The Complete Spectrum of Infiltrative Renal Masses: Clinical Characteristics and Prognostic Implications

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OBJECTIVE To analyze the full spectrum of patients presenting with radiologically-identified infiltrative renal masses (IRMs), including those managed surgically or otherwise, with focus on clinical presentation/prognosis.

METHODS All 280 patients presenting with radiologically-identified renal mass with infiltrative features (2008-2017) were retrospectively reviewed. Poorly-defined interface between tumor and parenchyma and irregular shape (nonelliptical) in one or more distinct/unequivocal areas were required for classification as IRM. IRM was confirmed in 265 and clinical characteristics and outcomes were assessed.

RESULTS Median age/tumor size were 65-years/6.9 cm, respectively, and 225 patients (85%) were R.E.N.A.L. = 10-12. Overall, 181 patients (68%) presented symptomatically, locally-advanced cancer (cT3-T4) was observed in 176 (66%) and disseminated disease and/or lymphadenopathy (>2 cm) in 181(68%). Clinical/radiographic findings were suggestive of etiology and could direct evaluation, but were nonspecific for definitive diagnosis. Renal-mass biopsy was performed in 103 patients and diagnostic in 97 (94%). Renal surgery was only performed in 82 patients (31%) and partial nephrectomy in 3 (1.1%). Overall, 72 patients (27%) received systemic chemotherapy and 59 (22%) targeted therapy. Final-diagnosis was renal cell carcinoma in 94 patients (35%), including 49 with highly-aggressive histology (sarcomatoid/rhabdoid/collecting-duct/medullary/unclassified). High-grade urothelial-carcinoma was found in 70 (26%), and lymphoma/metastatic cancer in 26 (10%)/25 (9%), respectively. Overall, 153 patients (58%) died; 138 (52%) cancer-related at median of 5 months. The majority of patients with renal cell carcinoma, urothelial-carcinoma, and renal metastasis died, almost exclusively cancer-related, at medians of 8, 3, and 2 months, respectively.

CONCLUSION Our series includes the full spectrum of IRMs and confirms predominance of symptomatic, poorly-differentiated, highly-lethal malignancies. Our study highlights the overriding importance of identifying infiltrative features, a simple radiologic diagnosis, during assessment of renal masses. UROLOGY 130: 86−92, 2019. © 2019 Elsevier Inc.

Most renal masses are solitary, elliptical, and well encapsulated, and thus amenable to nephron-sparing approaches.[1,2] At the other end of the spectrum are infiltrative renal masses (IRMs), which exhibit poorly-defined interface with the normal parenchyma and markedly irregular shape, although the reniform contour of the kidney is often preserved.[3,4] The differential diagnosis of IRMs is diverse and includes poorly-differentiated renal cell carcinoma (RCC), urothelial carcinoma (UC), lymphoma and metastatic processes involving the kidney, and a variety of other inflammatory or infectious entities.[5-14] The aggressive biological potential of malignant IRMs and potential implications for management are generally acknowledged[15,16]; however,

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the true incidence and ultimate prognostic implications for the complete clinical spectrum of IRMs warrant further study. Most IRM studies have focused primarily on surgically managed patients or isolated diagnoses such as collecting duct or sarcomatoid RCC, and most series have been limited in numbers reflecting the relatively low incidence of IRMs.[7-14] The largest published series of IRMs to date was limited to 116 patients and did not provide oncologic outcomes or survival data.[5] Estimates for median survival based on the current literature for the most aggressive variants of IRMs, namely renal medullary carcinoma, sarcomatoid RCC, and collecting duct RCC, have been 4 months, 5-19 months, and 10-30 months, respectively.[17-21]

In late 2018, the guidelines from the Society of Abdominal Radiology were changed to recommend routine documentation of whether a renal mass is circumscribed vs infiltrative, but consensus was not unanimous and was not reached until the final round of the Delphi process.[22] Furthermore, a recent survey by Davenport et al suggested that most radiologists and urologists believe that this information is not essential.[23,24] In an effort to address knowledge gaps in this field we conducted a comprehensive analysis of *all* patients with radiologic diagnosis of IRM at our center over a 10-year timeframe with focus on differential diagnosis, modes of presentation, evaluation and management strategies, and oncologic outcomes.

MATERIAL/METHODS

Patient Population

Using our institutional review board approved database, 869 patients from our center (2008-2017) were identified whose abdominal imaging report(s) included the following words/phrases in relatively close approximation: (1) infiltrative/infiltration; *and*(2) renal/kidney; *and*(3) mass/tumor/lesion/process. Three hundred and seven reports were redundant, that is, 2 or more reports from the same patient, and in another 195 the infiltrative process was documented for another organ system, such as the lung rather than the kidney. This yielded 367 unique cases initially read as IRM by our radiologists. Forty-nine patients had ultrasound only and 38 had poor-quality imaging, leaving 280 with IRM that could be rigorously assessed with high-quality CT or MRI. Retrospective data collection included demographics, clinical/tumor characteristics, radiological features, preoperative evaluation, management, and final outcomes.

Radiologic evaluation

All 280 cases were independently reviewed by 2 radiologists (RDW/EMR) and consensus confirmed IRM in 265 patients. Initial independent assessments were concordant for 266 cases (95%) and joint review was required to reach consensus in 14 cases. All IRMs were required to have poorly-defined interface between tumor and normal parenchyma *and* markedly irregular shape (nonelliptical/nonspherical) in one or more distinct/unequivocal area(s). Radiologic analysis also focused on medial or hilar extension and whether reniform contour was preserved. Staging characteristics were also defined.

Statistical Analysis

Continuous variables were presented as medians (interquartile ranges); categorical variables as numbers (percentages). Chi-square was used for comparison of clinical symptoms or radiologic features exhibited by the various diagnostic cohorts. Univariable/multivariable analyses of clinical/pathologic/radiologic factors potentially associated with IRM-specific mortality were evaluated by Cox-proportional hazard-regression. Variables with $P \leq .2$ in univariable analysis were further analyzed in multivariable regression. All tests were 2-tailed; $P < .05$ was considered significant. Data were analyzed using SPSS-20.0(SPSS-Inc., Chicago, IL).

RESULTS

Patient Characteristics

Our review process confirmed IRM in 265 patients. Median age was 65 years, 60% were male, and 61% were active or prior tobacco users (Table 1A). The percentage of patients with hypertension, diabetes mellitus, and cardiovascular disease were 57%, 20%, and 23%, respectively. Symptomatic presentation was observed in 181 patients (68%), with hematuria (38%), abdominal/flank pain (32%), unintended weight loss (16%), and fatigue (15%) representing the most common symptoms. Median preoperative glomerular filtration rate was 64 mL/min/1.73m^2 and 117 patients (44%) presented with preoperative chronic kidney disease. Median tumor size was 6.9 cm, although tumor diameter could not be reliably measured due to indistinct contours in 25 patients. R.E.N.A.L. score was 10-12 in 225 patients (85%), and could not be defined in 11% due to indistinct borders.[25] Locally advanced clinical stage (cT3-cT4) was observed in 176 patients (66%) and disseminated disease and/or lymphadenopathy (>2cm) in 181(68%).

Radiologic Characteristics

Radiologic features are summarized in Table 2 and representative cases are illustrated in Figure 1. All IRMs were required to have poorly-defined interface with normal parenchyma *and* markedly irregular shape (nonelliptical) in at least 1 unequivocal area. Such findings were observed focally in 16% and 15% of cases, respectively, and uniformly in all other instances. Preservation of the reniform contour was observed in 209 cases (79%) and medial extension into the hilar region was seen in 182 cases (69%) (Supplementary Fig. 1). Apparent necrosis on imaging was observed in 79 patients (30%), while calcification and cystic changes were only observed in 2% and 5%, respectively. Radiographic evidence suggesting invasion of the perinephric fat, sinus fat, or renal vein was observed in 37%, 64%, and 27% of cases, respectively. The primary managing physician (urologist or medical oncologist) mentioned infiltrative features or IRM in their notes for 221 patients (83%).

Evaluation and Final Diagnosis

Final diagnoses for all patients are detailed in Table 1B. Of 94 RCC cases, 49 (52%) exhibited highly aggressive elements including sarcomatoid or rhabdoid features, collecting duct or medullary cell histology, or poorly-differentiated, unclassified RCC. The next most common diagnosis was UC followed by lymphoma or metastasis involving the kidney. There were also 2 patients with leukemia, 2 with renal sarcoma, and 6 with benign, inflammatory processes. Overall, renal mass biopsy

Table 1. Patient characteristics and final diagnosis ($n = 265$)

A. Patient characteristics	
Age (y), median (IQR)	65 (59-76)
Gender, *n* (%): male, female	158 (60), 107 (40)
Race, *n* (%):	
Caucasian, African American, other	227 (86), 29 (11), 3 (1.1)
Missing values	6 (2)
CCI scoring, *n* (%)	
0-1, 2-4, 5-11	149 (56), 66 (25), 48 (18)
Missing values	2 (0.8)
ECOG performance status, *n* (%)	
Grade 0-1, grade 2-4	171 (65), 47 (18)
Missing values	47 (18)
Hypertension, *n* (%)	152 (57)
Diabetes mellitus, *n* (%)	53 (20)
Cardiovascular disease, *n* (%)	62 (23)
Body mass index (kg/m^2), median (IQR)	26.6 (23.2-31.0)
Tobacco use, active or prior, *n* (%)	162 (61)
Symptomatic presentation, *n* (%)*	181 (68)
Preoperative GFR (mL/min/1.73m^2) (median, IQR)	64 (49-80)
Preoperative GFR <60 mL/min/1.73m^2, *n* (%)	117 (44)
Tumor size (cm), median (IQR)[†]	6.9 (5.3-9.6)
Tumor complexity, *n* (%)	
Low (R.E.N.A.L score 4-6), intermediate (7-9), high (10-12)	1 (0.4), 10 (4), 225 (85)
R.E.N.A.L could not be estimated due to indistinct tumor contour	29 (11)
Locally advanced disease (≥cT3), *n* (%)	176 (66)
Metastatic/disseminated disease or lymphadenopathy (>2 cm), *n* (%)	181 (68)
B. Final diagnosis	
RCC	94 (35)
Clear cell	39 (41)
Papillary	6 (6)
Chromophobe	0
Sarcomatoid predominant, rhabdoid predominant[‡]	11(15), 5(5)
Collecting duct carcinoma	3 (3)
Medullary RCC	3 (3)
Unclassified RCC, poorly differentiated	27 (29)
UC	70 (26)
Low grade, high grade	2 (3), 48 (69)
Missing values	20 (28)
Lymphoma, leukemia	26 (10), 2 (0.8)
Metastasis	25 (9)
Sarcoma	2 (0.8)
Benign/inflammation	6 (2)
Unknown (no biopsy and no surgery)	40 (15)

CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; GFR, glomerular filtration rate; IQR, interquartile range; RCC, renal cell carcinoma; R.E.N.A.L., (R)adius (tumor size as maximal diameter), (E)xophytic/endophytic properties of tumor, (N)earness of tumor deepest portion to collecting system or sinus, (A)nterior (a)/posterior (p)descriptor and (L)ocation relative to polar lines; UC, urothelial carcinoma.

* Symptoms included hematuria in 101 patients (38%), abdominal/flank pain in 84 (32%), unintended weight loss (>5%) in 42 (16%), fatigue in 40 (15%), fever in 12 (5%), diaphoresis in 7 (3%), palpable abdominal mass in 4 (1.5%), and other systemic symptoms in 38 (14%).

[†] Available for 240 cases; for 25 cases the renal mass was indistinct and could not be reliably measured.

[‡] Some cases had both sarcomatoid and rhabdoid features, but the predominant finding is listed.

(RMB) was performed in 103 patients and diagnostic in 97 (94%) (Supplementary Table 1).

Of 94 patients with RCC, 35 were diagnosed primarily by RMB, 11 by percutaneous biopsy of a metastatic site, and 9 by both approaches. Confirmation of RCC was based primarily on the nephrectomy specimen in 34 patients and 5 were diagnosed presumptively based on clinical/radiographic presentation.

Of 70 patients with UC, 25 were diagnosed by RMB and 20 were diagnosed endoscopically (cystoscopy and ureteroscopy) and/or through urine cytology (Supplementary Table 1), and 7 were diagnosed by biopsy of a metastasis. Diagnosis of UC was made primarily based on the nephrectomy specimen in 15 patients, and 3 patients with disseminated UC were diagnosed presumptively and managed with palliative care and hospice.

Of 26 patients with lymphoma, diagnosis was made by RMB alone ($n = 13$), by biopsy at nonrenal sites ($n = 10$), by both approaches ($n = 1$), and presumptively in 2 patients. Of 25 patients with renal metastases, diagnosis was made by RMB alone ($n = 7$), by biopsy of a nonrenal site of disease such as the primary lesion ($n = 12$), primarily from the nephrectomy specimen ($n = 1$), and presumptively based on clinical and radiologic presentation ($n = 5$).

Table 2. Radiologic characteristics*

Infiltrative renal mass: Specific characteristics†	
Poorly defined interface with normal renal parenchyma, *n* (%)	
Uniformly, focally	222 (84), 43 (16)
Irregular shape (nonelliptical), *n* (%)	
Uniformly, focally	226 (85), 39 (15)
Generally preserves reniform contour, *n* (%)	209 (79)
Mass extending medially in infiltrative manner, *n* (%)	182 (69)
Other characteristics	
Area(s) of reduced attenuation within adjacent parenchyma, venous phase, *n* (%)‡	218 (82)
Heterogeneous enhancement, *n* (%)	169 (64)
Necrosis within the mass, *n* (%)‡	79 (30)
Calcification, *n* (%)	6 (2)
Cystic component, *n* (%)	12 (5)
Radiologic staging characteristics	
Perirenal fat invasion, *n* (%)	99 (37)
Sinus fat invasion, *n* (%)	169 (64)
Renal vein invasion, *n* (%)	72 (27)
Collecting system involvement, *n* (%)	114 (43)
Regional lymphadenopathy (>2cm), *n* (%)	130 (49)
Distant metastasis, *n* (%)	130 (49)

* Many infiltrative renal masses exhibit several of the listed characteristics.
† Characteristics either uniformly or commonly seen in infiltrative renal masses that are important for the diagnosis.
‡ Necrosis within the mass refers to patches of markedly decreased attenuation irregularly interspersed throughout a strongly enhancing tumor mass. In contrast, areas of reduced attenuation within the adjacent parenchyma represent regions in which malignant infiltration appears to be replacing the normal parenchyma leading to modestly reduced attenuation across a broader front. Reduced attenuation in this setting appears to be due to partial replacement of the normal parenchyma, which tends to be strongly enhancing under normal circumstances.

Relationships of Clinical, Radiologic, and Laboratory Findings With Final Diagnosis

Potential correlations of various factors with the final diagnosis of IRM are evaluated in Supplementary Table 2. Hematuria was most common in UC patients and least common with lymphoma, leukemia, or metastasis (*P* values ≤.03). Preservation of reniform contour was less common in RCC patients (*P* values ≤.003). Medial extension was less common in lymphoma, leukemia, or metastasis patients (*P* values <.001). While these considerations were suggestive of various etiologies none was specific enough for definitive diagnosis.

Lymphocyte/monocyte ratios, which distinguished RCC from UC in a previous study,[5] were 1.82 for patients with RCC, 1.63 for UC, and 1.46 for lymphoma, leukemia or metastasis, with *P* values for all comparisons ≥.24.

Treatment and Outcomes

Treatment and outcomes are reviewed in Table 3. Renal surgery was only performed in 82 patients (31%), representing 1.3% of patients managed with renal cancer surgery at our center in this timeframe. Renal cancer surgery was most commonly performed

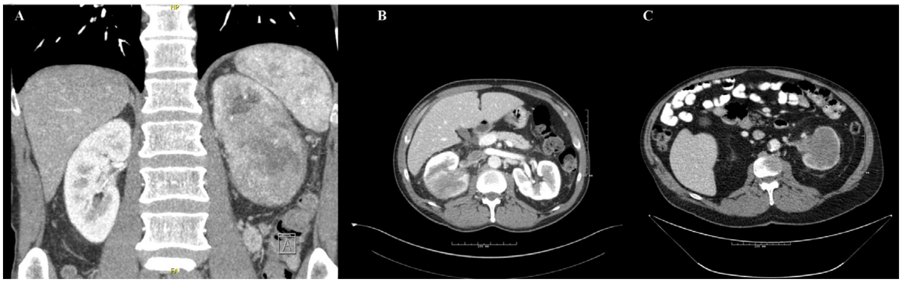

Figure 1. Representative cases of infiltrative renal masses (IRMs). (A) A 57-year-old man presented with hematuria and CT revealed an extensive left IRM generally preserving the reniform contour. Metastatic disease was also observed, and open cytoreductive radical nephrectomy demonstrated locally advanced rhabdoid RCC with nodal involvement. The patient died 7 months later with progressive decline in performance status that precluded additional therapy. (B) A 54-year-old man presented with abdominal pain and hematuria and CT demonstrated a right IRM that generally preserves the reniform contour. Level 2 IVC thrombus was also identified and RCC was presumed. Right radical nephrectomy and IVC thrombectomy was performed, but the final pathology demonstrated a poorly-differentiated urothelial carcinoma. The patient received adjuvant systemic chemotherapy but died 12 months later after disease recurrence and progression. (C) A 65-year-old man with a history of nonsmall cell lung cancer underwent CT demonstrating an asymptomatic IRM of the left kidney that was proven to be a renal metastasis. The mass was infiltrative with preservation of the reniform contour. The patient died 11 months later despite treatment with systemic chemotherapy.

for patients with RCC ($n = 47$) or UC ($n = 30$). Partial nephrectomy was only performed in 3 patients (1.1%) in this series. In addition, 72 patients (27%) received systemic chemotherapy, 59 (22%) targeted therapy, and 39(15%) radiation therapy, mostly to other organ systems for palliative purposes. Systemic chemotherapy was mostly used for patients with UC, lymphoma, or metastasis, and targeted therapy for patients with RCC (Table 3). Immunotherapy was also used in 17 patients, mostly for patients with RCC or UC.

Table 3. Treatment and final outcomes ($n = 265$)

Renal surgery, *n* (%)	82 (31)
RN*/PN, *n* (%)	79 (96)/3 (4)
Open/MIS, *n* (%)	50 (61)/32 (39)
Resection aborted	1 (1)
EBL (mL), median	300
Intraoperative blood transfusion, *n* (%)	14 (17)
Postoperative complication (Clavien grade ≥3), *n* (%)	6 (7)
Systemic chemotherapy, *n* (%)	72 (27)
RCC ($n = 94$)	7 (7)
UC ($n = 70$)	27 (39)
Lymphoma ($n = 26$)	20 (77)
Metastasis ($n = 25$)	12 (48)
Others ($n = 50$)	6 (12)
TKI or mTOR inhibitor, *n* (%)	59 (22)
RCC ($n = 94$)	51 (54)
UC ($n = 70$)	3 (4)
Metastasis ($n = 25$)	1 (4)
Others ($n = 50$)	4 (8)
Immunotherapy, *n* (%)	17 (6)
RCC ($n = 94$)	9 (10)
UC ($n = 70$)	6 (9)
Metastasis ($n = 25$)	2 (8)
Radiotherapy for renal mass, *n* (%)	2 (0.8)
Others ($n = 50$)	2 (4)
Radiotherapy to other organ systems, *n* (%)	37 (14)
RCC ($n = 94$)	20 (21)
UC ($n = 70$)	4 (6)
Metastasis ($n = 25$)	10 (4)
Others ($n = 50$)	3 (6)
Final status, *n* (%)	
Dead from malignancy involving kidney, overall	138 (52)
RCC ($n = 94$)	51 (54)
UC ($n = 70$)	41 (59)
Lymphoma ($n = 26$)	9 (35)
Metastasis ($n = 25$)	19 (76)
Other malignancy ($n = 44$)[†]	18 (42)
Dead of unrelated causes	15 (6)
Alive	83 (31)
Missing follow-up	29 (11)
Follow-up (mo), median (IQR)	6 (1-17)
Time from diagnosis to death from infiltrative renal malignancy (mo), median (IQR), overall ($n = 138$)	5 (1-10)
RCC ($n = 51$)	8 (4-16)
UC ($n = 41$)	3 (2-11)
Lymphoma ($n = 9$)	7 (1-8)
Metastasis ($n = 19$)	2 (0-10)
Other malignancy ($n = 18$)	1 (0-5)

EBL, estimated blood loss; MIS, minimally invasive surgery; mTOR, mammalian target of rapamycin; PN, partial nephrectomy; RN, radical nephrectomy; TKI, tyrosine kinase inhibitor.
* Including 25 nephroureterectomies.
† Excluding 6 cases with pathologically proven benign lesions.

Outcomes are also shown in Table 3. Median follow-up was 6 months and 153 patients (58%) were deceased. Overall, 138 patients died from malignancy (52%) with median time from diagnosis to cancer-related death of only 5 months. A majority of patients with RCC, UC, and metastasis to the kidney were deceased, almost exclusively cancer-related, and oncologic outcomes in all cohorts were uniformly poor (Table 3). Median time from diagnosis to cancer-related death was 8 months or less in all of the malignant cohorts under study.

Given the poor oncologic outcomes in all cohorts, pathologic diagnosis (RCC vs UC vs lymphoma vs renal metastasis vs other malignancy) did not correlate with cancer-specific mortality (Supplementary Table 3). Factors associated with cancer-specific mortality on univariable analysis were hematuria, fatigue, unintended weight loss, presence of metastatic disease or lymphadenopathy, or necrosis on imaging. On multivariable analysis predictors included hematuria, weight loss, and presence of metastatic disease or lymphadenopathy.

COMMENT

Most IRM studies have focused primarily on isolated diagnoses and/or surgically managed patients, thus providing a potentially biased perspective about IRMs.[5-16] Our study provides a more robust picture of IRMs by incorporating all patients presenting with a radiologically-documented infiltrative renal lesion over a 10-year timeframe, with no restrictions, and with comprehensive analysis of clinical, pathologic, and prognostic characteristics. Our data demonstrate that IRMs are typically symptomatic, locally advanced, and/or disseminated at time of diagnosis. Less than one-third of IRM patients were surgical candidates. Surgery was mostly performed for patients with RCC or UC, but even in these cohorts, only 50% and 43%, respectively, were managed with nephrectomy. IRMs were almost universally high-complexity and partial nephrectomy was only utilized in 3 patients (1.1%) in this series. Median time to IRM-related death was only 5 months, despite aggressive therapy in most patients. The majority of patients with RCC, UC, and renal metastasis died, almost exclusively cancer related, but oncologic outcomes in all cohorts were uniformly poor, and median time to cancer-related death was 8 months or less in all of the cohorts under study.

Oncologic outcomes in our study were more adverse than previous IRM series, likely due to inclusion of the full spectrum of patients with this diagnosis. The distinctive features of IRMs stand in stark contrast with the great majority of renal masses, which are typically asymptomatic, well encapsulated, amenable to nephron-sparing approaches, and associated with a favorable prognosis.[1,2]

As expected, the differential for IRMs in our series was diverse, primarily including poorly-differentiated RCC, UC, lymphoma, and metastasis and thus presenting diagnostic challenges. Clinically, presence of hematuria was most suggestive of UC, and at the other extreme, was particularly uncommon in patients with lymphoma/metastasis. Preservation of reniform contour was observed for most patients with UC (93%) or lymphoma/metastasis (85%), while this was only found in 60% of RCC patients.

Medial extension into the hilar region was common for RCC (80%) and UC (86%) but less common for lymphoma/metastasis (42%). While our study suggests potential ways to differentiate the various IRM diagnoses, these findings do not carry enough sensitivity/specificity to render definitive diagnoses. Of note, lymphocyte/monocyte ratios, which distinguished RCC from UC in a previous study,[5] were not significantly different for patients with RCC, UC, or those with other IRM-related diagnoses.

For more definitive diagnosis, RMB was performed in 103 patients and diagnostic in 97 (94%), a much higher yield than reported for conventional renal masses.[1] For RCC, most cases were diagnosed by RMB and/or percutaneous biopsy of a metastatic site, although about a third were diagnosed primarily from the nephrectomy specimen. For UC, almost half were diagnosed by RMB and/or percutaneous biopsy of a metastatic site, and 21% were diagnosed primarily from the nephrectomy specimen. In contrast, only 28% were diagnosed based on cytology or endoscopic evaluation (cystoscopy and ureteroscopy). This suggests that UC was not anticipated in many patients in this series, highlighting the diagnostic dilemmas that IRMs can present. Lymphoma was diagnosed by biopsy of nonrenal sites in 11 patients or by RMB in most of the remaining patients. Lymphoma was not diagnosed from the nephrectomy specimen in this series, suggesting that this particular diagnosis was suspected in most cases. In this manner the kidney could be preserved to facilitate administration of systemic therapies. Similarly, most metastases to the kidney were diagnosed by biopsy of the primary tumor or RMB, with only one such diagnosis made from the nephrectomy specimen. All other diagnoses were made from the nephrectomy specimen or presumptively based on clinical presentation.

There has been no established definition of IRM, although in previous studies renal lesions with ill-defined interface with the normal parenchyma were generally referred to as IRMs.[3-14] In this study, we defined IRMs as tumors that have "poorly-defined interface with the normal parenchyma *and* markedly irregular (nonelliptical) shape in one or more distinct/unequivocal areas." This was based on the hypotheses that the most aggressive component of the lesion may determine the prognosis, and that lack of a well-defined interface likely reflects an invasive/aggressive tumor biology that is not observed in most renal tumors. We found that all such tumors also had nonelliptical shape in at least 1 distinct area so this was also included in our definition. In our analysis, infiltrative features were only focal in 15%-16% of IRMs, but a similarly poor prognosis was observed in such patients, confirming the clinical relevance of focal IRMs. The biologic factors that account for infiltrative features on imaging will require further study, and may vary dependent upon the tumor type. For RCC, The Cancer Genome Atlas and other genomic analyses have identified CDKN2a alterations and a CpG island methylator phenotype as particularly aggressive,[26,27] and one might hypothesize that such genetic characteristics may associate with the infiltrative phenotype, at least for RCC.

In our series, renal surgery was performed for 82 patients with IRMs, representing 1.3% of all patients managed with renal cancer surgery at our center in the same timeframe. However, 183 IRM patients (69%) did not have renal cancer surgery, and the denominator for these patients, who were managed in a variety of ways (eg, systemic therapy, radiation therapy, and palliative care) cannot be reliably estimated. To some extent, the diagnosis of IRMs can be subjective, as not all cases are entirely "black or white." All cases in our series were reviewed by 2 radiologists and their initial independent assessments were concordant for all but 14 cases (5.0%), and further review of these led to consensus classification of 5 as IRM and 9 as non-IRM. Also, in our series, we reclassified 15 cases (5.4%) from the original 280 imaging reports describing IRM, essentially representing false positives. Of course, there may have also been "false negative" cases, that is, patients with an IRM that was either not recognized by the radiologist and/or not commented upon in the report. Our study design does not allow us to estimate the frequency of these events. A recent report demonstrated that only a minority of radiologists routinely document whether a renal mass is encapsulated vs infiltrative, and only 48% of radiologists and 32% of urologists believe that this information is essential.[23,24] Further study, ideally prospective, will be required to determine the true incidence of IRMs.

Previous studies have demonstrated that certain descriptors specifically related to the appearance of an enhancing renal mass on imaging can have important prognostic implications, independent of staging characteristics.[28] A prototype for this is cystic features, with several studies showing that when cystic features are identified on imaging within an enhancing renal mass most such lesions tend to exhibit relatively limited aggressiveness.[28-30] Strong consideration for active surveillance or nephron-sparing approaches have been advocated for such lesions, which are now commonly referred to as "cystic RCC" in the urologic lexicon.[1,30] Our study suggests that the presence of infiltrative features within an enhancing renal mass also has important prognostic implications, and defines another distinct cohort of radiologically-identified patients with renal masses, namely those with IRMs.

Our study has limitations including retrospective design and a study population that was derived from a single tertiary-care center, which could affect incidence and generalizability. Our study only included patients with high-quality cross-sectional imaging (CT or MRI) and may not be generalizable beyond this setting. Contrast enhanced ultrasound was not performed on at our center during the timeframe of this study, and while positron emission tomography/CT scans were occasionally obtained for metastatic evaluation, they were not incorporated into our assessment of infiltrative features. Clinical follow-up was limited although this was primarily due to rapid cancer progression leading to death within a matter of months in many patients. Heterogeneity of diagnoses is another limitation of our study, but our data support common features among all of the pathologic cohorts that constitute IRMs, in particular symptomatic presentation, frequent dissemination, and poor prognosis that was observed in each cohort. More specific analysis of each cohort is currently in progress and will further improve our knowledge about IRMs.

Strengths of our study include central radiologic review and a large, consecutive patient population, with no exclusions, and comprehensive analysis that includes clinical, radiologic, pathologic, and prognostic considerations, thereby providing a more complete perspective about IRMs, with focus on radiologically documented IRMs.

CONCLUSION

Our series represents the complete spectrum of radiologically-identified IRMs and confirms predominance of poorly-differentiated RCC, UC, and metastatic processes, and despite aggressive therapy, a strikingly poor prognosis was observed. Our data highlight the fundamental differences between infiltrative and non-IRMs and support recent recommendations that templates for radiologic reporting should routinely document infiltrative features when present. Future studies with more detailed analysis of each diagnostic cohort will be needed to further advance our understanding of IRMs.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.04.033.

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