Renal Hilar Lesions: Biological Implications for Complex Partial Nephrectomy

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OBJECTIVE To perform a comprehensive histopathologic review of sporadic resected solitary cT1 renal masses comparing those with and without radiographic involvement of the hilum.

MATERIALS AND METHODS A prospectively maintained database was queried for all cT1 renal masses undergoing resection classified per the R.E.N.A.L. nephrometry score. Hilar masses were defined as tumors that abut the main renal artery or vein on cross-sectional imaging. Demographic, treatment, renal mass, and histopathologic characteristics were compared between hilar and nonhilar renal masses. Multivariate regression model analyses were performed to assess factors associated with renal mass upstaging and disease recurrence.

RESULTS A total of 1324 stage 1 renal masses met criteria for analysis of which 226 (17.1%) were defined as hilar. Hilar masses were larger, scored with higher complexity, and more likely to undergo a radical nephrectomy. On histopathologic analysis, we found no difference between hilar and nonhilar masses regarding the incidence of malignancy, presence of high nuclear grade, or risk of upstaging. On multivariate analysis, a tumor's hilar location was not associated with upstaging or disease recurrence.

CONCLUSION We present a comprehensive histopathologic review of a large cohort of cT1 hilar lesions noting no difference in the risk of malignancy, high nuclear grade, upstaging, or recurrence when compared to nonhilar lesions. Together, these data suggest that there is no compelling cancer-specific rationale to perform a radical nephrectomy when managing renal hilar tumors. UROLOGY 123: 174−180, 2019.

Renal parenchymal tumors involving the hilum can present a considerable surgical challenge.[1] 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 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 branches.[2] The ABC score (Arterial Based Complexity) includes a category "3h" to reflect the same notion.[3]

The recent AUA guidelines recommend a risk-adapted approach to surgical decision making.[4] 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 grade[5−7] 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 stratification.[4] The decision to pursue active surveillance or complex partial nephrectomy[1] 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 are scarce, limited by small sample sizes, and inconsistencies.[5−8,10,11] To date, most of the available data are inferred

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from analyses aimed at a model development,[5,6] which included renal masses of all sizes and seldom discussion of the histopathologic differences between hilar and nonhilar 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 pathologic characteristics and recurrence risks of matched patients undergoing resection of localized, solitary, nonhereditary 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 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 preoperative cross-sectional imaging (CT and 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 2 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 pathologic review were noted to have pT3a characteristics (extra-capsular extension, sinus fat invasion, and histologic 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 3-arm technique with port location tailored to the location of the renal tumor and hilum.[12] Open approaches were generally performed via an extraperitoneal flank incision as previously described.[13]

Demographic, procedural, and pathologic characteristics were compared between hilar and nonhilar tumors. Associations were tested using Wilcoxson 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 $\rightarrow \geq$ pT3a) and disease recurrence, respectively. All analyses were performed using SAS 9.3 with P values $< .05$ 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 rates between the 2 cohorts were equivalent (hilar: 6.2% vs nonhilar: 7.0%, P = .516), with nonhilar masses having a nonsignificantly longer mean-time on active surveillance than hilar lesions (hilar: 8.8 ± 7.6 months vs nonhilar: 15.2 ± 19.6 months, P = .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. A total of 226 (17%) patients were

Table 1. Patient demographics and tumor characteristics

Variable	All		Nonhilar		Hilar		*P* value
N	1324		1098		226		
Age (years)	60	(20-89)	60	(20-89)	60	(27-87)	.986
Men	845	63.8%	705	64.2%	140	61.9%	.520
Race							
White	1141	86.2%	948	86.3%	193	85.4%	.709
African American	139	10.5%	118	10.7%	21	9.3%	.516
Other	44	3.3%	32	2.9%	12	5.3%	.065
Type of procedure							
Partial	1102	83.2%	937	85.3%	165	73.0%	< .01
Robotic	927	70.0%	777	70.8%	150	66.4%	.189
Tumor complexity							
Low complexity	403	30.4%	383	34.9%	20	8.8%	< .01
Moderate complexity	709	53.5%	575	52.4%	134	59.3%	.057
High complexity	212	16.0%	140	12.8%	72	31.9%	< .01
Tumor size (cm)	3.5	±1.6	3.4	±1.5	3.9	±1.6	< .01
Estimated blood loss (cc)	178	(< 20-2800)	178	(< 20-2800)	177	(< 20-1800)	.697
Operative time (min)	178	(< 60-550)	177	(< 60-486)	192	(< 20-550)	< .01
Length of stay (days)	3	(1-24)	3	(3-24)	3	(< 60-486)	.756
Active surveillance (AS)	91	7.0%	77	7.0%	3	(1-20)	.516
Mean time on AS (mo)	14.3	±18.6	15.2	±19.6	8.8	±7.6	.507
Recurrence	37	2.8%	26	2.4%	11	4.9%	.021

Table 2. Histopathologic characteristics of hilar and nonhilar lesion

Variable	cT1 Renal Masses					cT1a Renal Masses					cT1b Renal Masses				
	Nonhilar		Hilar		*P* value	Nonhilar		Hilar		*P* value	Nonhilar		Hilar		*P* value
N	1098		226			824		133			274		93		
Malignant	907	82.6%	197	87.2%											
Clear cell	630	57.4%	157	69.5%	< .01	449	54.5%	82	61.7%	.123	181	66.1%	75	80.6%	.01
Papillary	181	16.5%	29	12.8%	.171	134	16.3%	21	15.8%	.891	47	17.2%	8	8.6%	.046
Chromophobe	82	7.5%	9	4.0%	.059	67	8.1%	8	6.0%	.399	15	5.5%	1	1.1%	.073
Mixed CC/Pap	5	0.5%	0	0.0%	.595	4	0.5%	0	0.0%	.421	1	0.4%	0	0.0%	1.00
Other malignant	9	0.8%	2	0.9%	1.00	6	0.7%	1	0.8%	1.00	3	1.1%	1	1.1%	1.00
Benign															
Oncocytoma	115	10.5%	18	8.0%	.253	99	12.0%	15	11.3%	.808	16	5.8%	3	3.2%	.326
AML	47	4.3%	2	0.9%	.014	40	4.9%	1	0.8%	.03	7	2.6%	1	1.1%	.105
Other benign	29	2.6%	9	4.0%	.241	25	3.0%	5	3.8%	.656	4	1.5%	4	4.3%	.791
Grade															
High grade (FH 3&4)	377	34.3%	90	39.8%	.116	243	29.5%	46	34.6%	.235	134	48.9%	44	47.3%	.791
Upstaging (cT1 → ≥pT3a)	72	6.6%	22	9.7%	.09	33	4.0%	9	6.8%	.149	39	14.2%	13	14.2%	.951

noted to have a hilar lesion based on NS classification. Mass size (*P* < .01) and complexity (*P* < .01) were notably different between hilar and nonhilar masses (Table 1). Nephron-sparing procedures were also less likely to occur in hilar masses (73.0 % vs 85.3%, *P* < .01). Regarding perioperative factors, only operative time was significantly different between hilar and nonhilar masses (192 minutes vs177 minutes, *P* < .01); with a comparable mean estimated blood loss (177cc vs 178cc, *P* = .697) and median length of hospital stay (3 days for each, *P* = .756).

The histopathologic distribution of the cohort is shown in Table 2. On histopathologic assessment, there was no significant difference in the rate of malignancy between anatomically designated hilar and nonhilar masses (87.2% vs 82.6%, *P* = .09). The incidence of clear cell RCC was significantly higher in hilar masses (69.5% vs 57.4%, *P* < .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* = .123; cT1b: 80.6% vs 66.1%, *P* = .01). In contrast, angiomyolipoma histology was more common in nonhilar masses (4.3% vs 0.9%, *P* = .014). This trend was maintained in cT1a masses (*P* = .03), but not in cT1b masses (*P* = .105).

The incidence of high grade histology (Fuhrman grade 3 and 4) in the cohort was 35.2%. There was no significant difference in the incidence of high grade histology between hilar and nonhilar masses (39.8% vs 34.3%, *P* = .116), and this trend remained following stratification of masses into cT1a (*P* = .235) and cT1b (*P* = .791) subcategories (Table 2). Furthermore, the risk of upstaging on pathologic examination (ie, cT1 → ≥ pT3a) was equivalent for hilar and nonhilar masses (*P* = .09; Table 2). Extra-capsular extension was more commonly seen in nonhilar masses (*P* = .018); whereas, no difference was seen in regards to renal sinus fat invasion or vascular invasion (*P* = .269 and *P* = .236; Supplementary Table 1). On regression analysis (Table 3), predictors of upstaging were increasing age (odds ratio [OR] 1.02 [confidence interval {CI} 1.00-1.04], *P* = .037), Caucasian race (OR 2.52 [CI 1.04-6.09], *P* = .04), high complexity per NS (OR 2.40 [CI 1.12-5.11], *P* = .024), and increasing mass size (OR 1.46 [CI 1.21-1.76], *P* < .001). Hilar location was not associated with renal mass upstaging (OR 1.02 [CI 0.59-1.76], *P* = .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 3 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 (hazard ratio [HR] 1.04 [CI 1.00-1.07], *P* = .028), pT3a or greater pathology (HR 2.77 [CI 1.18-6.465], *P* = .019) and high grade disease (3.46 [CI 1.55-7.72], *P* = .002). Hilar location was not associated with disease recurrence (HR 1.87 [CI 0.88-4.01], *P* = .106).

DISCUSSION

The recent recommendation from the AUA guidelines[4] for a risk-adapted approach for the treatment of localized renal masses places special emphasis on the preoperative 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

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	.037
Gender (female vs male)	0.67	0.41	1.10	.117
race (Caucasian vs AA/other)	2.52	1.04	6.09	.040
cT1b (vs cT1a)	0.98	0.50	1.92	.953
Intermediate complexity (vs low complexity)	1.23	0.64	2.36	.527
High complexity (vs low complexity)	2.40	1.12	5.11	.024
Hilar location	1.02	0.59	1.76	.955
Mass size (cm)	1.46	1.21	1.76	< .001
BMI	1.02	0.98	1.05	.331
(B) Disease Recurrence Parameter	**Hazard Ratio**	**95% Confidence Limits**		***P* value**
Age (year)	1.04	1.00	1.07	.028
Gender (female vs male)	0.89	0.41	1.95	.770
Race (Caucasian vs AA/other)	1.15	0.34	3.88	.816
Intermediate complexity (vs low complexity)	1.68	0.46	6.17	.434
High complexity (vs low complexity)	3.16	0.76	13.20	.114
Hilar location	1.87	0.88	4.01	.106
≥ pT3a	2.77	1.18	6.46	.019
High grade disease	3.46	1.55	7.72	.002
Clear cell histology	2.02	0.74	5.48	.170
Mass size (cm)	1.09	0.87	1.37	.445
BMI	1.00	0.95	1.06	.945

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 histopathologic review of hilar masses remains lacking.

We aimed to analyze the histopathologic characteristics of hilar lesions compared to nonhilar lesion classified per the R.E.N.A.L. nephrometry score.[2] In our analysis, we noted no difference in the incidence of malignancy (hilar: 87.2% vs nonhilar: 82.6%, *P* = .612), or high grade disease (hilar: 39.8% vs nonhilar: 34.3 %, *P* = .116). The above findings are contrary to prior published reports and current conceptions on the histopathologic make-up of hilar masses. Kutikov et al[5] 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* = .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 histologic subtypes clear cell RCC was more common in hilar masses (69.5% vs 57.4%, *P* < .01), but the difference was only significant for larger cT1b lesions (*P* = .01). In contrast, angiomyolipoma histology (predominantly lipid-poor) was more common in nonhilar masses (4.3% vs 0.9%, *P* = .014). Several reports[10,11,20] correlating renal mass location with histologic 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 2 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 nonhilar masses (9.7 vs 6.6%, *P* = .09), a trend which was consistent when lesions were stratified by size into cT1a (*P* = .149) and cT1b (*P* = .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 peri-nephric fat was significantly higher in nonhilar masses; whereas, vascular and sinus fat invasion was comparable between the 2 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 3 recurrences occurring locally. All local recurrences occurred in patients with nonhilar masses, and 2 of these occurred following radical nephrectomy. On multivariate modeling, only age and pathologic factors ($\geq$ 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 pathologic validation. The retrospective nature of the study inherently adds selection bias to the findings. Nonetheless, the nonsignificant difference in the use of active surveillance between hilar and nonhilar 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. Last, 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-up.[23]

As we continue to rely heavily on preoperative 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 histopathologic review of hilar masses resected at a single institution over a 10-year period. In contrast to previous reports,[5–9] our results show no significant differences in the histopathologic make-up of hilar and nonhilar 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 pathologic risk features. Here we present a comprehensive histopathologic 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 nonhilar 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 nonrenal) 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.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.urology.2018.08.044.

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EDITORIAL COMMENT

Over the last 20 years, our understanding of renal cortical tumors (RCT) and their best management has evolved. Formerly, surgeons felt that tumors of all sizes and locations were best managed by radical nephrectomy (RN) if there was a functional contra lateral kidney. Partial nephrectomy (PN), initially used sparingly, was reserved for essential indications such as tumor in a solitary kidney, tumor in a patient with renal calculus disease or renal insufficiency, and for patients with bilateral renal tumors. Now we understand that RCT are a complex family of tumors with at least 31 separate subtypes described based on genomic and metabolomic studies.[1,2] These tumors pose a spectrum of oncologic threats ranging from benign (20%), indolent with limited metastatic potential (25%), and malignant (55%). This variable threat from RCT coupled with the understanding that PN provides equivalent tumor control to RN while at the same time preserving renal function, preventing, or delaying chronic kidney disease and its associated cardiovascular disease lead to enhanced utilization of PN in the elective setting.[3]

Yet, RN is still overused on the national level for the management of T1 tumors for reasons that are likely multi factorial and may include a surgeon's technical comfort level with PN (by any approach) and concern for common postoperative complications such as bleeding and urinary fistula.[4] Patients are often told that a tumor close to the major vessels of the renal hilum is not technically amenable to PN and likely to have especially aggressive biology. The authors debunk this latter notion in their 10-year review of 1324 T1 RCT patients of which 226 (17.1%) were classified as hilar in location. The authors note no difference in the risk of malignancy, high nuclear grade, upstaging, or recurrence when compared to nonhilar lesions. In this series of hilar tumors, 31% were benign (13%) or indolent in nature (18%). The authors should be congratulated for their high rate of utilization of PN (83.2%, overall and 73% for the hilar tumors) which is far above what is reported at the national level.[4] Based on this study, surgeons capable of performing PN should feel free to plan and proceed in cases of renal hilar tumors and not worry that these tumors are any more dangerous than tumors arising elsewhere in the kidney.

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AUTHOR RESPONSE

The concept of kidney-sparing surgery or partial nephrectomy (PN) was first reported by Czerny[1] in the 1980's and then revisited by Vermooten[1] in 1950 for the management of encapsulated peripherally located renal tumors. Since, the use of nephron-sparing surgery for the management of renal cell carcinoma (RCC) has seen tremendous growth stimulated by our greater understanding of the deleterious effects of chronic kidney disease (CDK), experience with renovascular surgery, and the growing numbers of incidentally discovered small renal masses[1]; becoming the standard of care for the management of cT1 renal masses. As we continue to develop and expand the indications of organ-sparing surgical techniques in order to minimize treatment-related side effects, we must also recognize that these techniques are not absolute and must be tailored to the patient's specific tumor biology, physical capacity and treatment expectations.

In the present manuscript, we demonstrate the technical feasibility and oncological safety of the use of partial nephrectomy in patients presenting with hilar lesion measuring 7 cm or less in diameter. The impetus for the publication was not to advocate for "partial nephrectomy for all," but to provide a greater understanding of the biology of renal mass located near the hilar vessels. Hilar lesions, opposed to those located in the periphery, are less amenable for percutaneous sampling, the mainstay of renal mass risk stratification, and are managed as a homogenous entity of presumed high-grade potential. Here we note that hilar renal masses are no different to peripheral renal masses in regards to histology, nuclear grade, and oncological outcomes. Moving forward, nuclear medicine radiotracers such as 99mTc-Sestamibi (oncocytic masses) and G-250 Immuno-PET (clear cell RCC), hold promise for the histologic discrimination of renal masses not amenable to percutaneous biopsy but remain limited in the biological information provided. Advances in the detection of circulating tumor DNA (ctDNA), liquid biopsy, may ultimately provide the best method for renal mass risk stratification,[2] which in combination with increase understanding in the genetic basis of chronic medical conditions would allow us to individualize treatment options to optimize cancer control while minimizing treated associated side effects.

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