

Comparison of Survival Between Unilocular Cystic and Purely Solid Renal Cell Carcinoma

Yapeng Wang

First Affiliated Hospital of Zhengzhou University

Xiaoyu Niu

First Affiliated Hospital of Zhengzhou University

Lihui Wang

First Affiliated Hospital of Zhengzhou University

Yunlong Li

First Affiliated Hospital of Zhengzhou University

Baoping Qiao (✉ zhangyaling@zzu.edu.cn)

First Affiliated Hospital of Zhengzhou University

Research Article

Keywords: renal cell carcinoma, unilocular cystic, survival, MCRNLMP, multilocular cystic

Posted Date: December 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1139632/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Purpose

To evaluate clinicopathologic features and survival outcomes of unilocular cystic renal cell carcinoma (cRCC) compared with purely solid renal cell carcinoma (RCC), and to evaluate the oncologic aggressiveness of unilocular cRCC.

Methods

The relevant data of 957 patients with sporadic unilateral RCCs underwent surgical treatment in 2 institutions from Jan 2014 to Oct 2018 were obtained. We excluded multilocular cystic renal neoplasm of low malignant potential (MCRNLMP), RCCs with multilocular cysts and necrotic RCCs. 74 unilocular cRCCs were identified by pathology reports. We performed propensity score matching (PSM) and randomly selected 148 purely solid RCCs. The clinicopathologic features and survival outcomes were compared properly.

Results

After PSM, age, BMI, Charlson Comorbidity Index, and postoperative Chronic Kidney Disease grade were not significantly different. Both overall survival and cancer-specific survival of unilocular cRCCs were significantly better than the purely solid RCCs by the log-rank test. Twenty-five cases of solid RCCs were in the pT3 or pT4 stage, while no pT3 or pT4 tumors were found in unilocular cRCCs. Fuhrman grade, pT stage, lymphatic metastasis and tumor diameter were found to be independent prognostic factors.

Conclusion

Unilocular cRCCs have a lower Fuhrman grade and pathological stage and a better prognosis compared with solid RCC. Unilocular cRCCs still probably have lymphatic metastasis at diagnosis and may have postoperative metastasis, which is different from MCRNLMP. We recommend that the diagnosis of unilocular cRCC should be reflected in pathology reports. Different subtypes of cRCC should be taken into consideration in counseling and management.

Introduction

Cystic renal cell carcinoma (cRCC) was first defined as renal carcinoma with cystic or cystic-solid changes on imaging and confirmed by pathology and classified into 4 subtypes by Hartman et al [1].

In 2016, the World Health Organization redefined multilocular cystic renal cell carcinoma, a subtype of cRCC, as the multilocular cystic renal neoplasm of low malignant potential (MCRNLMP) based on the

excellent prognosis wherein more than 200 patients were followed up for more than 5 years without recurrence or metastasis [2-]. Some studies have also found that most of MCRNLMP have Von Hippel-Lindau (VHL) mutations and 3p deletions, which suggests that they are related to clear cell carcinoma at the molecular level [5-]. Compared with solid clear cell carcinoma, the MCRNLMP has a very distinctive histology and an excellent prognosis. In terms of tumor morphology, we can classify RCC into the following types: MCRNLMP; RCC with a multilocular cystic component (not meeting the diagnosis of MCRNLMP); unilocular cRCC and purely solid RCC.

MCRNLMP is a morphology and prognosis distinctive subtype of cRCCs and accounts for only about 1% of RCCs, while the whole cRCC accounts for 15% [2,4,9,10]. Many previous studies failed to identify it separately, but classified MCRNLMP together with all other cRCCs as the cRCC, and investigated their outcomes [11-15].

Although those studies have discovered that the cystic morphology of renal cell carcinoma (RCC) is associated with a good prognosis [11-15], other types of cRCCs actually do not have as good prognosis as MCRNLMP [7,16,17]. In that way, those previous studies have made incorrect judgments on the prognosis of many other types of cRCCs besides MCRNLMP, especially unilocular cRCCs. Few studies have previously classified this type of tumors, which are completely different from MCRNLMP, into a separate category for survival research.

In this review, we intend to analyze the clinicopathological data of unilocular cRCCs and compare it with those of purely solid RCCs to improve clinician's understanding of this subtype of cRCC and provide new perspective for clinical management decisions and follow-up for cRCCs.

1. Materials And Methods

1.1 Inclusion and exclusion criteria

The data of 993 patients was obtained from January 2014 to October 2018 at two different institutions with approval from Ethics Committee of Zhengzhou University. We excluded 16 cases of multiple RCCs (including 6 cases of VHL syndrome), 20 cases with incomplete preoperative images, 12 cases of MCRNLMP, 62 cases of RCCs with multilocular cystic component (not meeting the diagnosis of MCRNLMP), 48 cases with necrotic cysts confirmed by surgical pathology (including 9 cases misdiagnosed as true cysts by radiologists). Finally, 835 patients were included in this study, among which 74 cases were identified as unilocular non-necrotic cRCCs by surgical pathology reports and placed in group A [Figure 1]. The optimistic cut off value for determining cRCCs is different in various studies (ranging from 5% to 75%) [12,15,18], and the number of deaths in RCCs with cystic components was relatively small in our study. Therefore, we were not able to select a reliable cut off for unilocular cRCCs but included all RCCs with obvious single cysts on preoperative CT imaging and confirmed by pathology reports as non-necrotic in group A. Meanwhile, we used Stata ® to perform 1:2 propensity score matching

(PSM; Match tolerance set at 0.05, Maximize execution performance) by age, BMI, Charlson Comorbidity Index (CCI), and postoperative Chronic Kidney Disease (CKD) grade (which was evaluated from the estimated glomerular filtration rate at the 6th month) using the abbreviated Modification of Diet Renal Disease Study Group in 761 cases of pathologic confirmed solid RCCs, and randomly identified 148 patients enrolled in group B.

1.2 Image measurements

All renal lesions underwent CT scan (Philips Diamond Select Brilliance 64-Slice CT scanner) and were reviewed by experienced radiologists unaware of the clinical data. The record content included: R.E.N.A.L. score of the lesions, the respective volume of the entire tumor and cystic components calculated by computer software multiplying the area of all sections by the thickness of each layer, and tumor diameter that was the average of the diameter on each axis of the tumor. Although our study relied on pathology results to diagnose unilocular cRCC, we also required radiologists to judge the nature of cysts when reviewing CT. The criteria radiologists applied to determine the true cystic component were: 1) The CT-value in the capsule being less than 20 Hu and unmixed density at routine scan. 2) There was no obvious enhancement in the capsule during the cortical phase(≤ 40 Hu).

1.3 Statistics

All statistical analyses were conducted with SPSS®, version 26.0. Continuous variables were presented as mean \pm SD and compared by the t test. Categorical variables were described by frequencies with proportions and compared by chi-square and Wilcoxon rank sum test as appropriate. The primary end points were overall survival (OS) and cancer specific survival (CSS). The median follow-up time is 4.57 years (1.25-6.74). The overall survival (OS) and cancer specific survival (CSS) were estimated by the Kaplan-Meier curves, and differences between curves were assessed with log rank test. Moreover, cox proportional hazards models of univariable and multivariable analyses were applied to identify factors associated with cancer specific survival, expressed using hazard ratio (HR), 95% confidence interval (95% CI). Results were considered statistically significant only with $p \leq 0.05$.

2. Results

1. Clinicopathology features and radiology characteristics

Tables 1 and 2 summarize and compare the clinicopathology and radiological data of purely solid RCCs and unilocular cRCCs. After PSM, there were no significant differences in age, BMI, CCI, and postoperative CKD grade between the 2 groups. Gender composition, tumor diameter, R.E.N.A.L. score and surgical approach were not significantly different as well. The average diameter and volume of tumors in group A were 4.45 ± 1.10 cm and 100.63 ± 74.02 cm³ respectively, while those in group B were 4.59 ± 0.98 cm and 108.82 ± 69.40 cm³ respectively, and there with no significant difference ($p=0.353$, $p=0.418$). In terms of the Fuhrman grade, only 2 cases in group A were G3, and there were no G4 tumors. However, G3 and G4 tumors in group B accounted for 37.8%, and the difference between 2 groups was significant ($p \leq 0.05$).

0.001). In group A, 5 patients underwent lymphadenectomy due to preoperative CT findings of enlarged lymph nodes, and 3 of them were pathologically confirmed to have lymphatic metastasis. In group B, 20 patients underwent lymphadenectomy, of which 14 had confirmed lymphatic metastasis. In addition, 4 patients in group B were found to have distant metastases at the time of diagnosis and received palliative surgery. Sixty-six (89.2%) cases of group A were in the pT1 stage and the remaining 8 (10.8%) were in the pT2 stage. While no pT3 or pT4 tumors were found in group A. Meanwhile, 25 (16.9%) cases in group B were in the pT3 or pT4 stage. The difference between the 2 groups is statistically significant ($p=0.01$). The most common histology type in the 2 groups was clear cell carcinoma [Figure 2], but there were significantly more ($p=0.018$) cases of papillary carcinoma in group A (12%) than in group B (3%). None of the patients in the 2 groups who underwent partial nephrectomy showed positive margins in the pathology reports. We also noticed that 26 (35.1%) unilocular cysts in group A had irregularly thickened inner walls greater than 2mm and 11 (14.9%) cysts had irregular internal structures [Figure 3]. These structures only protrude into the cavity, but do not form a septum separating the cysts, which is different from the septa of multilocular cRCCs. The average cystic proportion of tumors in group A was 33.08%, and the volume of smallest cyst only accounted for 4%, while the largest accounted for 78%.

Table 1 Demographic data of unilocular cystic and solid RCC

| | Unilocular cRCC | Solid RCC | <i>P</i> value |
|---------------------|-----------------|----------------|-----------------|
| | <i>n</i> = 74 | <i>n</i> = 148 | |
| Age | 52.04±10.68 | 52.22±11.04 | <i>P</i> =0.910 |
| Gender | | | <i>P</i> =0.366 |
| Male | 52±70.3% | 95±64.2% | |
| Female | 22±29.7% | 53±35.8% | |
| Location | | | <i>P</i> =0.634 |
| Left | 42±56.8% | 79±53.4% | |
| Right | 32±43.2% | 69±46.6% | |
| BMI | 25.34±2.95 | 24.99±2.92 | <i>P</i> =0.401 |
| Surgery approach | | | <i>P</i> =0.330 |
| Partial nephrectomy | 32±43.2% | 54±36.5% | |
| Radical nephrectomy | 42±56.8% | 94±63.5% | |
| CCI | | | <i>P</i> =0.743 |
| <5 | 55±74.3% | 113±76.4% | |
| ≥5 | 19±25.7% | 35±23.6% | |
| CKD | | | <i>P</i> =0.623 |
| 1~2 | 45±60.8% | 95±64.2% | |
| 3~4 | 29±39.2% | 53±35.8% | |

Table 2 Pathology and radiology characteristics of unilocular cystic and solid RCC

| | Unilocular cRCC | Solid RCC, | <i>P</i> value |
|--------------------------|-----------------|----------------|------------------|
| | <i>N</i> = 74 | <i>N</i> = 148 | |
| Fuhrman grade | | | <i>P</i> = 0.001 |
| G1 | 33 (44.6%) | 8 (5.4%) | |
| G2 | 39 (52.7%) | 84 (56.8%) | |
| G3 | 2 (2.7%) | 45 (30.4%) | |
| G4 | / | 11 (7.4%) | |
| Metastasis | | | <i>P</i> = 0.200 |
| NOMO | 71 (95.9%) | 135 (91.2%) | |
| Greater than NOMO | 3 (4.1%) | 13 (8.8%) | |
| pT | | | <i>P</i> = 0.010 |
| 1 | 66 (89.2%) | 113 (76.4%) | |
| 2 | 8 (10.8%) | 10 (6.8%) | |
| 3 | / | 22 (14.9%) | |
| 4 | / | 3 (2%) | |
| Histology | | | <i>P</i> = 0.018 |
| Clear cell | 64 (86.4%) | 141 (95.3%) | |
| Papillary | 9 (12.2%) | 4 (2.7%) | |
| Chromophobe | 1 (1.4%) | 3 (2%) | |
| Diameter of tumor | 4.45 ± 1.10 | 4.59 ± 0.98 | <i>P</i> = 0.353 |
| mean ± SD, cm | | | |
| R.E.N.A.L. score | | | <i>P</i> = 0.971 |
| ≤ 7 | 3 (4.1%) | 5 (3.4%) | |

| | | |
|-------|------------|------------|
| 7~9 | 25 (33.8%) | 51 (34.5%) |
| 10~12 | 46 (62.2%) | 92 (62.2%) |

2.2 Survival analysis

Kaplan-Meier curves of the 2 groups as shown in Fig. 4. Both overall survival ($p=0.026$) and cancer-specific survival ($p=0.025$) of the unilocular cRCCs were significantly better than the purely solid RCCs by the log-rank test. Nineteen patients in group B died, of whom 15 died of RCCs. A patient of group B was reported to have local recurrence 2 years post-partial nephrectomy and was treated with radical nephrectomy. Lumbar metastasis was found 2 years later and currently VEGFR inhibitors treatment is being administered. In group A, only 1 patient died of lung metastasis after radical nephrectomy. Furthermore, we applied the Cox proportional hazards regression model to perform univariable and multivariable regression analysis of survival data (Table 3). The factors age, CCI, CKD grade, pT stage, lymphatic metastasis, Fuhrman grade and tumor diameter were identified to be significant predictors in univariate regression analysis of cancer-specific survival. Fuhrman grade, pT stage, lymphatic metastasis and tumor diameter were independent prognostic factors according to the multivariate analysis.

Table 3 Cox regression analysis of cancer-specific survival for 222 patients

| | Univariate | | Multivariate | |
|----------------------|---------------------|---------|------------------|---------|
| | HR(95% CI) | P Value | HR(95% CI) | P Value |
| Age | 1.10(1.05-1.16) | 0.001 | 1.06(0.85-1.32) | 0.623 |
| CCI | 1.77(1.38-1.2.26) | 0.001 | 1.11(0.56-2.22) | 0.762 |
| CKD grade | 7.91(2.30-27.17) | 0.001 | 1.33(0.34-5.26) | 0.682 |
| BMI | 0.85(0.72-1.01) | 0.07 | / | |
| Fuhrman grade | 14.63(6.50-32.93) | 0.001 | 6.36(1.08-37.63) | 0.041 |
| pT stage | 11.14(5.46-22.74) | 0.001 | 4.88(1.02-23.26) | 0.047 |
| Lymphatic metastasis | 94.09(26.43-334.92) | 0.001 | 5.75(1.19-27.77) | 0.029 |
| R.E.N.A.L. score | 2.84(0.85-9.44) | 0.089 | / | |
| Diameter of tumor | 5.59(2.94-10.64) | 0.001 | 5.86(1.44-23.89) | 0.014 |

3. Discussion

In this study, we found that unilocular cRCCs has a lower pathological stage and Fuhrman grade and a better prognosis than purely solid RCCs.

The cystic component in RCC has been the focus of scholars for a long time. Hartman first reported unilocular cRCCs and divided cRCCs into 4 categories: 1) intrinsic multiloculated growth; 2) intrinsic unilocular growth; 3) cystic necrosis; 4) origin from the epithelial lining of a preexisting simple cyst [1].

However, this classification has not been widely accepted by pathologists. Cystic necrosis, for example, is actually caused by the imbalance of tumor growth and insufficient blood supply. It is not only found in various pathological types of RCC, but also common in other malignant tumors. The existence of malignant transformation of simple cysts is still debatable and there are rare related reports. Therefore, many pathologists believe that the above two subtypes should be excluded from the subcategories of cRCC, which means that cRCC should only include the unilocular cystic and the multilocular cystic [19,20].

With the continuous increase of related researches, multilocular cRCC has gradually become the focus. Both the 2004 revised and 2016 WHO guidelines only defined multilocular cRCC without mentioning unilocular cRCC [21,4]. Although unilocular cRCC has been reflected in some studies, there is no specific study with a large sample size. Meanwhile, many studies did not emphasize the classification of cRCC subtypes. As a result, the two concepts of continuously redefined “MCRNLMP” and “cystic renal cell carcinoma” have been implemented without coming into conflict, which has caused a lot of confusion for researchers and clinicians.

In some studies, it was found that there were many papillary RCCs in unilocular cRCCs [1,22]. This is consistent with our findings. Group A had significantly more papillary RCC than group B, which is somewhat inconsistent with the findings of previous studies in that, the main histology of unilocular cRCCs in our study is clear cell carcinoma, not papillary RCCs. This discrepancy may be due to the small number of samples used in previous studies. At the same time, Hartman also noticed that a few cysts discovered on CT imaging are actually extensive necrosis and tumor necrosis is one of the negative indicators in many prognostic models of RCC [23]. In this study, we defined unilocular cRCC, which excludes necrotic cysts through surgical pathology. However, it is worth noting that it is not reliable to determine whether the cystic component is a true cyst or a necrotic cyst only through preoperative CT imaging. For instance, radiologists with more than 3 years of work experience reviewed the imaging data in this study, but among the 83 cases initially judged as true cysts, 9 cases (11%) were still pathologically confirmed as necrotic cysts. Some studies have shown that MRI may be more advantageous than CT in the differential diagnosis of true cysts [24] but due to lack of relevant imaging data, we did not investigate that.

Numerous studies on MCRNLMP have shown that the malignancy of this type of tumor is low, and no recurrence or metastasis have been reported so far [2,3]. Therefore, its definition is changed from “cancer” to “neoplasm”. However, of the 74 cases of unilocular cRCCs in our study, 1 patient died of metastasis of the RCC. Although no distant metastasis was found at the time of diagnosis, 3 cases of lymphatic metastasis were found in surgical pathology of lymphadenectomy. It can be seen that although the unilocular cRCC is less malignant than the purely solid RCC, its prognosis is not as excellent as that of the MCRNLMP defined by the WHO in 2016.

In this study, we did not set the cut off for unilocular cRCCs like other studies but included all RCCs with true cystic components. But we found that the cystic proportion of 1 case who died of RCC in group A was not low (52%), and the cystic proportion of 1 case who had lymphatic metastasis at diagnosis in group A also reached 78%. We believe that unilocular cRCCs even with a high cystic proportion also probably had lymphatic metastasis at the time of diagnosis and recurrence after surgery. Although the presence of cystic components in RCCs might predict lower malignant potential, the correlation between high cystic proportion and the mostly indolent outcome has not been fully proven, studies with larger sample sizes are needed in the future.

In previous studies conducted before and after 2016, MCRNLMP was not clearly distinguished from other types of cystic RCCs [11-15]. Given that the MCRNLMP is a rare type and was differently defined in previous studies, the true incidence of MCRNLMP was uncertain. According to some recent studies, it can be inferred that it accounts for roughly 1% of RCCs [9,10], while cRCCs account for 15% [1,25,26]. Defining the MCRNLMP as being similar with all other types of cRCCs and making survival comparison with solid RCC certainly will mask the relatively poor prognosis and relatively high malignancy of other types of cRCCs such as the unilocular cRCCs. As a result, when making clinical decisions, surgeons may underestimate the malignancy of cRCCs other than MCRNLMP. It is a bit puzzling that although the pathological stage and Fuhrman grade of 74 unilocular cRCC cases are relatively low, 3 cases (4.1%) still have lymphatic metastasis at diagnosis and the difference with that of solid RCC (8.8%) is not significant ($p=0.200$). We speculated that this may be due to the relatively small sample size. It may also be because that 3 cases of tumors were large in size. The average maximum diameter of the tumors in group A was 4.45 ± 1.10 cm, while that of 3 cases with lymphatic metastasis were 6.57cm, 6.37cm, and 6.63cm, respectively.

The excellent prognosis of MCRNLMP may suggest that the existence of the cystic component of renal carcinoma is somehow related to a favorable prognosis. According to existing researches, it can be seen that the prognosis of MCRNLMP, unilocular cRCC, and solid RCC shows a decreasing trend [7,16,17]. Therefore, the clinical treatment and follow-up decisions of them should be made pertinently. Many studies have pointed out that for MCRNLMP, nephron sparing method should be used as much as possible [27,28]. In view of the findings of this study, we recommend that unilocular cRCCs should also be treated with nephron sparing approaches when feasible. Radical nephrectomy is still needed when the tumor is large, and regional lymph nodes should be removed if the preoperative imaging shows the sign of enlarged lymph nodes. However, our proposal and specific implementation plan need to be confirmed by further prospective studies.

For most cases, the diagnosis of different subtypes of cRCC based on imaging data ultimately needs to be confirmed by postoperative pathology, which means that clinical decisions on nephron sparing or radical approaches have always been made. Clarifying that the tumor belongs to a specific subtype of cRCC can only be used as a guide for postoperative follow-up or retrieval reoperation. Therefore, it is particularly important to judge different subtypes by preoperative imaging, especially to identify MCRNLMP and necrotic cysts. Several relevant studies published may help on this issue, but there is still room for improvement in the accuracy of diagnosis [29].

There are several limitations to our study. 1). This study is retrospective in nature; the pathological features were summarized based on the surgical pathology reports. We were unable to personally obtain tumor specimens for further analysis, such as cyst fluid properties, more comprehensive immunohistochemistry, etc. 2). As a result of the intention to investigate unilocular cRCCs and because the total number and the number of cancer-specific deaths in group A were small, the optimistic cut off related to prognosis could not be calculated. 3). Twenty patients were excluded due to incomplete imaging data, which may have caused selection bias to the outcomes. 4). In order to eliminate

confounders, we performed 1:2 PSM in 761 solid RCC cases, and eventually enrolled 148 cases in the control group. Therefore, when performing Cox regression, the Goodness of Fit may be not ideal enough. Although the PSM method adopted to select matching objects is random, the solid RCC group still has the possibility of underrepresentation. However, the characteristics of solid RCC in other similar studies with larger sample size can be corroborated [7,11,12].

4. Conclusion

We reported the first large series of long-term survival of unilocular cRCCs. Compared with purely solid RCCs, unilocular cRCCs have a lower Fuhrman grade and pathological stage and a better prognosis but some patients still probably have lymphatic metastasis at the time of diagnosis and may have postoperative relapse, which is different from that in MCRNLMP. The presence of unilocular cyst should be documented in the pathology report like the multilocular one, and when making clinical decisions and follow-up plans for cRCC, the different subtypes of cRCC could be taken into consideration as a factor.

Declarations

Potential conflict of interest We have no relevant conflicts of interest.

Research involving Human Participants and/or Animals This study is a review of existing data and does not involve any studies with human participants or animals performed by other authors.

Ethics approval and Informed consent All methods in this study involving human participants were performed in accordance with the ethical standards of the institutional research committee and were permitted by Ethics Committee of Zhengzhou University, with no living animals involved. This study is a retrospective study, Ethics Committee of Zhengzhou University therefore waived the informed consent.

Acknowledgements

Baoping Qiao: Study design, Project development

Yapeng Wang: Project development, Data collection, Manuscript writing

Xiaoyu Niu: Data collection

Lihui Wang: Project development

Yunlong Li: Manuscript writing

Funding

This work was supported by the Key Technology Research and Development Program of He'nan Educational Committee (grant number: 202102310447).

Reference

1. Hartman DS, Davis CJ Jr, Johns T et al., Cystic renal cell carcinoma. *Urology* 1986; 28:145
2. Tretiakova M, Mehta V, et al., (2018) Predominantly cystic clear cell renal carcinoma and multilocular cystic renal neoplasm of low malignant potential from a low-grade spectrum. *Virchows Archiv* 473(1), 85-93
3. Warren, A.Y., Harrison, D. (2018) WHO/ISUP classification, grading and pathological staging of renal cell carcinoma: standards and controversiers. *World J Urol* 36, 1913-1926(2018)
4. Teng L, Chen J.C., et al., (2016) Multilocular Cystic Renal Cell Neoplasm of Low Malignant Potential: A Series of 76 Cancer, *Clinical Genitourinary Cancer*, Volume 14, Issue 6, e553-e557
5. S. Suzigan, R. Montironi, et al., (2006) Multilocular cystic renal cell carcinoma: a report of 45 cases of a kidney tumor of low malignant potential, *Am.J.Clin.Pathol.* 125, 217-222
6. von Teichman A, Comperat E, et al., (2011) VHL mutations and dysregulation of pVHL- and PTEN-controlled pathways in multilocular cystic renal cell carcinoma. *Mod Pathol* 24:571-578
7. Tretiakova M, Mehta V, et al., (2018) Predominantly cystic clear cell renal carcinoma and multilocular cystic renal neoplasm of low malignant potential from a low-grade spectrum. *Virchows Archiv* 473(1), 85-93
8. Warren, A.Y., Harrison, D. (2018) WHO/ISUP classification, grading and pathological staging of renal cell carcinoma: standards and controversiers. *World J Urol* 36, 1913-1926(2018)
9. Teng L, Chen J.C., et al., (2016) Multilocular Cystic Renal Cell Neoplasm of Low Malignant Potential: A Series of 76 Cancer, *Clinical Genitourinary Cancer*, Volume 14, Issue 6, e553-e557
10. S. Suzigan, R. Montironi, et al., (2006) Multilocular cystic renal cell carcinoma: a report of 45 cases of a kidney tumor of low malignant potential, *Am.J.Clin.Pathol.* 125, 217-222
11. Mazzucchelli R, Scarpelli M, Montironi R, et al., (2012) Multilocular cystic renal cell neoplasms of low malignant potential. *Anal Quant Cytol Histol* 34:235-238
12. Kuroda N, Ohe C, et al. (2012) Multilocular cystic renal cell carcinoma with focus on clinical and pathobiological aspects. *Histol Histopathol* 27(8):969-974
13. H. Moch, A.L. Cubilla, P.A. Humphrey, V.E. Reuter, WHO Classification of Tumours of the Urinary System and Male Genial Organs, fourth edition, World health Organization classification of Tumours. International agency for research in cancer, Lyon, France, 2016, pp. 11-76 Chapter 1
14. Halat S, Eble JN, et. al., Multilocular cystic renal cell carcinoma is a subtype of clear cell renal cell carcinoma. *Mod Pathol* 23:931-936
15. von Teichman A, Comperat E, et al., (2011) VHL mutations and dysregulation of pVHL- and PTEN-controlled pathways in multilocular cystic renal cell carcinoma. *Mod Pathol* 24:571-578
16. Gladell P.P, Alessia C, Caitlin M.D., (2020) Surgical pathology of cystic renal cell carcinoma: is there an overestimation of malignancy? *Diagnostic Histopathology*, Volume 26, Issue 7, 320-329

17. Westerman ME, Cheville JC, Lohse CM, et al. (2019) Long-term outcomes of patients with low grade cystic renal epithelial neoplasms, *Urology*; 133: 145-50
18. Park H.S., Monn K.C., (2011) Determination of the Cutoff Value of the Proportion of Cystic Change for Prognostic Stratification of Clear Cell Renal Cell Carcinoma, *The Journal of Urology*, Volume 186, Issue 2, 423-429
19. Deslignères S. Clear cell unilocular and multilocular cystic renal tumors and in situ clear cell intratubular carcinoma. *Journal D'urologie*,1993,99(3):111-117.
20. Bielsa o, Lloreta J, Gelabaert-Mas A. Cystic renal cell carcinoma: pathological features, survival and implications for treatment. *BJU*, 1998,82(1):16-20.
21. Theresa Y. Chan, World Health Organization classification of tumours: Pathology & genetics of tumours of the urinary system and male genital organs, *Urology*, Volume 65, Issue 1,2005, 214-215.
22. Yamashita, Y.; Watanabe, O.; Miyazaki, T.; Yamamoto, H.; Harada, M.; Takahashi, M. (1994). Cystic Renal Cell Carcinoma. *Acta Radiologica*, 35(1),19-24
23. Klatte, T., Rossi, S.H. Stewart, G.D. (2018) Prognostic factors and prognostic models for renal cell carcinoma: a literature review. *World J Urol* 36, 1943-1952
24. Rossi, S.H., Prezzi, D., Kelly-Morland, C. et al. (2018) Imaging for the diagnosis and response assessment of renal tumors. *World J Urol* 36, 1927-1942
25. Jhaveri K, Gupta P, Elmi A, et al., Cystic renal cell carcinomas: do they grow, metastasize, or recur? *AJR Am J Roentgenol*, 201:W292-W296
26. Moch H, (2010) Cystic renal tumors: new entities and novel concepts. *Adv Anat Pathol* 17:209-214
27. Mahyar K., Mazyar G., et al. Cystic Renal Cell Carcinoma: A Report on Outcomes of Surgery and Active Surveillance in Patients Retrospectively Identified on Pretreatment Imaging, *The Journal of Urology*, Volume 200, Issue 2,2018,275-282.
28. Jaimin R. Bhatt, Michael A.S. Jewett, et al. Multilocular cystic renal cell carcinoma: pathological t staging makes no difference to favorable outcomes and should be reclassified. *The Journal of Urology*, Volume 196, Issue 5,2016,1350-1355.
29. Xu Y, Zhang S, Wei X, et al. Contrast enhanced ultrasonography prediction of cystic renal mass in comparison to histopathology[J]. *Clin Hemorheol Microcirc*, 2014, 58(3): 429-438.

Figures

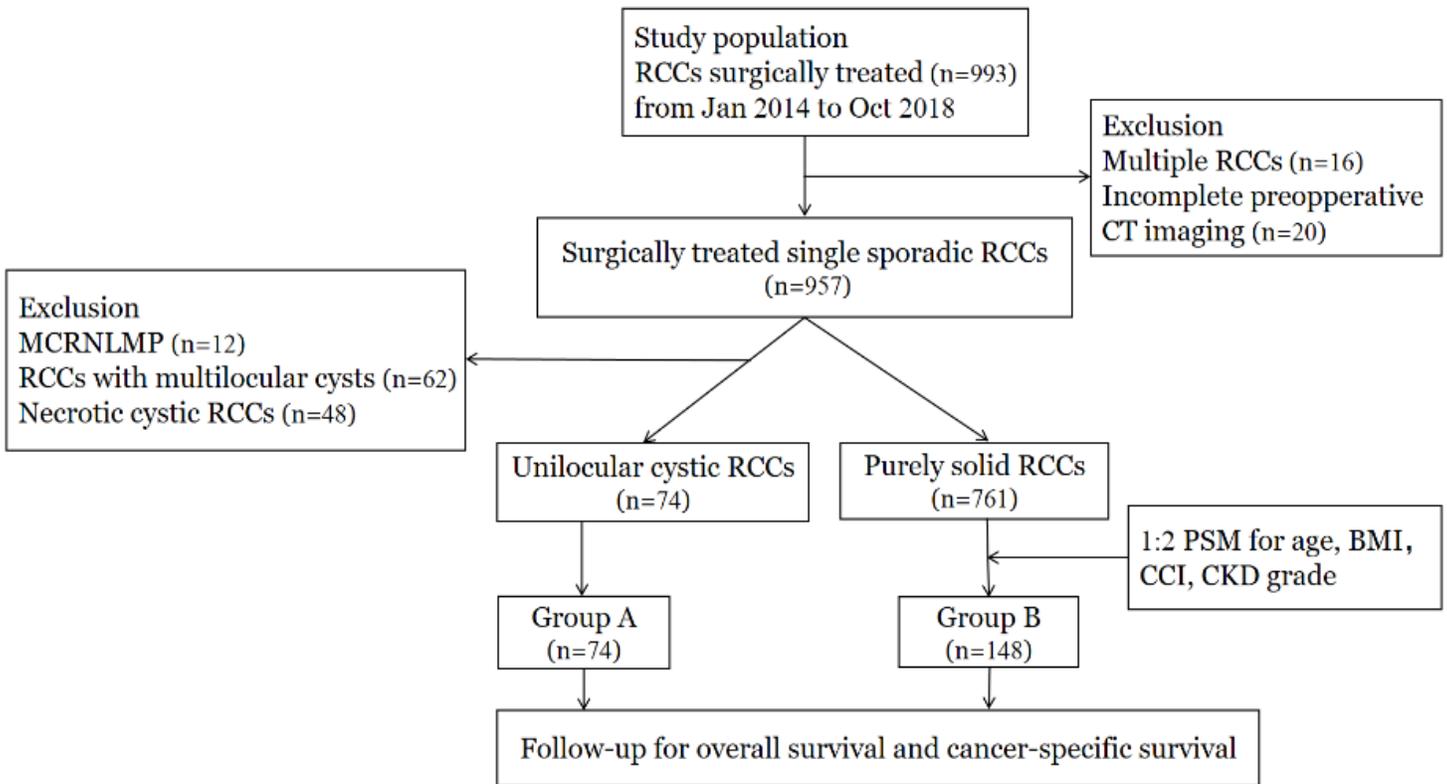


Figure 1

Flowchart of enrolling procedure

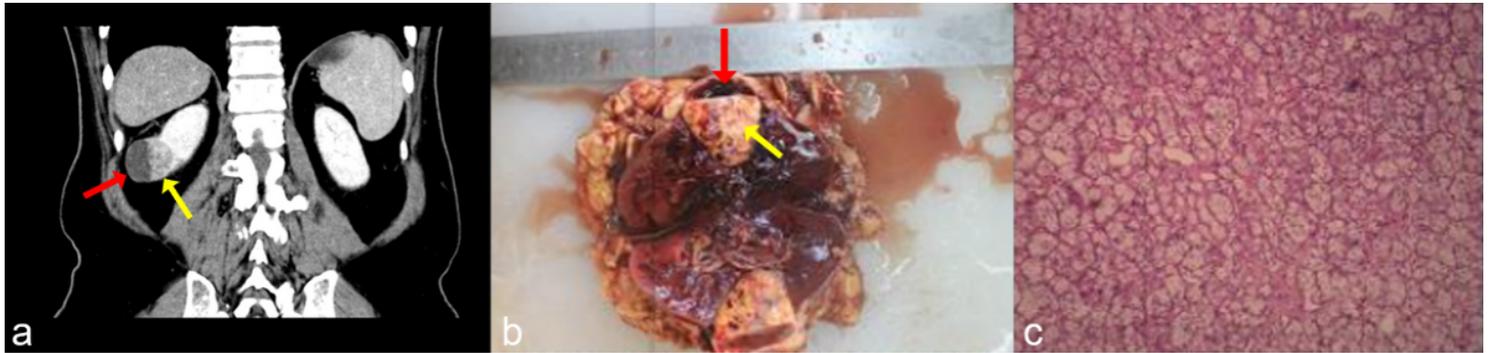


Figure 2

A 60-year-old male with a unilocular cRCC. a) Postcontrast CT: unenhanced cyst fluid (red arrow) and solid component (yellow arrow). b) c) Pathology report: Non-necrotic cyst and Fuhrman grade 2 clear cell carcinoma of the solid component.

Figure 3

a b c) Postcontrast CT: cystic (red arrow) and solid (yellow arrow) components of unilocular cystic clear cell RCCs. e f g) irregular internal structures (green arrow) in the unilocular cystic papillary RCCs.

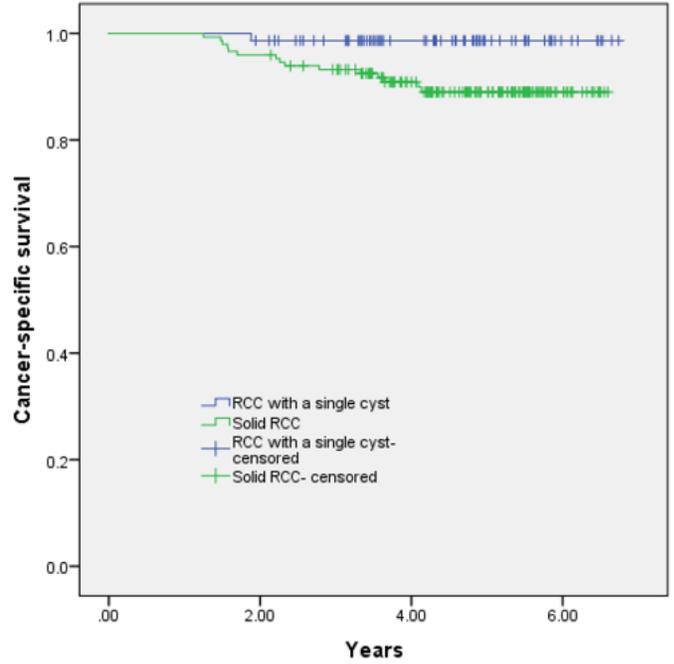
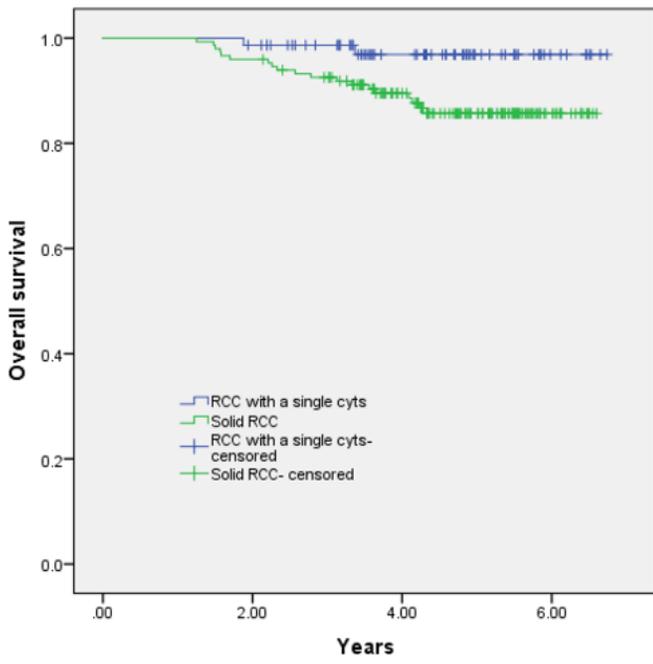


Figure 4

Kaplan-Meier curves of overall and cancer-specific survival for unilocular cystic and solid RCC.