Original Article

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Renal Cell Carcinoma: Epidemiological Profile and Histopathological Features

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Abstract

Objective: Nowadays, with the use of advanced imaging methods, the incidence of renal cell carcinomas (RCCs) has increased steadily and they have become recognizable at early stage. Morphologically and immunophenotypically, RCCs are divided into many different types and are divided into three main subtypes. Each type has differences in terms of genetics, biology, and behavior. The objectives of this study is to investigate the histopathological features of tumor specimens of patients operated with diagnosis of RCC.

Materials and Methods: The pathology specimens and reports of 77 patients with RCC who underwent radical or partial nephrectomy were reviewed retrospectively. Descriptive and clinical data of the patients were obtained. The size, lateralization, focality, histopathological type, Fuhrman nuclear grading system (NGS), sarcomatoid change, renal sinus and vein invasions, perirenal fat tissue invasion, hilar fatty tissue invasion, ureter surgical margin, and primary tumor stage of RCC were determined.

Results: According to the histopathologic type, 77.9% of the patients had clear cell RCC, 10.4% chromophobe RCC, 9.1% papillary RCC, and 2.6% multilocular RCC. The Fuhrman NGS values were 5.2% for grade 1, 61% for grade 2, 26% for grade 3, and 7.8% for grade 4. There were sarcomatoid features in only 7.8% of the patients. There were 6 patients (7.8%) with renal sinus invasion, 3 patients (3.9%) with renal vein invasion, 8 patients (10.4%) with perirenal adipose tissue invasion, 2 patients (2.6%) with hilar fat tissue invasion, and 2 patients (2.6%) with tumors at the ureter surgical margin. Pathological changes were significantly differentiated according to gender except for the primary tumor stage.

Conclusion: RCCs are divided into many different types and each type has differences in terms of genetics, biology, and behavior. Due to this, the pathologist must differentiate cell types routinely by morphology and immunohistochemical markers as well as by cytogenetic and molecular genetic analysis particularly when the cell type is equivocal.

Keywords: Renal cell carcinoma, histopathology, kidney tumors

Introduction

Prevalence of renal cell carcinomas (RCCs) is approximately 2% among adult cancers and RCC accounts for about 85% of all parenchymal kidney tumors. Among urological cancers, RCC is the 3rd most common cancer after prostate and bladder tumors. RCC is the 6th leading cancer type in men and the 10th in women, worldwide (1,2). RCCs do not respond to conventional chemotherapy and have the highest mortality rate (more than a third of the patients will die from RCC) among the genitourinary cancers and RCC is the 13th most common cause of cancer death worldwide. Surgical resection of the tumor with minimal risk of recurrence is applied during early stages. Nowadays, with the use of advanced imaging methods, RCCs are recognizable at early stage. With the use of advanced imaging methods and incidental detection of renal masses, the incidence of RCCs has increased steadily (3,4).

Nomenclature, categorization, and standardization of RCC have been made by many organizations such as The International Society of Urological Pathology, The World Health Organization (WHO) (5), The College of American Pathologists (6), and The American Joint Committee on Cancer (AJCC) (Staging Manual) (7) and revisions are ongoing. Morphologically and immunophenotypically, RCCs are divided into many different types and are divided into three main subtypes (≥5% incidence) with the malignant course: Clear cell, papillary, and chromophobe RCCs. Each type has differences in terms of

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genetics, biology, and behavior (8). The remaining subtypes are very rare (each with ≤1% total incidence) and in cases where a tumor does not fit any subtype's diagnostic criteria, it is designated as unclassified RCC (9,10).

Clear cell RCC, also called conventional RCC, is the most common and malignant renal tumor, accounting for approximately ~75% of all RCCs. It is thought to arise from the epithelium of the proximal tubule (11). Papillary RCC is observed at frequency of ~15% and is thought to arise from the epithelium of the proximal tubule, like clear cell RCC. Chromophobe RCC makes up ~5% of kidney tumors and is believed to derive from the distal nephron, probably from the epithelium of the collecting tubule (3,9). The pathologist differentiates cell types routinely by morphology and immunohistochemical markers as well as by cytogenetic and molecular genetic analysis particularly when the cell type is equivocal. Of RCCs, 3-5% cannot be classified and are termed unclassified RCC (3).

These tumors, which are detected in early period, are usually small in size and are low-grade. Prognostic models are being developed for this purpose. In these models, the Fuhrman nuclear grading system (NGS) has an important role along with prognostic parameters such as tumor node metastasis (TNM) stage and performance score. Fuhrman NGS, which has been defined by Fuhrman et al. (12) and has been the most widely used histopathologic grading system since 1982, has been shown to be an independent prognostic factor of RCC survival (5,13).

The objectives of this study is to investigate the histopathological features of tumor specimens of patients operated with RCC diagnosis.

Materials and Methods

Data collection and ethical permission: The study was performed at a university hospital. The pathology specimens and reports of 77 patients with RCC who underwent radical or partial nephrectomy between the years 2010 and 2018 were reviewed retrospectively. Descriptive and clinical data of the patients (age, gender, hospital admission complaints, surgical procedure) were obtained. The study was approved by the University for the Non-interventional Clinical Research Ethics Board (Date: 08.08.2019, Decision No: 17).

Pathological parameters including the size, lateralization and focality of tumors were obtained from the pathology reports. The largest tumor diameter was determined from macroscopic examination. Histopathological type, Fuhrman NGS, sarcomatoid feature, renal sinus, and vein invasions, peri-renal fat tissue invasion, hilar fatty tissue invasion, ureter surgical margin, and primary tumor stage of RCC were determined by re-examination of preparations. Fuhrman NGS was used to define the tumor cell differentiation (14,15) and histological subtype classification was made using 2016 WHO scheme (10,16).

Fuhrman et al. (12) evaluated the effects of nuclear grade, tumor size, renal vein invasion, stage, tumor pattern and histopathological tumor type on survival. The most significant difference of this evaluation from other rating systems is evaluation of nucleolus visibility and size of the nucleolus under a light microscope. Accordingly, Fuhrman NGS is classified into four groups.

Grade 1: The tumor nucleus is small (10 μ in diameter), round, and uniform. No or inconspicuous nucleoli resemble lymphocyte nuclei (very rare).

Grade 2: The tumor nucleus is approximately 15 μ in diameter, has slightly irregular borders and open chromatin (40% of tumors). Nucleolus can be seen at 400 magnifications.

Grade 3: The tumor nucleus is about 20 μ (large) in diameter, has markedly irregular borders and open chromatin (30-40% of tumors). The large nucleolus can be seen even at 100 magnifications.

Grade 4: Tumor nuclei are similar to the nuclei in grade 3 and they are bizarre and multi-lobated. The cells are pleomorphic. The cells may have multiple nuclei and chromatin coarseness. They have macro-nucleoli (15% of tumors) (mitosis findings).

A significant difference was found between grade 1 and grade 2-4 tumors in terms of metastasis. In the study, four different nucleus degrees were defined when evaluating survival, but when evaluating the results, group 2 and 3 were grouped together and it was reported that there was a statistically significant difference in terms of the survival among grade 1, grade 2+3 and grade 4. Although there was no statistically significant difference in terms of survival rates among the nucleus grades in this first study, the differences between Fuhrman NGS grades were revealed in subsequent studies (13,17).

Statistical Analysis

The data obtained from the study were analyzed using IBM SPSS Statistics 24 software program. Quantitative variables were expressed as mean ± standard deviation and categorical variables were expressed as number (n) and percentage (%). "chi-square test" and "Fisher's exact test" were used to compare qualitative data and "Studen's t-test" was used to compare independent groups. A p value <0.05 was accepted as significant. The binary logistic regression coefficient was calculated for the relationship analysis of RCC.

Results

Descriptive and clinical data of the patients included in the study are shown in Table 1. According to this table, the mean age of the patients was 61.29 years and the average size of the tumors was 7.65 cm. Twenty-five (32.5%) of the participants were female and 52 (67.5%) were male. Distribution of the signs and symptoms were as follows: Flank pain was found in 50 patients (64.9%), followed by hematuria in 17 (22.1%) and palpable mass in 10 (13%) patients. Sixty-six (85.7%) of the surgical procedures were radical nephrectomy and 11 (14.3%) were partial nephrectomy.

Table 2 shows the histopathological features of the RCC. Tumors were localized in the right kidney in 41 (53.2%) patients and left kidney in 36 (46.8%) patients. The majority of the patients had unifocal (n=75, 97.4%) tumor. According to the histopathologic type, 60 (77.9%) of the patients had clear cell RCC, 8 (10.4%) chromophobe RCC, 7 (9.1%) papillary RCC, and 2 multi-locular

Table 1. Descriptive and clinical data of 77 patients			
Age (years)		61.29±14.68	
Tumor size (cm)		7.65±3.84	
		n	**%**
Gender	Female	25	32.5
	Male	52	67.5
Complaint	Flank pain	50	64.9
	Hematuria	17	22.1
	Palpable mass	10	13.0
Surgical Procedure	Radical nephrectomy	66	85.7
	Partial nephrectomy	11	14.3

Table 2. Histological features of renal cell carcinoma			
Histological Features		**n**	**%**
Lateralization	Right	41	53.2
	Left	36	46.8
Focality	Unifocal	75	97.4
	Multifocal	2	2.6
Histopathological type	Clear cell	60	77.9
	Chromophobe	8	10.4
	Papillary	7	9.1
	Multilocular	2	2.6
Fuhrman NGS	1.00	4	5.2
	2.00	47	61.0
	3.00	20	26.0
	4.00	6	7.8
Sarcomatoid changes	Yes	6	7.8
	No	71	92.2
Renal sinus invasion	Yes	6	7.8
	No	60	77.9
	Could not be assessed	11	14.3
Renal vein invasion	Yes	3	3.9
	No	63	81.8
	Could not be assessed	11	14.3
Perirenal fat tissue invasion	Yes	8	10.4
	No	69	89.6
Hilar fatty tissue invasion	Yes	2	2.6
	No	64	83.1
	Could not be assessed	11	14.3
Surgical margin of ureter	Negative	64	83.1
	Positive	2	2.6
	Could not be assessed	11	14.3
Primary tumor stage	1a	13	16.8
	1b	19	24.7
	2a	19	24.7
	2b	12	15.6
	3a	14	18.1
NGS: Nuclear grading system			

RCC (2.6%) (Figure 1). The Fuhrman NGS values were 5.2% for grade 1,60% for grade 2, 26% for grade 3, and 7.8% for grade 4. There were sarcomatoid features in only 6 (7.8%) patients.

There were 6 patients with renal sinus invasion (7.8%), 60 patients (77.9%) without renal sinus invasion and 11 patients (14.3%) were not evaluated. Also, there were 3 patients with renal vein invasion (3.9%), 63 patients (81.8%) without renal vein invasion and 11 patients (14.3%) that could not be evaluated. There were 8 patients (10.4%) with perirenal adipose tissue invasion. There were 2 patients (2.6%) with hilar fat tissue invasion, 64 (83.1%) without hilar fat tissue and 11 (14.3%) patients that could not be evaluated. There were 2 patients (2.6%) with tumors at the ureter surgicalmargin, 64 patients (83.1%) without tumors at the ureter surgical margin and 11 patients (14.3%) that could not be evaluated. There were 13 patients with primary tumor stage 1a (16.8%), 19 patients stage 1b (24.7%), 19 patients stage 2a (24.7%), 12 patients stage 2b (15.6%), and 14 patients stage 3a (18.1%). (Figure 2)

The relationship between histopathological features and gender is shown in Table 3. Accordingly, pathological changes were significantly differentiated according to gender except for the primary tumor stage ($p<0.001$).

Table 4 shows the distribution of major histopathological types by age. The number of patients according to age groups "18-39", "40-59", and "60 or over" were 4 (3.9%), 28 (36.8%) and 45 (59.2%), respectively. In the 18-39 age group, there were 3 (75%) patients with clear cell RCC and 1 (25%) with chromophobe RCC. The most common type was found to be clear cell RCC (22 patients, 78.6%) in patients aged 40-59 years, followed by chromophobe (3 patients, 10.7%), multilocular (2 patients, 7.1%) and papillary (1 patient, 3.6%) RCC. The distribution of the types in the age group of ≥60 years was as follows; Clear cell RCC in 35 patients (77.8%), papillary RCC in 6 patients (13.3%), and chromophobe RCC in 4 patients (8.9%).

Table 5 shows the results of the regression analysis between the tumor lateralization and tumor size, histopathological type, and primary tumor stages. It was found that these 3 features did not have a predictive value on lateralization ($p>0.05$).

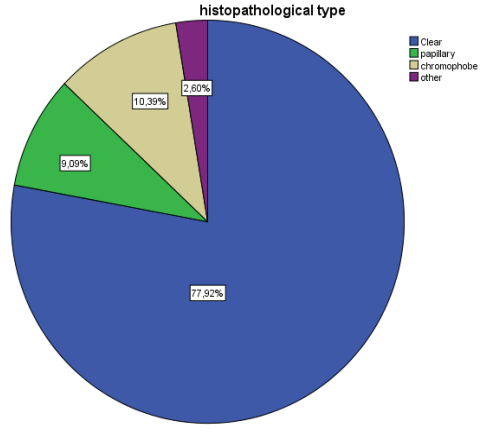

Figure 1. Distribution of patients according to tumor types

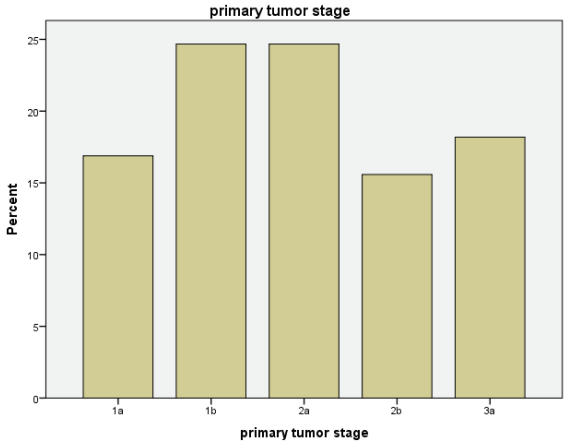

Figure 2. Graphical representation of the primary tumor stage

Table 3. The relationship between histopathological features and gender				
		Female	**Male**	**p**
Histopathological type	Clear cell	22 (88%)	38 (73.1%)	<0.001
	Chromophobe	1 (4%)	7 (13.5%)	
	Papillary	1 (4%)	6 (11.5%)	
	Multilocular	1 (4%)	1 (1.9%)	
Fuhrman NGS	1.00	1 (4%)	3 (5.8%)	<0.001
	2.00	16 (64%)	31 (%59.4)	
	3.00	6 (24%)	14 (26.9%)	
	4.00	2 (8%)	4 (7.7%)	
Sarcomatoid changes	Yes	3 (12%)	3 (5.8%)	<0.001
	No	22 (88%)	49 (94.2%)	
Renal sinus invasion	Yes No Could not be assessed	2 (8%) 18 (72%) 5 (20%)	4 (7.7%) 42 (80.8%) 6 (11.5%)	<0.001
Renal vein invasion	Yes	1 (8%)	2 (3.8%)	<0.001
	No	19 (72%)	44 (84.6%)	
	Could not be assessed	5 (20%)	6 (11.5%)	
Hilar fatty tissue invasion	Yes	1 (4%)	1 (1.9%)	<0.001
	No	19 (76%)	45 (86.5%)	
	Could not be assessed	5 (20%)	6 (11.5%)	
Surgical margin of ureter	Negative	20 (80%)	44 (84.6%)	<0.001
	Positive	0 (0%)	2 (3.8%)	
	Could not be assessed	5 (20%)	6 (11.5%)	
Primary tumor stage	1a	6 (24%)	7 (13.5%)	0.30
	1b	8 (32%)	11 (21.2%)	
	2a	6 (24%)	13 (25%)	
	2b	3 (12%)	9 (17.3%)	
	3a	2 (8%)	12 (23.1%)	
NGS: Nuclear grading system				

Discussion

Numerous prognostic factors have been identified in RCCs. Among these, the most important prognostic factors are stage, diameter, NGS, histologic subtype, presence of lympho-vascular invasion and presence of sarcomatoid component of the tumor (18).

The incidence of RCC increases markedly with age and is higher in men than women (the gender ratio approximately male:female is 2:1) (3,9). In a study conducted in Turkey, Turk et al. (18) examined the records of 230 patients with RCC and they found that the mean age of the patients was 57.5 years and the female/male ratio was 3/7. In the Surveillance, Epidemiology, and End Results database in the ultrasonography (USG), the median age of patients with RCC was 64 years. Also, it should be kept in mind that if RCC was diagnosed at younger ages (≤46 years), the possibility of a hereditary Kidney Cancer syndrome - which was 3-5% of all RCCs - should be considered (19). In our study, the mean age of the patients was 61.29 years. Of the patients, 32.5% were female and 67.5% were male. Our findings were consistent with the literature.

The early clinical manifestations of RCC are diverse and most are non-specific. Only 10% of individuals with RCC present with the classic triad of hematuria, flank pain, and mass (the tumor is already advanced in those with this triad). None of the 3 symptoms is present in more than 40% of individuals with RCC and the tumor is found incidentally in 60% of patients. This shift is a result of widespread use of non-invasive radiological techniques such as USG or abdominal computer tomography imaging performed for another reason (3,9). In our study, the most common complaints of patients were flank pain (64.9%), followed by hematuria (22.1%) and palpable mass (13%).

Early stage RCCs (T1-2, limited within the kidney) can be treated surgically. Radical nephrectomy is the traditional and preferred method. The radical nephrectomy is currently practiced using a

Table 4. Distribution of major histopathological groups by age			
Age	**Histopathologic Type**	**n**	**%**
18-39 (n=4)	Clear cell	3	75.0
	Chromophobe	1	25.0
40-59 (n=28)	Clear cell	22	78.6
	Papillary	1	3.6
	Chromophobe	3	10.7
	Multilocular	2	7.1
≥60 (n=45)	Clear cell	35	77.8
	Papillary	6	13.3
	Chromophobe	4	8.9

Table 5. Regression analysis						
		B	S.E.	Wald	Sig.	Exp (B)
Lateralization	Tumor size	0.138	0.095	2.091	0.148	1.148
	Histopathological type	0.062	0.306	0.042	0.838	1.064
	Primary tumor stage	0.088	0.243	0.133	0.716	1.092

conventional laparoscopic approach in most patients with stage I and II RCC, and the open surgery remains the gold standard in the treatment of more complex patients (9). However, nephron-sparing surgery which reduces the risk of premature death due to heart disease and late renal failure in small and localized tumors is also becoming widely used today (3). Turk et al. (18) reported that 88% of patients with RCC (n=230) underwent radical nephrectomy and 12% had nephron-sparing surgery. In our study, 85.7% of the surgical procedures were radical nephrectomy and 14.3% were partial nephrectomy in 77 patients. Our findings were consistent with the literature.

Turk et al. (18) found that the mean tumor diameter was 6.9 cm. In our study, the average size of the tumors was 7.65cm, the tumor was localized at the right kidney in 53.2% of patients and at left kidney in 46.8% of them, and the majority of the tumors (97.4%) were unifocal.

Clear cell RCC is the most common malignant renal tumor, accounting for approximately 70% of all renal cancers. At the macroscopic examination, the surface area of the clear cell tumors is golden yellow with mostly hemorrhagic, necrotic and cystic fields. At the microscopic investigation, clear cell RCC is consisted of tumor cells with clear cytoplasm arranged in nests or tubules surrounded by a rich vascular network. The clear presence of the cytoplasm is due to the accumulation of glycogen and lipids. A variable proportion of tumor cells with granular eosinophilic cytoplasm can be observed and, in some patients, these cells constitute the entire tumor mass (9,20). In their study, Turk et al. (18) found the rate of clear cell, papillary and chromophobe RCCs as 85%, 8%, and 3.5%, respectively (n=230). In our study, rate of clear cell RCC was was (77.9%) as histopathological type. This was followed by chromophobe (10.4%), papillary (9.1%), and multi-locular cell RCCs (2.6%).

In their study, Fuhrman et al. (12) evaluated RCC in 4 grades according to cell nucleus morphology (brief details were given in the method section). Fuhrman grades of I–IV have been shown to correlate with survival in clear cell and papillary RCCs but these grades do notcorrelate with survival in other histologic types (21,22). For better interobserver compliance; 2 working groups, Union Internationale Contre le Cancer and AJCC, published a report in 1997. It was suggested that the NGS should be used only in conventional (clear cell) and papillary RCCs and that in order to facilitate the reproducibility of Fuhrman NGS, grade 1 and 2 would be collected under a single group, thus there would be 3 groups (grade 1+2, 3, and 4) (22).

However, when grade 2 and 3 were grouped together (as grade 1, 2+3, and 4), there were also studies indicating statistically significant differences in terms of survival between groups (13,17). In many studies, double grouping (grade 1+2 and 3+4) and triple grouping (grade 1+2, 3, and 4 or grade 1, 2+3 and 4) were used instead of the classical quadruple Fuhrman NGS to achieve better interobserver agreement (13,17,23). In both univariate and multivariate analyses, it has been reported that classical quadruple Fuhrman NGS, double (grade 1+2 and 3+4) and triple (grade 1+2, 3 and 4) grouped NGSs have an independent prognostic value for survival in RCC (14,15). In our study, we used quadruple Fuhrman NGS scale. The rate of patients with Fuhrman grade 1, 2, 3 and 4 was 5.2%, 61%, 26%, and 7.8%, respectively. In other words, more than half of the patients were Fuhrman grade 2.

It should be kept in mind that all types of RCC may contain foci of high-grade malignant spindle cells (sarcomatoid differentiation). Sarcomatoid RCC is no longer considered as a true subtype since sarcomatoid changes represent undifferentiated cells associated with progression of disease in all RCC cell types (3,9). Turk et al. (18) found the rate of sarcomatoid variant as 3.5% in their study (n=230). In our study, sarcomatoid changes were found only in 6 subjects (7.8%).

In our study, renal sinus, renal vein, perirenal adipose tissue, hilar adipose tissue, and ureter surgical margin invasions were observed in 7.8%, 3.9%, 10.4%, 2.6%, and 2.6% of patients, respectively.

Pathologic stage, based on the diameter of the tumor and the extent of invasion, is the most important indicator of survival. The TNM staging system describes local extension of the primary tumor (T), involvement of regional lymph nodes (N), and presence of distant metastases (M). In the AJCC Cancer Staging guidelines, stage of RCC is defined as follows: T1a tumor is ≤4 cm in greatest dimension and limited to the kidney; T1b tumor is between 4 cm and 7 cm; T2a tumor is >7 cm but ≤10 cm in size and limited to the kidney; T2b tumor is >10 cm in size but confined within the kidney; T3 tumor extends into major veins or invades adrenal gland or perinephric tissues, but not beyond Gerota's fascia; and T4 tumor invades beyond Gerota's fascia (includes contiguous extension into ipsilateral adrenal gland) (24,25).

In a study on the incidence of RCC in the US between 1986 and 1998, 54% of patients had localized tumor (stage I and II), 21% had regional tumor (stage III), and 25% had advanced tumor (stage IV) (26). In their study, Turk et al. (18) reported that stage 1, 2, 3, and 4 (n=230) patients were 49%, 32%, 14% and 5%, respectively. In our study, the tumor stages of RCCs were mostly stage 1 and 2 and the ratio of each was 40%. Grade 3a was observed only in 18.1% of the patients, whereas grade 4 was oserved in none of the patients. We believe that early stage tumors can be diagnosed with advanced imaging techniques.

In our study; it was observed that all pathological changes were significantly differentiated by gender except for the primary tumor stage ($p<0.001$). The rates of tumor according to age groups were 3.9%, 36.8% and 59.2% in patients aged "18-39" (n=4), "40-59" (n=28) and "60 or above" (n=45) years, respectively. Clear cell RCC rates in these age groups were; 75%, 78.6% and 77.8%, respectively; chromophobe RCC rates were 25%, 10.7% and 8.9%, respectively; and papillary RRC rates were 0%, 3.4% and 13.3%, respectively. Multilocular RCC was observed only in 7.1% of the patients in 40-59 age group.

According to the results of the regression analysis between the tumor lateralization and tumor size, histopathological type, and primary tumor stages, it was found that these 3 features did not have a predictive effect on lateralization.

Study Limitations

Genetic factors (2-4% of RCC is hereditary), chronic kidney disease (and therefore long-term dialysis) kidney transplantation, and acquired cystic disease of kidney are major factors for the

etiology of RCC. Smoking, obesity, hypertension, and/or the use of medications associated with these diseases -although the risk is low - have been identified as risk factors. In our study, we focused on and discussed the pathological data. Therefore, some clinical data were not included in our study. For the same reason, we did not correlate survival rates with Fuhrman NGS.

Conclusion

RCCs are the 3rd most common cancer after prostate and bladder tumors among urologic cancers. Morphologically and immunophenotypically, RCCs are divided into many different types and are divided into three main subtypes (≥5% incidence) with the malignant course. Each type has differences in terms of genetics, biology, and behavior. Due to this, the pathologist must differentiate cell types routinely by morphology and immunohistochemical markers as well as by cytogenetic and molecular genetic analysis particularly when the cell type is equivocal.

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Ethics

Ethics Committee Approval: The study was approved by the University for the Non-Interventional Clinical Research Ethics Board (Date: 08.08.2019, Decision No: 17).

Informed Consent: Retrospective study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Supervision: S.H., S.G., Critical Review: S.H., S.G., Concept D.G., Design: D.G., İ.E.S., Data Collection or Processing: D.G., İ.E.S., S.G., Analysis or Interpretation: D.G., İ.E.S., Literature Search: D.G., İ.E.S., S.H., Writing: D.G.

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