Original Article

Characterization of Adolescent and Pediatric Renal Cell Carcinoma: A Report From the Children's Oncology Group Study AREN03B2

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BACKGROUND: The current study was conducted to characterize the epidemiology, histology, and radiographic features of as well as the surgical approach to pediatric and adolescent renal cell carcinoma (pRCC). **METHODS:** pRCC cases prospectively enrolled on the Children's Oncology Group study AREN03B2 underwent central pathology, radiology, surgery, and oncology review. **RESULTS:** As of June 2012, 120 of a total of 3250 patients enrolled on AREN03B2 (3.7%) were found to have unilateral RCC (median age, 12.9 years [range, 1.9-22.1 years]; 52.5% were female). Central review classified these as translocation morphology (56 patients), papillary (20 patients), renal medullary carcinoma (13 patients), chromophobe (4 patients), oncocytoma (1 patient), conventional clear cell (1 patient), and RCC not otherwise specified (25 patients). Lymph node (LN) involvement (N+) was found in 35 of 73 cases (47.9%) for which LNs were sampled, including 19 of 40 cases with primary tumors measuring <7 cm (47.5%). Using a size cutoff of 1 cm, imaging detection of LN involvement had a sensitivity of 57.14% (20 of 35 cases; 95% CI, 39.35%-73.68%) and a specificity of 94.59% (35 of 37 cases; 95% CI, 81.81%-99.34%). Distant metastases were present in 23 cases (19.2%). Initial surgery was radical nephrectomy in 88 patients (73.3%), nephron-sparing surgery in 18 patients (15.0%), and biopsy in 14 patients (11.7%). Compared with patients undergoing radical nephrectomy, those treated with nephron-sparing surgery were less likely to have LNs sampled (6 of 18 patients [33.3%] vs 65 of 88 patients [73.9%]; $P = .002$). **CONCLUSIONS:** Translocation RCC is the most common form of pediatric and adolescent RCC. Lymph node disease is common and observed among patients with small primary tumors. Imaging has a high specificity but relatively low sensitivity for the detection of such lymph node disease. Failure to sample LNs results in incomplete staging and potentially inadequate disease control for younger patients with RCC. ***Cancer*** **2015;121:2457-64.** *© 2015 American Cancer Society.*

KEYWORDS: translocation renal cell carcinoma, pediatric, adolescent, lymph node.

INTRODUCTION

Renal cell carcinoma (RCC) is the second most common renal malignancy diagnosed among pediatric and adolescent patients (pRCC), accounting for 2% to 6% of renal cancers.[1,2] In contrast to Wilms tumor, which has well-defined therapies and excellent outcomes, the understanding of pRCC is limited, and treatment recommendations are based on small retrospective case series and reports or taken from guidelines for "adult" RCC. However, over the past few years, it has become clear that pRCC is different from the "typical" adult RCC with regard to both tumor biology and clinical behavior. For example, pRCC is most commonly translocation-type, often harboring chromosomal translocations involving the transcription factor E3 (*TFE3*) gene at Xp11.2 rather than clear cell RCC as typically observed in adults.[2-4] A second distinguishing feature of pRCC relates to a higher incidence of regional lymph node (LN) involvement yet a potentially more favorable prognosis when involved LNs are completely resected in the absence of distant metastases.[1,3,5] However, insights have been limited by either the small size of the reports and or a lack of centralized expert review. To our knowledge to date, there has been no systematic, large, prospective series that has documented the demographic, pathological, radiographic, or surgical approach to pRCC.

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The Children's Oncology Group (COG) study AREN03B2 was designed to prospectively collect biological tissue, histologic data, radiographic imaging, and surgical data to be used for the assignment of patients to a series of therapeutic protocols, to explore novel biological insights, and to help refine future guidelines. Using the centrally collected and reviewed data from this prospective study, we herein report our experience with pRCC, highlighting epidemiologic, histologic, radiographic, and surgical insights. The impact of the data reported herein on the management of young adult patients with RCC is also discussed, especially as it relates to the impact of the surgical approach on obtaining LNs.

MATERIALS AND METHODS

Study Population

The COG AREN03B2 Renal Tumor Biology and Classification Study (ClinicalTrial.gov NCT00898365) classifies patients with renal tumors by histology, radiological features, stage of disease, presence of metastasis, age at diagnosis, congenital abnormalities and genetic cancer predispositions, and tumor weight to define eligibility for a series of therapeutic studies. All participants provide informed consent at participating institutions that have had the AREN03B2 study approved by their local Institutional Review Board (IRB). AREN03B2 guidelines require LN sampling for several associated therapeutic (Wilms tumor) trials; formal LN dissections are not routinely recommended. Data are collected regarding patients aged <30 years with a first occurrence of any kidney tumor. Enrollment on AREN03B2 is required before the establishment of a risk assignment enabling enrollment to COG renal tumor therapeutic studies. Central review of radiological, histological, and surgical data is completed in real time to ensure appropriate risk stratification. For the current study, we reviewed patients enrolled in the COG AREN03B2 study with central pathologic review of RCC.

Study Design

The current study is a descriptive review of the previously described prospective clinical trial.[6] Data extracted included epidemiological/demographic data (eg, age, sex, race, and American Joint Committee on Cancer TNM stage [using the 6th edition]), histologic category, radiographic imaging findings (laterality, size of the primary tumor, presence and evaluation of LNs and distant metastatic disease), initial surgical approach (biopsy, nephron-sparing surgery [NSS] or radical nephrectomy [RN]), and the presence or absence of surgical LN sampling. Pathology specimens are reviewed as previously described.[6]

Pathology review

A full set of hematoxylin and eosin-stained slides was submitted for review. The tumors were classified based on histology, complemented by any available immunohistochemistry performed by the submitting institution or as part of central pathology review.

Radiological methods

Institutions enrolling cases are responsible for the assessment of distant metastatic disease. Central review is mandatory for required chest and abdominal cross-sectional imaging to determine the status of pulmonary metastasis and synchronous renal tumors.[6] For the purpose of this report, all cross-sectional imaging was reviewed centrally to determine the presence of enlarged (>1 cm in short axis) retroperitoneal LNs and distant metastasis.

Surgical methods

Surgical reports were available for central review for all cases. NSS was assigned for cases approached as partial nephrectomy or tumor enucleation, whereas RN was assigned when the affected kidney was completely removed. The presence or absence of surgical LN sampling was determined by the presence or absence of lymphatic tissue submitted, reviewed by both the treating institutional pathologist and central review pathologist, and correlated with surgical notes indicating the surgeon's attempt (or lack thereof) to sample LNs.

Statistical Analysis

The collected data were analyzed with nonparametric methods. Independent continuous variables were compared using a Mann-Whitney U test and independent categorical variables were compared using a Fisher exact test. In addition, a logistic regression model for LN status (positive vs negative) as determined by pathology was fit with radiographically determined LN status as the predictor. For all tests, statistical significance was set at a $P < .05$.

RESULTS

Epidemiology/Demographics

As of June 2012, 3250 patients had been enrolled on AREN03B2 and of these, 122 patients (3.75%) were found to have central pathologic confirmation of RCC. Two cases were bilateral RCC and 120 were unilateral RCC. The current report focuses on the 120 unilateral cases. The median age at diagnosis was 12.9 years (range, 1.9-22.1 years) and 63 patients (52.5%) were female.

TABLE 1. TNM Stage of Pediatric and Adolescent RCC in COG Study AREN03B2

Stage	Total (N = 120)	Translocation (N = 56)
T classification		
Tx	14 (11.6%)	4 (7.1%)
T1	40 (33.3%)	17 (30.4%)
T2	15 (12.5%)	4 (7.1%)
T3a-c	49 (40.8%)	29 (51.8%)
T4	2 (1.7%)	2 (3.6%)
N classification		
N0	36 (30%)	11 (19.6%)
N1	35 (29.2%)	23 (41.1%)
Nx	49 (40.8%)	22 (39.3%)
M classification		
M0[a]	98 (81.7%)	50 (89.3%)
M1	22 (18.3%)	6 (10.7%)
Overall TNM stage		
I	35 (29.2%)	15 (26.8%)
II	11 (9.2%)	2 (3.6%)
III	43 (35.8%)	29 (51.8%)
IV	25 (20.8%)	6 (10.7%)
Unclassifiable	6 (5%)	4 (7.1%)

Abbreviations: COG, Children's Oncology Group; RCC, renal cell carcinoma.
[a] Cases without submission of a metastatic disease case report form and without any obvious metastases on central review were presumed to have M0 disease.

Racial background was 63 white patients (52.5%); 42 black or African American patients (35%); 3 Asian patients (2.5%); 1 patient who was American Indian, Aleutian, or Eskimo (0.8%); 5 patients classified as other (4.2%); and 6 patients with unknown race (5%). Patients with renal medullary carcinoma (RMC) were all noted to have sickle cell trait, and the single patient with clear cell RCC had multiple endocrine neoplasia type 1.

Histology and Stage

Tumor histology was noted as being of translocation morphology (tRCC) in 56 patients (46.7%), RCC not otherwise specified in 25 patients (20.8%), papillary in 20 patients (16.7%), RMC in 13 patients (10.8%), chromophobe in 4 patients (3.3%), oncocytoma in 1 patient (0.8%), and clear cell in 1 patient (0.8%). Table 1 shows TNM stage of disease for the entire cohort and for the translocation morphology subgroup. The most common sites of metastases at the time of diagnosis reported by the institutions were the lung (15 patients; 12.5%), liver (7 patients; 5.8%), and bone (3 patients; 2.5%). A total of 49 patients (40.8%) failed to have LNs sampled. In sum, 48 patients (40%) presented with either lymphatic or hematogenous spread. By histology, 92.3% of patients with RMC presented with stage IV disease, 62.5% of patients with tRCC presented with stage III or IV disease, and 39.2% of patients without tRCC or RMC presented with stage III or IV disease ($P = .00087$).

Radiographic Features

Contrast-enhanced computed tomography or magnetic resonance imaging of the abdomen was available for central review in 118 of 120 cases. The distribution of laterality was 60 on the right and 58 on the left. Based on the size criterion of >1 cm for enlarged LNs, 32 of 118 cases (27.1%) were classified as having LN involvement at imaging. The size of the primary renal tumor was <7 cm in 12 of 32 patients who were noted to have enlarged LNs (37.5%). Pathologic proof of LN status was available in 73 of 120 cases (60.83%), 35 of which were positive for tumor. Imaging correctly identified 20 of 35 LNs as positive for tumor, thereby providing a sensitivity of 57.14% (95% confidence interval [95% CI], 39.35%-73.68%). Although the sensitivity of imaging was poor, specificity was high (94.59% [35 of 37 cases]; 95% CI, 81.81%-99.34%), with patients who were LN positive radiographically having an odds of being diagnosed with positive LNs by pathology of 23.33 times (95% CI, 4.833-112.643; $P<.0001$) that for patients who were LN negative radiographically. Among 40 patients whose primary renal tumor measured <7 cm and who had histologic assessment of LN status, LNs were positive by pathology in 19 cases (47.5%). Of 73 sets of independent central reviews, there was agreement between reviewers in 55 cases (75.34%) with respect to imaging and pathology findings regarding LN status. At central review, distant metastatic disease was noted in 23 cases (lung in 19 cases, liver in 5 cases, mediastinal LNs in 5 cases, supraclavicular LNs in 2 cases, bone in 2 cases, and muscle in 1 case) with multifocal metastasis noted in 9 of 23 cases at the time of initial presentation.

Surgical Features

The initial surgical approach was RN in 88 cases (73.3%), NSS in 18 cases (15.0%), and biopsy or surgical resection of metastasis in 14 cases (11.7%), 7 of which went on to RN and 7 of which had no further definitive resection (Table 2). Unfortunately, only 71 cases (59.2%) had surgical/pathologic evaluation of the LNs, 35 of which (49.3%) were positive for tumor histologically. At the time of the initial surgery, patients undergoing NSS were less likely than those undergoing RN to have LNs sampled (6 of 18 patients [33.3%] vs 65 of 88 patients [73.9%]; $P = .002$), as were patients with lower T classification ($P = .003$) (Table 3). The median age of the patients undergoing surgical LN sampling was younger compared

TABLE 2. Surgical Approach to Patients With Unilateral RCC in COG Study AREN03B2

Initial Procedure	N = 120 (%)
RN	88 (73.3%)
NSS	18 (15.0%)
Biopsy/peripheral resection	14 (11.7%)
Definitive renal surgery	
RN	95 (79.2%)
NSS	18 (15.0%)
No definitive renal surgery	7 (5.8%)
Cases with clinically or pathologically positive LNs	36 (30.0%)
Cases with LNs sampled	73 (60.8%)
Cases with pathologically evaluated positive LNs	35/73 (47.9%)
Venous tumor thrombus	7 (5.8%)

Abbreviations: COG, Children's Oncology Group; LNs, lymph nodes; NSS, nephron-sparing surgery; RCC, renal cell carcinoma; RN, radical nephrectomy.

TABLE 3. Lymph Node Sampling at the Time of Initial Resection of the Renal Mass

	Yes	No	*P*
No.	71 (67.0%)	35 (33.0%)	
Median age (range), y	12.4 (1.9-20.3)	13.4 (3.0-22.1)	.043
T classification (% within stage)			.003
Tx	1 (33.3%)	2 (66.7%)	
T1	18 (46.2%)	21 (53.8%)	
T2	13 (76.5%)	4 (23.5%)	
T3a	32 (80.0%)	8 (20.0%)	
T3b	6 (100%)	0 (0%)	
T3c	NA	NA	
T4	1 (100%)	0 (0%)	
Initial surgery			.002
RN (% of initial RNs performed)	65 (73.9%)	23 (26.1%)	
NSS (% of initial NSSs performed)	6 (33.3%)	12 (66.7%)	

Abbreviations: NA, not applicable; NSS, nephron-sparing surgery; RN, radical nephrectomy.

TABLE 4. Initial Surgical Approach to Renal Mass in Patients With Unilateral RCC

Characteristic	RN (n=88)	NSS (n=18)	*P*
Median age (range), y	12.7 (1.9-22.1)	13.3 (3.0-18.0)	.467
T classification (% in procedure)			.001
Tx	1 (1.1%)	2 (11.1%)	
T1	26 (29.6%)	13 (72.2%)	
T2	15 (17.1%)	2 (11.1%)	
T3a	39 (44.3%)	1 (5.6%)	
T3b	6 (6.8%)	0 (0%)	
T3c	0 (0%)	0 (0%)	
T4	1 (1.1%)	0 (0%)	

Abbreviations: NSS, nephron-sparing surgery; RCC, renal cell carcinoma; RN, radical nephrectomy.

TABLE 5. Demographics Based On Lymph Node Status

Characteristic	LN+ (N = 35)	LN- (N = 36)	LNx (N = 49)
Age at diagnosis, y			
Range	1.9-17.8	2.44-20.3	3-22.1
Median	12.8	10.7	13.4
Mean	12.1	10.7	12.9
SD	4.3	4.3	4.4
Primary tumor size, cm			
Range	0.8-19.7	2.5-16.3	4.6-8.6
Median	6.5	6.7	5.6
Mean	7.3	7.5	6.3
SD	4.2	3.8	2.1
Histology			
Translocation	23	11	22
Papillary	3	12	5
Other	3	10	12
Renal medullary	6	0	7
Chromophobe	0	2	2
Clear cell	0	0	1
Oncocytoma	0	1	0

Abbreviations: +, positive; -, negative; LN, lymph node; SD, standard deviation.

with those who did not have LNs sampled (12.4 years vs 13.4 years; $P = .043$). In addition, there was a trend toward the increasing use of NSS in those patients with masses with a lower T classification ($P = .001$) (Table 4). Primary tumor size, age, and histology, in relation to LN status, are presented in Table 5.

DISCUSSION

pRCC represents a unique therapeutic challenge because of its rarity and its differences from adult RCC or other pediatric renal tumors. The results of the current study, which to our knowledge is the first prospective and the largest series of well-characterized pRCC tumors published to date, provide insight into the distinctive epidemiology, demographics, histologic heterogeneity, biology, radiographic imaging, and surgical management.

Epidemiological and demographic data, derived from 6 years of systematic prospective enrollment of 3250 patients with renal tumors from approximately 210 centers, confirm that 3.7% of pediatric renal cancers among patients aged <22 years are RCC. Although patients aged >22 years through aged 30 years were also eligible for enrollment in the AREN03B2 study, such patients did not accrue, most likely due to referral patterns of enrolling institutions. There appears to be no sex predilection in pRCC overall, although there is a slight female predominance for translocation or TFE RCC (tRCC) specifically. Contrary to what may be suspected or reported,[7] RCC genetic cancer predisposition syndromes were not found to be prevalent in the current study cohort except for an expected association between RMC and sickle cell trait; the single patient with clear cell RCC was found to have multiple endocrine neoplasia type 1, there was 1 case of associated congenital adrenal hyperplasia, and 1 case of

osteopetrosis that was treated with bone marrow transplant. Referral bias, which was not likely a factor in the current study cohort, may have contributed to previous reports suggesting that cancer predispositions are more prevalent in patients with pediatric and adolescent RCC.[7] The data from the current study suggest that clear cell RCC in the young is vanishingly rare and when found warrants an exploration into possible genetic risk factors.

The most common form of pRCC is tRCC, accounting for 47% of all cases. tRCC is found in all age groups and all races,[3,4,8,9] and was first formally recognized by the World Health Organization in 2004 as a distinct, typically translocation-associated, RCC with characteristic morphology[10-13] along with immunohistochemical expression of TFE3 or transcription factor EB (TFEb).[14,15] TFE3 and TFEb are members of the MiTF/TFE family, a subgroup of basic helix-loop–helix-leucine zipper transcription factors that share homology in DNA-binding domains.[10,16,17] Cytogenetic analysis often reveal *TFE3-ASPS, TFE3-PRCC*, *TFEb-α* or one of the less common variant translocations, although mechanisms for TFE upregulation are likely heterogeneous.[11,18-22] Diagnostic challenges with TFE immunohistochemical antibodies, the lack of available cytogenetics, and inconsistent appreciation for the morphologic spectra of tRCC may explain the variable frequencies of tRCC noted in published adult series, ranging from 0.9% to 9%.[8,9,23-28] Rates as high as 23% have been reported when focusing on patients aged $\leq$40 years,[27] and a rate of 2.4% was reported when focusing on patients with RCC who were aged $>$50 years.[28]

The significance of positive LNs, a common finding among patients with tRCC with rates of 41% reported in the younger cohort presented herein and up to 50% to 80% in older cohorts,[4,29-32] is debated, with reports suggesting both a favorable[3,25,33] and unfavorable[32] outcome. It is possible that age may impact such clinical behavior, pending clarification of referral patterns in medical oncology reports, because more advanced patterns have been reported in relatively older patients with tRCC.[4,32] Rates of hematogenous metastatic disease also vary, ranging from 9% to 11% in predominantly pediatric reports[25] to 35% to 75% in select older tRCC cohorts.[32] Overall, in the current pRCC series, approximately 62.5% of tRCC cases presented with TNM stage III or IV disease.[34]

The medical management of unresectable tRCC is evolving, and is most notable for objective responses and rare durable complete remissions in pediatric, adolescent, and adult patients treated with vascular endothelial growth factor receptor tyrosine kinase inhibitors.[4,29-31,35-39] Although the numbers are small, reports of anti-tRCC activity with mechanistic target of rapamycin inhibitors are available.[35,36] Predicated on the rationale that tRCC shares a biology that is similar to that of other TFE translocation-associated cancers such as sarcomas[40] and a reported clinical benefit of chemotherapy for patients with sarcomatoid RCC variants,[41,42] conventional chemotherapies (typically gemcitabine-based) have been used with anecdotal response and disease stabilization.[3] Similarly, the medical management of patients with RMC, the most aggressive variant of RCC observed in the current series, may include gemcitabine-based, platinum-based, or taxane-based therapy, as well as biological-based therapy.[43,44] It is hoped that expanding our understanding of the biological bases of tRCC and RMC will lead to improved targeted therapies.

The use of radiology to aid in the staging of patients with RCC is well established in adult patients with RCC, but to the best of our knowledge only limited data are available regarding pRCC.[25,45,46] In the current study, the sensitivity for the radiologic determination of LN positivity was poor, missing $>$42% of subsequently histologically confirmed tumor LN metastases, suggesting that imaging alone is not sufficient to rule out lymph node involvement in patients with pRCC. A related critical finding was the lack of LN sampling in 40.8% of cases. The clinical relevance is compounded by the finding that positive LNs were found in 47.5% of primary tumors measuring $<$7 cm. This contrasts with adult RCC, in which LN positivity is uncommon with smaller tumors.[47] Among the 73 patients in the current study (60.8%) who had LNs sampled, 35 (29.2% overall; 47.9% of those with LNs sampled) had pathological evidence of LN involvement. Failure to sample LNs was more likely in to occur among those with a lower T classification and patients undergoing NSS. Reasons for omitting LN sampling were not collected in the AREN03B2 study, although we noted a trend to omit sampling during NSS (Table 3) and among patients with smaller primary tumors (Table 5). The relatively increased predilection for patients with tRCC to present with involved LNs, a notable finding of involved LNs in patients with small primary tumors, the low sensitivity of imaging to detect involved LNs, and current surgical patterns in both pediatric and adult patients with RCC with small primary tumors in whom regional LN dissection is often omitted collectively present an opportunity for an improved surgical approach to this patient population, among whom a more compulsive approach to LN sampling and surgical dissection

appears to be warranted. It should be reinforced, as it has been in children with Wilms tumor, that surgical LN sampling is a fundamental part of the surgery for renal tumors in pediatric and adolescent patients. Efforts regarding such education and quality control have led to rates of surgical LN sampling of as high as 90% in the Wilms tumor population.[48] The importance of LN sampling is not likely limited to patients aged birth to 22 years, however, as a more aggressive approach to LN surgery might be extrapolated to "young adult" patients with RCC (age <40 years), among whom tRCC remains prevalent and in whom insensitive imaging and LN-positive disease remain an issue even in the setting of small primary tumors. In balance, among patients with both Wilms tumor and RCC, it is to our knowledge unproven that a formal LN dissection or mandating a minimum number of LNs improves or impacts event-free or overall survival, a question that warrants formal prospective study.

RN remained the most common initial surgical treatment (79%) compared with NSS (15%). NSS via partial nephrectomy is widely used in adults with small renal masses.[49] Given a bias for presenting more unique and uncommon cases, there are several reports describing partial nephrectomy for patients with pRCC, provided the size and location of the tumor are amenable to such an approach.[50,51] However, as the data from the current study indicate, RN is clearly the predominant surgical approach. This likely reflects the finding that many of these tumors were larger or more locally advanced, with >65% of the cases in the current study undergoing upfront primary tumor surgery if T2 or greater and at least 30% having positive LNs. This was noted specifically by the statistically significant trend toward increased NSS use among patients with a lower T classification. It is important to stress that the role of NSS is yet to be elucidated in this disease, and thus its use should be reserved for selected patients in which complete resection with negative surgical margins can be obtained. Given that current adjuvant medical therapies are not typically curative for unresected disease, it is important that localized disease be completely resected.[1,3,52]

To the best of our knowledge, the current study represents the largest series of children and adolescents with RCC presented to date, collected prospectively in a systematic fashion. One inherent limitation is a lack of treatment and survival data, which could add measure to the insights provided. This is a function of the study design of the AREN03B2, which is a biologic banking and risk classification study. Eligible patients with RCC could have enrolled on COG study AREN0321. The AREN0321 study examines the question of whether pediatric and adolescent patients with RCC with completely resected N+M0 disease maintain a relatively favorable outcome without adjuvant therapy, and further collects treatment response data and outcome data for all enrolled patients. AREN0321 just recently closed and the treatment and event-free and overall survival data are not yet available. We also cannot present any long-term outcome or renal function data, which are particularly important in children and adolescents with a longer life expectancy.

pRCC typically presents at an advanced stage, with translocation morphology being the most common. LN-positive disease is common, even among patients with small associated primary tumors, and imaging sensitivity for the detection of LN metastases remains poor. In such a context, failure to sample LNs is a significant problem, resulting in incomplete staging and potentially impacting long-term survival. It is important to educate surgeons treating this population that even among patients with tumors with a lower T classification, LN sampling is fundamental and should not be omitted for "younger" patients with RCC, perhaps inclusive of young adults managed in adult RCC clinics.

The data generated from the current study help to lay the ground work for future studies investigating optimal medical and surgical therapy for pediatric, adolescent, and young adult patients with RCC. The COG and the Eastern Cooperative Oncology Group have begun planning for a joint study of tRCC across all age groups. As we work toward understanding the outcomes for LN-positive disease, the role of adjuvant medical therapy, or the role of aggressive surgical resection it is important that future studies consider the upfront surgical approach for such patients. Similarly, expanding our understanding of the histologic and biologic heterogeneity of RCC in the young, as well as improved imaging sensitivity for metastatic disease, will likely improve our management, both surgical and medical, as surgical aggressiveness is refined and newer targeted therapies are applied.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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