Long-Term Outcomes of Patients With Low Grade Cystic Renal Epithelial Neoplasms

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OBJECTIVE To report on the long-term oncologic outcomes of 3 subtypes of low grade cystic renal epithelial neoplasms—multilocular cystic neoplasm of low malignant potential (MCLMP), cystic clear cell RCC (ccRCC), and cystic clear cell papillary RCC (ccpRCC), following 2016 reorganization by the World Health Organization.

MATERIALS AND METHODS A total of 3865 patients underwent radical or partial nephrectomy for unilateral, sporadic ccRCC between 1970 and 2010, of which 145 had previously been classified as cystic ccRCC. One genitourinary pathologist, blinded to outcome, rereviewed and reclassified the specimens by 2016 WHO criteria. Oncologic outcomes were estimated using the Kaplan-Meier method.

RESULTS Of 145 specimens, 18 (12%) were classified as MCLMP, 95 (66%) cystic ccRCC, and 32 (22%) cystic ccpRCC. Those with MCLMP were more likely female (61% vs 29% vs 31%, $P = .03$) with larger tumors (median 4.6 cm vs 3.0 cm vs 2.3 cm, $P = .02$) compared to those with cystic ccRCC and cystic ccpRCC, respectively. Only 2% of cystic ccRCC had tumor necrosis or grade 3 nucleoli present. Median follow-up for survivors was 10.3 years (interquartile range 7.4-14.9). Overall, 1 MCLMP, 5 cystic ccRCC, and 4 ccpRCC recurred during follow-up. Ten- and 20-year cancer-specific survival was 100% across all subtypes.

CONCLUSION In a large cohort of patients previously classified as cystic ccRCC with pathologic rereview and long-term follow-up, we noted that MCLMP is the least common subtype of low grade cystic renal epithelial neoplasms. Regardless, all subtypes are associated with an excellent long-term prognosis following surgical resection. UROLOGY 133: 145–150, 2019. © 2019 Elsevier Inc.

In 2019, it is estimated that there will be 73,820 new kidney cancer diagnoses, of which clear cell renal cell carcinoma (ccRCC) remains the most common histologic subtype.[1-3] However, the classification of renal neoplasms has undergone significant change as our understanding of basic morphology, immunohistochemistry, and molecular pathology has advanced.[4] Although ccRCC is associated with a poorer prognosis compared to other subtypes, a small percentage of these tumors (1%-2%) are considered cystic ccRCC.[5,6]

In 2004, the World Health Organization (WHO) defined cystic ccRCC as "a tumor composed of numerous cysts, the septa of which contain small groups of clear cells indistinguishable from grade I clear cell carcinoma."[7] This distinct ccRCC subtype accounts for <5% of all RCCs and has been reported to have a favorable prognosis in multiple retrospective studies.[5-14] Because of these findings, the International Society of Urologic Pathology (ISUP) recommended that multicystic ccRCC be renamed multilocular cystic neoplasm of low malignant potential (MCLMP) following their 2012 Vancouver consensus conference.[4] In addition, they recommended that 5 new epithelial malignancies be added to the 2004 WHO histologic classification of kidney tumors, including clear cell (tubulo) papillary RCC.[4]

Subsequently, the 2016 WHO classification of renal tumors included both MCLMP and clear cell papillary RCC (ccpRCC) as separate subtypes of renal epithelial neoplasms, both considered to have borderline or uncertain behavior.[15] In addition, both ccRCC and ccpRCC may demonstrate a predominately cystic morphology.[16] Recently, Raspollini et al reported that low malignant potential lesions comprise 7% of masses less than 4 cm and 3.7% between 4 and 7 cm.[17] We previously reported on 85 patients at our institution found to have cystic ccRCC following extirpative surgery.[18] Notably in that series, renal cystic tumors composed of cysts lined by a single layer of cells without clusters or nodules of clear cells within the cyst walls were not considered cystic ccRCC.[18] In most instances, these were either simple

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renal cortical cysts or multilocular cysts.[18] Herein, we provide a comparison of 145 patients with low grade cystic renal epithelial neoplasms—MCLMP, cystic ccRCC, and cystic ccpRCC—with long-term oncologic outcomes.

MATERIALS AND METHODS

Patient Selection

Following Institutional Review Board approval, the Mayo Clinic Nephrectomy Registry was queried to identify 3865 patients treated with radical or partial nephrectomy for sporadic, unilateral ccRCC between 1970 and 2010. Of these, 152 were classified as cystic ccRCC and 145 (95%) had pathologic specimens available for rereview.

Clinical Features

Clinical features studied included age, sex, race, smoking status, Charlson score, body mass index (BMI), Eastern Cooperative Oncology Group (ECOG) performance status, surgical approach, and radiographic evidence of a cystic tumor or the presence of indeterminate cysts.

Pathologic Features

Pathologic features collected included histologic subtype, tumor size, the 2018 American Joint Committee on Cancer primary tumor, regional lymph node, and distant metastases classifications,[19] WHO/ISUP grade, coagulative necrosis,[20] and presence of sarcomatoid differentiation. To obtain the pathologic features in accordance with 2016 WHO guidelines,[15] 1 genitourinary (GU) pathologist (J.C.C.) rereviewed the microscopic slides from all specimens previously classified as cystic ccRCC without knowledge of patient outcome.

Pathologic Subtypes

In accordance with the 2016 WHO reclassification, MCLMP were defined during pathology rereview by cysts lined by a single (rarely multiple) layer of epithelial cells with abundant clear cytoplasm and low grade nuclear features (WHO/ISUP grade 1 or 2).[15] On low power, they may closely resemble cystic ccRCC (Fig. 1A). The septae of the cysts are thin and contained nonexpansile clusters of clear cells (Fig. 1B).[15] Nodular hyalinization, hemosiderin deposition, and stromal neovascularization were absent.[15]

Cystic ccRCC were characterized by cysts which comprised ≥75% of the tumor volume with variably fibrotic septae lined by a single or multiple layers of clear cells (Fig. 2A). Tumors with degenerative features and Scattered cysts were not considered cystic clear cell ccRCC. Expansile nodules of clear cells were present (Fig. 2B), as were degenerative features including hyalinization, hemosiderin deposition, and neovascularization in loose stroma.

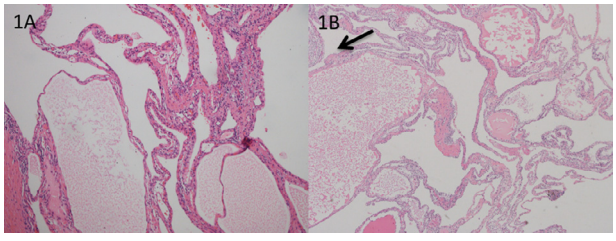

Figure 1. (**A**) Cystic ccRCC indistinguishable from MCLMP in this field. (**B**) MCLMP. The tumor is composed entirely of thin walled cysts lined by epithelial cells with grade 1 nuclei and clear cytoplasm. A nonexpansile cluster of clear cells is focally present in a septum (arrow). (Color version available online.)

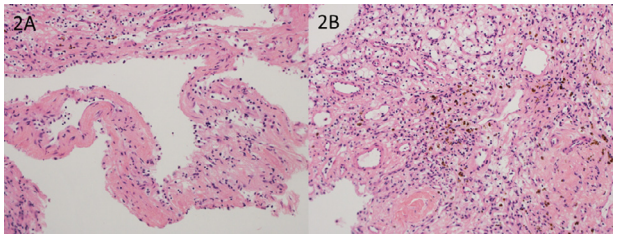

Figure 2. (**A**) Cystic ccRCC demonstrating numerous cysts lined by single layers of bland clear cells. (**B**) Area taken from a solid area within the cyst wall demonstrating both expansile nests of clear cells, required for the diagnosis of cystic ccRCC as well as the degenerative changes—hemosiderin, inflammation, and fibrosis, and expansile nest of clear cells which distinguish it from MCLMP. (Color version available online.)

Cystic ccpRCC tumors were composed of variably sized cystic and solid areas (Fig. 3A), with low-grade features (WHO/ISUP grade 1 or 2), and clear epithelial cells arranged in tubules and papillae.[15] Solid areas were either fibrous or contained bundles of smooth muscle (Fig. 3B) while the epithelial cell nuclei were oriented toward the lumen of the tubules and cysts (detached from the basement membrane) (Fig. 3C).[15] Degenerative features may be present, but not as common as in cystic ccRCC.

Statistical Methods

The clinical and pathologic features studied were summarized with medians and interquartile ranges or frequency counts and percentages. Comparisons of features among the 3 subtypes were evaluated using Kruskal-Wallis, chi-square, and Fisher exact tests. Oncologic outcomes including local recurrence free

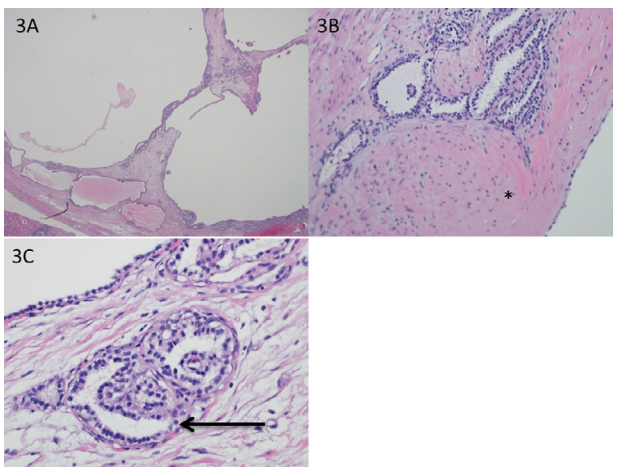

Figure 3. (**A**) Cystic ccpRCC with cyst formation on low power view. (**B**) Fibromuscular component (asterisk) of cystic ccpRCC cyst wall. (**C**) Cystic ccpRCC demonstrating that in more solid areas, tubules are present with nuclei oriented toward the luminal (apical) surface (arrow). (Color version available online.)

survival, contralateral recurrence free survival, metastasis-free survival, and cancer-specific survival (CSS) were estimated using the Kaplan-Meier method. The duration of follow-up was calculated from the nephrectomy date to the recurrence, metastases, death, or last follow-up date. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC). All tests were 2-sided and *P*-values <.05 were considered statistically significant.

RESULTS

A total of 145 (4%) patients with low grade cystic renal epithelial neoplasms were identified among the 3865 ccRCC patients studied. Of these, 18 (12%) were classified as MCLMP, 95 (66%) were cystic ccRCC, and 32 (22%) were cystic ccpRCC. A comparison of clinical and pathologic features is shown in Table 1. Those with MCLMP were more likely female (61% vs 29% vs 31%, *P* = .03) and with larger tumors (median 4.6 cm vs 3.0 vs 2.3, *P* = .02) compared to those with cystic ccRCC and cystic ccpRCC, respectively. Patients with cystic ccpRCC were more likely to have higher ECOG scores (ECOG ≥1: 23% vs 10% vs 0%, *P* = .03) and diminished renal function (median eGFR: 65.1 mL/min vs 73 vs 77, *P* = .02) than those with cystic ccRCC and MCLMP, respectively.

In terms of pathologic features, patients with MCLMP had a higher pathologic tumor (pT) stage (≥pT1b: 71% vs 34% vs 25%, *P* = .02) compared to those with cystic ccRCC and cystic ccpRCC, respectively. While 98% of tumors were considered low grade, MCLMP were more likely to be grade 1 compared to cystic ccRCC and cystic ccpRCC (67% vs 33% vs 38%, *P* = .02). Two patients (2%) with cystic ccRCC had high grade tumors and 2 (2%) demonstrated coagulative necrosis.

At last follow-up, 60 of the 145 patients had died, although only 1 patient died from RCC after experiencing distant

Table 1. Comparison of clinical and pathologic features among patients with MCLMP, cystic ccRCC, and cystic ccpRCC, N=145

	MCLMP N=18	*Cystic ccRCC N=95*	*Cystic ccpRCC N=32*	*P-value*[1]
Median age at surgery (years) (IQR)	55 (42-61)	57 (45-68)	63.5 (55-71)	0.06
Median BMI (kg/m^2) (IQR)	30.1 (28.1-31.9)	29.5 (25.3-33.6)	28.3 (26.4-32.5)	0.8
Median Charlson score (IQR)	0.5 (0-1)	1 (0-2)	1.5 (0-2)	0.6
Median eGFR (mL/min/1.73m^2) (IQR)	77.3 (66.6-91.2)	72.7 (57.2-85.6)	65.1 (51.1-76.4)	0.02
Sex *(%)*				
Female	11 (61)	28 (29)	10 (31)	0.03
Race *(%)*				
White	17 (94)	82 (96)	24 (92)	0.4
Black or African American	1 (6)	2 (2)	1 (4)	
American Indian/Alaskan Native	0	0	1 (4)	
Other	0	1 (1)	0	
Smoking history *(%)*				
Never	4 (24)	30 (33)	13 (42)	0.2
Current	8 (47)	20 (22)	8 (26)	
Former	5 (29)	42 (46)	10 (32)	
ECOG *(%)*				
0	18 (100)	82 (90)	23 (77)	0.03
1	0	8 (9)	5 (17)	
2	0	1 (1)	1 (3)	
3	0	0	1 (3)	
Median Tumor size (cm) (IQR)	4.6 (3.0-6.0)	3.0 (2.0-5.0)	2.3 (1.7-4.2)	0.02
2018 pT				
pT1a	5 (29)	62 (66)	24 (75)	0.02
pT1b	11 (65)	17 (18)	7 (22)	
pT2a	1 (6)	10 (11)	0	
pT2b	0	2 (2)	1 (3)	
pT3a	0	3 (3)	0	
2018 pN				
pNX	17 (94)	90 (95)	30 (94)	1.0
pN0	1 (6)	5 (5)	2 (6)	
pN1	0	0	0	
M1	0	0	0	NA
ISUP Nuclear Grade				
1	12 (67)	31 (33)	12 (38)	0.02
2	6 (33)	62 (65)	20 (63)	
3	0	2 (2)	0	
Coagulative tumor necrosis	0	2 (2)	0	1.0
Sarcomatoid differentiation	0	0	0	NA
Radiographically cystic *(%)*	14 (78)	51 (54)	21 (70)	0.07

[1] Obtained using Kruskal-Wallis, chi-square, and Fisher exact tests.

metastases to the lungs, bone, and brain 22 years after surgery. This patient underwent nephrectomy for a pT2aNxM0, grade 2, cystic ccRCC without necrosis. The median duration of follow-up for the 85 patients who were still alive at last follow-up was 10.3 years (interquartile range 7.4-14.9). Oncologic outcomes are summarized for the 3 subtypes in Supplementary Table 1. Thirteen recurrence events occurred in 10 patients during follow-up. In total, 4 of the 32 patients with cystic ccpRCC experienced a recurrence event (1 contralateral recurrence and metastases, 1 ipsilateral and contralateral recurrence, 1 ipsilateral recurrence, and 1 contralateral recurrence) compared to 1 of the 18 patients with MCLMP (1 contralateral recurrence) and 5 of the 95 patients with cystic ccRCC (1 distant metastases and subsequent death from RCC at 22 years postsurgery, 1 ipsilateral and contralateral recurrence, 1 ipsilateral recurrence, and 2 contralateral recurrence). Ten- and 20-year CSS was 100% for all subtypes.

DISCUSSION

We found here, in a large institutional dataset with long-term follow-up, that approximately 4% of patients with surgically treated ccRCC had low grade cystic epithelial renal masses.[18] Upon pathologic rereview, more than one-third (34%) of these tumors were reclassified as either MCLMP (12%) or cystic ccpRCC (22%). In the largest study to date with pathologic rereview we offer a comparison of 3 types of low grade cystic epithelial renal masses—MCLMP, cystic ccRCC, and cystic ccpRCC.

We previously reported on the indolent nature of cystic renal neoplasms, finding 100% CSS at 5 years among 85 patients with cystic ccRCC.[18] In the current study, we find that 20 year CSS is 100% regardless of subtype. This is consistent with previously reported favorable outcomes in the literature for MCLMP and cystic ccRCC in which multiple publications report no recurrences with greater than 5 years of follow-up.[11,12,21-23] For example, Li et al retrospectively identified 76 patients with MCLMP with no recurrences at a median of 52 months of follow-up.[23] Likewise, Bhatt et al analyzed 168 cases of cystic RCC from 1995 to 2008, and after excluding cystic necrosis, found that 57% were MCLMP and 41% were cystic ccRCC.[22] Notably, no centralized pathologic rereview was performed so classification is based solely on the pathologist's written description of the microscopic specimen.[22] Regardless, at a median of 9.75 years of follow-up overall survival and CSS were 82.1% and 100%, respectively, with no impact of tumor size, grade, or stage.[22] Here, in patients with MCLMP, we identified a single patient who subsequently developed a contralateral renal neoplasm, although we do not know whether this was a new primary tumor or a recurrence of the previously treated MCLMP.

Cystic ccpRCC is a recently described entity that may share overlapping features with MCLMP: (1) predominantly multilocular cystic architecture, (2) cysts lined by bland optically clear cells with low nucleolar grade, and (3) the presence of nests, cords, or single cells of clear cells within the septae.[16] However, micropapillary projections, solid areas as well as a tubular architecture, and nuclear alignment away from the basement membrane distinguish cystic ccpRCC from MCLMP.[16] Recently, Raspollini et al reported on outcomes of low grade epithelial neoplasms, including 13 ccpRCC and 12 MCLMP, and found no recurrences with 18 months of follow-up.[17] We find here that while CSS is excellent for surgically treated cystic ccpRCC, there were multiple recurrence events over 20 years of follow-up. Careful differentiation of MCLMP and cystic ccpRCC is needed in order to ensure appropriate postoperative surveillance.

In our series, we found that patients with MCLMP were more likely to be younger females with excellent performance status and larger tumors as compared to those with either cystic ccRCC or cystic ccpRCC. Pathologically, those with MCLMP had a higher tumor stage, strictly due to size. However, similar to Bhatt et al, we found the difference in tumor stage was not associated with an adverse impact on survival.[22] Patients with MCLMP should be reassured that their long-term prognosis is excellent. Although histologically different from MCLMP, multilocular cystic nephroma has a second peak among females during their fifth decade of life.[24] Given the similar age/gender profile and uncertainty regarding the cells of origin of MCLMP, future research regarding genetic overlap such as DICER-1 or hormone receptor status (estrogen/progesterone) may be warranted.[24]

All 3 cystic entities are pathologic diagnoses, and in fact do not universally have cystic features on imaging in our study. Pathologically, the main differential diagnosis includes RCC with extensive cystic change, cystic nephroma, and RCC with extensive cystic necrosis.[4] Differentiating these entities is vital as RCC with extensive cystic necrosis has been shown to behave aggressively.[20,25] Likewise, even among the low grade neoplasms in this series, we note distant metastatic disease and death from RCC amongst non-MCLMP patients. Previously, You et al attempted to identify preoperative imaging features predictive of MCLMP compared to ccRCC.[26] They found that benign cysts and MCLMPs were more likely to be classified as Bosniak III lesions while the mean Hounsfield unit during the corticomedullary phase was significantly higher in ccRCCs.[26] A mean Hounsfield unit ≥38 had a 83% sensitivity and 80% specificity for predicting ccRCC vs benign lesions or MCLMPs.[26] Ultimately, given the excellent prognosis following surgical resection and current inability to definitively identify MCLMP based on preoperative factors alone, we do not believe that nonoperative management or observation for all patients with cystic lesions is currently supported by the literature. However, lesions identified as highly likely to be MCLMP can be considered for nephron-sparing surgery, regardless of size.[22,27]

We note that in our series of patients with cystic ccRCC, only a small percentage of them met criteria for MCLMP on pathologic rereview, although a significant number were reclassified as cystic ccpRCC. Both

pathologic reviews were performed by the same GU pathologist, which we believe is the major strength of our analysis. We believe that as additional renal neoplasms are identified, caution must be used when interpreting retrospective data without pathologic review, whether from a single institution or national datasets.

While our study is retrospective, outcome data were prospectively collected and pathologic specimens were reviewed by a single, highly-experienced GU pathologist. We recognize that not all institutions may have access to a dedicated GU pathologist, which may limit the applicability of our findings. Our cohort comprised only those patients with an initial pathologic diagnosis of cystic ccRCC. Therefore, we may not have captured all cases of MCLMP and ccpRCC that occurred during the study time period as some MCLMP and ccpRCC may have been initially classified as other entities (ie, benign or papillary RCC). In addition, there is no standardized definition for cystic ccRCC, so care must be taken in applying these results. We used ≥75% cystic components to define cystic ccRCC in this study, but previously Tretiakova et al reported similar, excellent outcomes using ≥50% cystic as a cut point.[28] Furthermore, given the prolonged time frame during which patients were included, changes in surgical practices, advances in imaging, and changes in management approach for renal mass patients may have influenced our findings. However, we believe that the subtypes of low grade cystic epithelial neoplasms are a pathologic diagnosis that cannot be reliably made based on imaging alone. As such, future studies, ideally with prospective multicenter datasets, are needed to define the optimal surveillance and management strategies in this patient population.

CONCLUSION

MCLMP, cystic ccRCC, and cystic ccpRCC represent 3 distinct entities and should be assessed routinely on pathologic evaluation. Patients with low grade cystic renal epithelial neoplasms can expect an excellent long-term prognosis following surgical resection.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.07.017.

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