median follow-up of 39 months may be too short to identify some late recurrences as this has been found to occur past 60 month follow-up²³.

As we continue to rely heavily on pre-operative information to better counsel patients in their treatment options, it is important we continue to re-evaluate preconceived risk factors. Here we provide a detailed histopathological review of hilar masses resected at a single institution over a 10 year period. In contrast to previous reports⁵⁻⁹, our results show no significant differences in the histopathological make-up of hilar and non-hilar tumors. These findings suggest that concern for more aggressive tumor biology in hilar lesions may be unfounded and should not present a contraindication to nephron-sparing procedures alone. Clinical decision making in cases of hilar cT1 lesions should focus on surgical techniques and perioperative risks rather than biological ones. The results of this review should be externally validated and integrated into the decision-making process when counseling patients presenting with these complex lesions.

Conclusion:

Renal lesions located near the hilum present a treatment quandary to the treating physician due to difficulties with preoperative biopsy and the technical complexity associated with a nephron-sparing procedure. Moreover, existing published data report that these masses exhibit higher pathological risk features. Here we present a comprehensive histopathological review of a large cohort of cT1 of hilar lesions, noting no difference in the risk of malignancy, high nuclear grade, or upstaging when compared to non-hilar lesions. These data suggest that there is no compelling biological reason to perform a radical nephrectomy

solely based on a renal tumor's hilar location. Differences in surgical risks, perioperative complications, and competing functional (renal and non-renal) considerations should be at the core of decision-making for complex renal hilar lesions. We hope that these findings add to the information available to practicing physicians so they might better counsel their patients presenting with complex renal hilar tumors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table. 1

Patient Demographics and Tumor Characteristics

Variable	All	Non-Hilar	Hilar	p-value
N	1324	1098	226	
Age (years)	60 (20–89)	60 (20–89)	60 (27–87)	0.986
Men	845 (63.8%)	705 (64.2%)	140 (61.9%)	0.520
Race				
White	1141 (86.2%)	948 (86.3%)	193 (85.4%)	0.709
African American	139 (10.5%)	118 (10.7%)	21 (9.3%)	0.516
Other	44 (3.3%)	32 (2.9%)	12 (5.3%)	0.065
Type of Procedure				
Partial	1102 (83.2%)	937 (85.3%)	165 (73.0%)	<0.01
Robotic	927 (70.0%)	777 (70.8%)	150 (66.4%)	0.189
Tumor Complexity				
Low Complexity	403 (30.4%)	383 (34.9%)	20 (8.8%)	<0.01
Moderate Complexity	709 (53.5%)	575 (52.4%)	134 (59.3%)	0.057
High Complexity	212 (16.0%)	140 (12.8%)	72 (31.9%)	<0.01
Tumor Size (cm)	3.5 ± 1.6 (<20–2800)	3.4 ± 1.5 (<20–2800)	3.9 ± 1.6 (<20–1800)	<0.01
Estimated Blood Loss (cc)	178 (<60–550)	177 (<60–486)	192 (<20–550)	0.697
Operative Time (min)	178 (<60–550)	177 (<60–486)	192 (<20–550)	<0.01
Length of Stay (days)	3 (1–24)	3 (3–24)	3 (<60–486)	0.756
Active Surveillance (AS)	91 (7.0%)	77 (7.0%)	3 (1–20)	0.516
Mean time on AS (mo)	14.3 ± 18.6	15.2 ± 19.6	8.8 ± 7.6	0.507
Recurrence	37 (2.8%)	26 (2.4%)	11 (4.9%)	0.021

Table 2.

Histopathological Characteristics of Hilar and Non-Hilar Lesion

Variable	cT1 Renal Masses			cT1a Renal Masses			cT1b Renal Masses				
	Non-Hilar	Hilar	p-value	Non-Hilar	Hilar	p-value	Non-Hilar	Hilar	p-value		
N	1098	226		824	133		274	93			
Malignant	907	197	87.2%								
Clear Cell	630	157	69.5%	<0.01	82	61.7%	181	66.1%	75	80.6%	0.01
Papillary	181	29	12.8%	0.171	21	15.8%	47	17.2%	8	8.6%	0.046
Chromophobe	82	9	4.0%	0.059	8	6.0%	15	5.5%	1	1.1%	0.073
Mixed CC/Pap	5	0	0.0%	0.595	4	0.5%	1	0.4%	0	0.0%	1.00
Other Malignant	9	2	0.9%	1.00	6	0.7%	3	1.1%	1	1.1%	1.00
Benign											
Oncocytoma	115	18	8.0%	0.253	15	11.3%	16	5.8%	3	3.2%	0.326
AML	47	2	0.9%	0.014	40	4.9%	7	2.6%	1	1.1%	0.105
Other Benign	29	9	4.0%	0.241	25	3.0%	4	1.5%	4	4.3%	0.791
Grade											
High Grade (FH 3&4)	377	90	39.8%	0.116	46	34.6%	134	48.9%	44	47.3%	0.791
Upstaging											
(cT1 → pT3a)	72	22	9.7%	0.09	33	4.0%	39	14.2%	13	14.2%	0.951

Table 3. Multivariate Models Assessing the Probability of A) Upstaging and B) Recurrence

A) Upstaging (cT1 → pT3a)				
Parameter	Odds Ratio	95% Confidence Limits	p value	
Age (year)	1.02	1.00	1.04	0.037
Gender (Female vs Male)	0.67	0.41	1.10	0.117
race (Caucasian vs AA/Other)	2.52	1.04	6.09	0.040
cT1b (vs cT1a)	0.98	0.50	1.92	0.953
Intermediate Complexity (vs Low Complexity)	1.23	0.64	2.36	0.527
High Complexity (vs Low Complexity)	2.40	1.12	5.11	0.024
Hilar location	1.02	0.59	1.76	0.955
Mass Size (cm)	1.46	1.21	1.76	<0.001
BMI	1.02	0.98	1.05	0.331

B) Disease Recurrence				
Parameter	Hazard Ratio	95% Confidence Limits	P value	
Age (year)	1.04	1.00	1.07	0.028
Gender (Female vs Male)	0.89	0.41	1.95	0.770
Race (Caucasian vs AA/Other)	1.15	0.34	3.88	0.816
Intermediate Complexity (vs Low Complexity)	1.68	0.46	6.17	0.434
High Complexity (vs Low Complexity)	3.16	0.76	13.20	0.114
Hilar Location	1.87	0.88	4.01	0.106
pT3a	2.77	1.18	6.46	0.019
High Grade Disease	3.46	1.55	7.72	0.002
Clear cell Histology	2.02	0.74	5.48	0.170
Mass Size (cm)	1.09	0.87	1.37	0.445
BMI	1.00	0.95	1.06	0.945