Original Article

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Postoperative and Mid-term Outcomes of Unclassified Renal Cell Carcinoma

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Abstract

Objective: To present the postoperative and oncological outcomes of patients diagnosed with unclassified renal cell carcinoma (uRCC).
Materials and Methods: Radiological and pathological data of patients who underwent radical nephrectomy for renal tumour diagnosed with uRCC according to histopathologic evaluation were investigated between 2006 and 2013. Follow-up data, such as metastasis-free and overall survivals, were also evaluated. Patients' characteristics and data were compared between localised tumour (T1-T2) and locally invasive tumour (T3-T4) groups and metastasis positive and negative groups during follow-up, separately.
Results: A total of 17 patients participated in the study, wherein 7 had adrenalectomy in addition to radical nephrectomy and 3 had lymph node dissection. The mean tumour diameter was 91.9±44 mm (30-200 mm), and seven patients were pathologically T3a, two were T3b and one patient had T4 tumour, whereas eight had Fuhrman grade 4 and five had Fuhrman grade 3 tumours. Pathologically, seven patients had tumours with sarcomatoid features, whereas four had microvascular invasion and seven had renal sinus invasion. T-stage correlated with renal sinus invasion and was identified as an important factor in metastasis progression. The overall survival time was observed to be low in locally invasive and metastasis positive groups. Nevertheless, differences were not statistically significant. In the investigation of factors affecting metastasis development, microvascular invasion and renal sinus invasion were significant.
Conclusion: The study revealed more aggressive nature (advanced stage, bigger tumour, more aggressive histopathological features and more metastasis and shorter survival on follow-up) of uRCC tumours, even without obtaining statistically significant differences.
Keywords: Renal cell carcinoma, mid-term follow-up, survival, unclassified renal cell carcinoma

Introduction

Renal cell carcinomas (RCC) contains the most-commonly observed subtypes of conventional (clear cell) RCC (cRCC), chromophile (papillary) RCC and chromophobe RCC. Additionally, apart from these three, collecting duct carcinoma was described. In 1997, the World Health Organization (WHO) classified RCCs not meeting the criteria for these four types as a fifth type called unclassified RCCs (uRCC) (1,2,3,4,5,6,7). The effect of each RCC subtype on prognosis is reported at certain rates, with many studies available for the commonly observed subtypes. However, very few studies assessing the effect of uRCC on prognosis are reported and many have very small series (4,5,6,7,8,9,10,11). This situation is due to the fact that uRCC comprise 3%-5% of all RCC (2,12). Studies about uRCC have generally reported them as heterogeneous, high grade and aggressive tumours with high metastasis rates and low life expectancy (4,5,12).

This study aimed to present the mid-term follow-up outcomes of patients diagnosed with uRCC along with radiologic, pathologic and clinical data because uRCC comprises rarely-observed aggressive tumours of the kidney.

Materials and Methods

Patients diagnosed with uRCC according to the 2004 WHO criteria after radical nephrectomy treatment at our clinic from 2006 to 2013 were retrospectively evaluated in accordance with the Helsinki Declaration. Demographic data (age and gender), radiologic data (tumour diameter, laterality, location, adrenal

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invasion, lymph node metastasis and central necrosis), pathologic data [pathologic T-stage, tumor-node-metastasis (TNM) stage, Fuhrman grade, sarcomatoid features, microvascular invasion, renal vein invasion, perinephric invasion and renal sinus invasion, adrenal invasion and lymph node metastasis], intraoperative data [operation time, need for adrenalectomy and lymph node dissection (LND)], need for adjuvant treatment (interferon-alpha and sunitinib treatments), laboratory data and indexes [neutrophil/lymphocyte ratio (NLR), albumin/globulin ratio (AGR), aspartate aminotransferase/alanine aminotransferase (De-Ritis) ratio (AAR), lactate dehydrogenase (LDH), platelet levels and calcium levels] and postoperative oncological data (occurrence of metastasis, overall survival, metastasis-free survival and mortality) were investigated. LND was performed for only detected positive lymph nodes on radiological imaging and/or during exploration. Patients were divided into two groups as pathologic T1 and T2 (localised tumours) and pathologic T3 and T4 (locally invasive) tumours; then all patients were divided again into two new different groups as those who were metastasis positive or negative in follow-up. Patient data were compared between groups.

Statistical Analysis

Patients' data were comparatively assessed between groups using the Mann-Whitney U test and Pearson χ^2 test. Significant data were then assessed with the multivariate binary logistic regression analysis. Overall survival and metastasis-free survival were evaluated with the Kaplan-Meier survival analysis. Statistical Package for the Social Sciences (Version 20.0; SPSS, Chicago, Illinois, USA) programme was used for all statistical analyses. Data are given as mean and standard deviation; however, statistical analyses were calculated using median values. For analysis results, a p-value of <0.05 was accepted as significant.

Results

A total of 17 patients diagnosed with uRCC were evaluated in the study. Characteristics and radiological findings from all patients are given in Table 1. In the examination of radiological data, nine patients had upper pole tumour and one had both adrenal gland invasion and T4 stage tumour findings. In a total of 10 patients who had upper pole tumour including the radiological T4 patient, 7 underwent radical nephrectomy and additional adrenalectomy. Lymph node metastasis on preoperative radiological imaging was observed in three patients who then underwent radical nephrectomy and additional LND.

Table 1. Patients' characteristics and radiological findings

Variables	N=17, Mean ± SD (min-max)
Mean age (year)	62±7.4 (51-75.2)
Gender: Male/Female, n (%)	11 (64.7%)/6 (35.3%)
Laterality of tumour: Right/Left, n (%)	8 (47.1%)/9 (52.9%)
Location of tumour: Upper pole/Mid/Lower pole, n (%)	9 (52.9%)/4 (23.5%)/4 (23.5%)
Tumour diameter (mm)	91.9±44 (30-200)
Adrenal invasion in radiologic images, n (%)	1 (5.9%)
T4 stage tumour in radiologic images, n (%)	1 (5.9%)
Lymph node metastasis in radiologic images, n (%)	3 (17.6%)
Central necrosis in radiologic images, n (%)	7 (41.2%)

SD: Standard deviation, Min: Minimum, Max: Maximum

When pathologic data are investigated, the mean tumour diameter was 91.9±44 mm (30-200 mm), and seven patients had pathologic T3a, two had T3b and one had T4 stage tumour, eight patients had Fuhrman grade 4 and 5 had Fuhrman grade 3 tumours. Pathologically, 7 tumours contained sarcomatoid features, whereas 4 had microvascular invasion. Additionally, seven patients had renal sinus invasion, five had perinephric invasion, one had adrenal invasion, one had collecting system invasion and three had renal vein invasion. Three patients with LND were identified to have lymph node metastasis. The median follow-up for patients was 22 months [mean was 52.9±29.6 (1-118.5) months], with mean overall survival of 86.7±13.9 months and mean metastasis-free survival of 41.4±13 months.

When all of the preoperative variables were analysed (age, gender, NLR, AGR, AAR, calcium level, LDH level, platelet level and tumour diameter) and compared between groups (localised vs locally invasive tumour groups), any statistical significance was not found (Table 2). The locally invasive group were identified to have higher renal sinus invasion (0% vs 70%, p<0.05), perinephric invasion (0% vs 50%, p<0.05) and metastasis rate (28.6% vs 80%, p<0.05) during the follow-up compared to the localised tumour group (Table 3). Other pathologic data and operation time were similar between groups. T-stage was not observed to affect interferon-alpha treatment and targeted therapy rates. Overall survival and metastasis-free survival in the locally invasive group (38.4±7.3 months and 20.1±5.5 months, respectively) were shorter than the localised tumour group (90.6±24.2 months and 77.8±23.9 months, respectively) but were not statistically significant.

In the investigation of factors affecting the metastasis during follow-up, the adrenalectomy rate (14.3% vs 60%, p=0.05) and operation time (137.8±58.6 min vs 201±47 min, p<0.05) were higher in the metastasis positive group (Table 3). The pathologic data for microvascular invasion (0% vs 40%, p<0.05) and renal sinus invasion (14.3% vs 60%, p=0.05) were significantly higher in the metastasis group. During follow-up, 10 patients in the metastasis group had interferon-alpha treatment, whereas 1 patient was exitus in the early period before treatment. Sunitinib was given to four patients, everolimus was given to a patient as targeted therapy, whereas no targeted therapy was given to six patients. The currently popular data of NLR, AGR and AAR did not have a significant correlation with metastasis (Table 2). No significance was identified between groups in terms of prognostic factors like LDH, calcium and platelet levels. The mean overall survival in the metastasis positive group (23.5±5.1 months) was shorter compared to metastasis negative group (101.7±15.6 months), but did not reach statistical significance.

Discussion

In 1997, the WHO classified RCCs without the characteristics of the four subtypes of RCC under the name uRCC (1,2,3,4,5,6,7). Accordingly, when the WHO 2004 classification is examined,

Table 2. Preoperative data and analysis results between localised (T1 and T2) and locally invasive (T3 and T4) according to pathological T-stage and metastasis positive and negative in follow-up, respectively

Variables (n=17), mean ± SD	T1 and T2 stage tumours (n=7)	T3 and T4 stage tumours (n=10)	p*	Metastasis negative in follow-up (n=7)	Metastasis positive in follow-up (n=10)	p*
Mean age (year)	59.5±6.8	63.8±7.7	0.205	61.2±7.3	62.6±7.9	0.813
Gender, Female/Male, n (%)	3 (42.9%)/4 (57.1%)	3 (30%)/7 (70%)	0.585	3 (42.9%)/4 (57.1%)	3 (30%)/7 (70%)	0.585
NLR	1.56±1.25	7.3±5.69	0.120	9.2±3.9	5.1±3.4	0.120
AGR	1.1±0.05	1.2±0.2	0.378	1±0.1	1.2±0.2	0.243
AAR	1.3±0.4	0.8±0.3	0.121	0.4±0.2	1±0.3	0.121
Calcium level	9.2±0.9	9.5±0.8	0.510	9.7±0.9	9.2±0.5	0.124
LDH level	182±75.6	242.4±84.9	0.827	135±73	249.1±76.4	0.127
Platelet level	272.8±61.8	321.3±98.6	0.386	302±111.7	304.8±83.8	0.733
Tumour diameter (cm)	106.1±56.1	82±32.8	0.494	90±41.5	93.3±47.9	0.883

*Mann-Whitney U test vs Pearson χ^2 test, NLR: Neutrophil/lymphocyte ratio, AGR: Albumin/globulin ratio, AAR: Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) (De-Ritis) ratio, SD: Standard deviation, LDH: Lactate dehydrogenase

Table 3. Pathologic and postoperative findings and analysis results between localised (T1 and T2) and locally invasive (T3 and T4) according to pathological T-stage and metastasis positive and negative in follow-up, respectively

Variables (n=17), mean ± SD		T1 and T2 stage tumours (n=7)	T3 and T4 stage tumours (n=10)	p	Metastasis negative in follow-up (n=7)	Metastasis positive in follow-up (n=10)	p
Operation time (s)		165.7±53.2	181.5±65.7	0.553	137.8±58.6	201±47	**0.043**
Pathological T-stage, n (%)	pT1 and pT2	-	-	-	5 (71.4%)	2 (20%)	**0.034**
	pT3 and pT4				2 (28.6%)	8 (80%)	
TNM stage, n (%)	Stage 1	2 (28.6%)	0 (0%)	-	2 (28.6%)	0 (0%)	**0.048**
	Stage 2	5 (71.4%)	0 (0%)		3 (42.8%)	2 (20%)	
	Stage 3	0 (0%)	7 (70%)		2 (28.6%)	5 (50%)	
	Stage 4	0 (0%)	3 (30%)		0 (0%)	3 (30%)	
Fuhrman grade, n (%)	Grade 2	2 (28.6%)	1 (10%)	0.672	2 (28.6%)	1 (10%)	0.672
	Grade 3	2 (28.6%)	3 (30%)		2 (28.6%)	3 (30%)	
	Grade 4	3 (42.8%)	5 (50%)		3 (42.8%)	5 (50%)	
Adrenalectomy-applied, n (%)		2 (28.6%)	5 (50%)	0.377	1 (14.3%)	6 (60%)	**0.050**
LN dissection-applied, n (%)		0 (0%)	3 (30%)	0.057	0 (0%)	3 (30%)	0.057
Sarcomatoid features, n (%)		3 (42.8%)	4 (40%)	0.906	2 (28.6%)	5 (50%)	0.377
Microvascular invasion, n (%)		1 (14.3%)	3 (30%)	0.442	0 (0%)	4 (40%)	**0.024**
Renal vein invasion, n (%)		0 (0%)	3 (30%)	0.057	1 (14.3%)	2 (20%)	0.761
Perinephric invasion, n (%)		0 (0%)	5 (50%)	**0.026**	2 (28.6%)	3 (30%)	0.949
Renal sinus invasion, n (%)		0 (0%)	7 (70%)	**0.004**	1 (14.3%)	6 (60%)	**0.050**
Interferon-alpha treatment, n (%)		3 (42.8%)	7 (70%)	0.263	1 (14.3%)	9 (90%)	**0.002**
Sunitinib treatment, n (%)		1 (14.3%)	3 (30%)	0.452	0 (0%)	4 (40%)	**0.024**
Metastasis in follow-up, n (%)		2 (28.6%)	8 (80%)	**0.034**	-	-	-
Overall survival (months)		90.6±24.2	38.4±7.3	0.514	101.7±15.6	23.5±5.1	0.514
Metastasis-free survival (months)		77.8±23.9	20.1±5.5	0.187	-	-	-
Exitus, n (%)		1 (14.3%)	3 (30%)	0.452	1 (14.3%)	3 (30%)	0.452

LN: Lymph node, SD: Standard deviation

some pathologic data for distinction of uRCC were found. This data lists pure sarcomatoid morphology without compositions and epithelial elements of four defined RCC subtypes, mucin production, rare involvement of epithelial and stromal elements and unknown cell types (4). Pathologic studies about this topic are limited, stating that the presence of vacuole cytoplasm

and *Wilms' Tumour 1 (WT1)* gene expression are in favour of uRCC unless otherwise stated (13). Additionally, Bruder et al. (8) defined additional morphologic findings. However, in general, the use of current WHO criteria for pathologic assessment is recommended (13).

The diagnosis of uRCC is observed more rarely (3%-5%) compared to other RCC subtypes (2,12,14). When series in the literature are investigated, a variety of studies report a variety of rates (0.7%-5.7%) (4,5,6,7,8,9,10,11). The mean rate in large series was identified as 2.9% in the study by Zisman et al. (12), and uRCC prevalence was identified as 5.2% in the study by Karakiewicz et al. (14). There are many small-series studies on this topic (15,16,17), with three noteworthy basic studies on oncologic outcomes of uRCC. Zisman et al. (12) compared 31 uRCC and 317 cRCC cases and identified that the uRCC group had higher metastatic disease development during follow-up compared to the cRCC group (94% vs 83%). A higher tumour size, 25% adrenal metastasis, 42% direct invasion to neighbouring organs, 52% bone metastasis, 52% regional lymph node metastasis and 41% non-regional lymph node metastasis were observed in uRCC. Additionally, the median survival for uRCC was identified as 4.3 months (12). However, in this study only 19 patients in the uRCC group had nephrectomy (61%, nephrectomy rate in the cRCC group was 90, with the importance of nephrectomy for cancer control not clearly stated. A large series and multicentre study by Karakiewicz et al. (14) compared 85 uRCC with 4322 cRCC and emphasised that uRCC was more aggressive.

Accordingly, the uRCC group in the study had higher Fuhrman grade (grade 3 and 4) and higher distant organ metastasis rates at time of nephrectomy (54.1% vs 16.8%) and lower cancer-specific survival (1 year CSS 48.7% vs 89.9% and 5 year CSS 32.6% vs 74.3%) compared to the cRCC group. Additionally, the cancer-specific mortality in the uRCC group was identified to be 1.7 times higher (14). However, the median survival was identified to be higher compared to the study by Zisman et al. (12) (1.9 years vs 4.3 months). The difference in median survival between the two studies may be explained by the fact that in the study by Karakiewicz et al. (14) the patient rate operated in the early stages was higher and patient performance was better, while the study by Zisman et al. (12) had low nephrectomy rates. Additionally, the immunotherapy administration rates and treatment times may affect survival. In the study examination, our data had better progression compared to the literature; however, bad prognostic findings were observed. In our study 58.8% of patients were in advanced stage and 76.5% had high Fuhrman grade. During follow-up, 58.8% of patients developed metastasis. Mean follow-up time and overall survival were 22±29.6 and 86.7±13.9 months, respectively, and mortality was observed in four patients. Additionally 41.2% had renal sinus invasion. However, as adrenalectomy was performed for seven patients and LND for three patients in our series, only one patient (5.9%) had adrenal metastasis and three patients (17.6%) had lymph node metastasis. These rates may be said to be lower than the rates in literature.

The study by Lopez-Beltran et al. (13) assessed 56 patients with uRCC. A study reported that histologic subtype, tumour grade, TNM stage, presence of necrosis, tumour size and microvascular invasion were independent risk factors for disease-free survival and cancer-specific survival (18,19). Another 38-patient series reported high rates of lymph node metastasis, high Fuhrman grade tumour rates, tumour necrosis and sarcomatoid features in uRCC; they identified overall survival and cancer-specific survival were similar to cRCC (10). In our study, in accordance with these two studies, mean tumour diameter, central necrosis on radiologic imaging, microvascular invasion and sarcomatoid properties were observed to be high at 9.2 cm, 41.2%, 23.5% and 41.2%, respectively.

Generally, small-series studies were reported; however, specific findings of uRCC are unclear in some large studies. The reason for this may be the small number of patients, comparison of uRCC data with other commonly observed histologic subtypes and large proportional difference between the patient numbers in these groups. Additionally, the experience of the pathologist is important for pathologic diagnosis as emphasised in studies. As a result, we presented a 17-patient series with uRCC diagnosed by experienced uropathologists (BT and KY) without making comparisons. In addition to general patient data in our study, we assessed the patient data for locally invasive tumours and metastasis positive tumours in the follow-up. Accordingly, the development of metastasis rate was identified as high and mean metastasis-free survival was low (but insignificant) in the locally invasive group compared to the localised tumour group. Metastasis positivity in the follow-up was found to be correlated with high T-stage, microvascular invasion and renal sinus invasion. Additionally, the operation time and adrenalectomy rates in the metastasis group were identified to be high. However, in spite of the low overall survival time in the metastasis group, no significant difference was identified. The majority of the patient group with adrenalectomy had upper pole tumours; however, no correlation was shown between metastasis development and tumour location. After metastasis development, interferon-alpha treatment was used for 58.8% of patients; sunitinib and everolimus were used for 23.5% and targeted therapy for 5.9% of patients. When prognostic markers are investigated in our study, the NLR, AGR and AAR ratios, popular in recent times, and LDH, calcium and platelet levels were not shown to be related to metastasis development.

Study Limitations

The most important limitations of our study are the small number of patients and the retrospective data.

Conclusion

This study revealed a more aggressive nature of uRCC tumours, even without reaching statistically significant differences (such as more frequent adrenal and lymph node involvement, more advanced stage, larger tumour diameter, more aggressive histopathological features and more metastasis and shorter survival during follow-up). Large series studies are necessary to determine the real radiological, pathological and oncological characteristics of this aggressive subtype of RCC tumours although performing it is difficult because of low incidence.

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Ethics

Ethics Committee Approval: Patients diagnosed with uRCC at our clinic from 2006 to 2013 were retrospectively evaluated in accordance with the Helsinki Declaration.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: S.Ç., C.A., M.D.D., O.B., Ö.D., B.T., K.Y., M.S., G.A., Design: S.Ç., C.A., M.D.D., O.B., Ö.D., B.T., K.Y., M.S., G.A., Data Collection or Processing: S.Ç., C.A., M.D.D., O.B., Ö.D., B.T., K.Y., M.S., G.A., Analysis or Interpretation: S.Ç., C.A., M.D.D., O.B., Ö.D., B.T., K.Y., M.S., G.A., Literature Search: S.Ç., C.A., M.D.D., O.B., Ö.D., B.T., K.Y., M.S., G.A., Writing: S.Ç., C.A., M.D.D., O.B., Ö.D., B.T., K.Y., M.S., G.A.

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