

## Research Article

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# Compare fuhrman nuclear and chromophobe tumor grade on chromophobe RCC

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**Abstract:** Background: Chromophobe renal cell carcinoma (chRCC) has a favorable prognosis. Due to irregular nuclei and nuclear pleomorphism, chRCC has a high Fuhrman nuclear grade (FNG). The chromophobe tumor grade (CTG) is a novel three-tier grading system that has been reported to be a better prognosticator than the traditional FNG. We compared the two nuclear grading systems in terms of patients' clinical outcomes.

**Patients and Method:** We performed this retrospective chart review of all patients with chRCC from 2000 to 2017. All pathologic features and CTG and FNG results were re-evaluated.

**Result:** Eighteen patients' records were reviewed with a mean follow-up of 70.6 months. The nuclear grading distribution was as follows: FNG 2, 56%; FNG 3, 39%; FNG 4, 5%; CTG 1, 78%; CTG 2, 17%; and CTG 3, 6%. Only one patient died. This patient had adrenal invasion, lung metastasis, sarcomatoid change and tumor necrosis, and the tumor was graded as FNG 4 and CTG 3. Overall survival was associated with both FNG and CTG.

**Conclusion:** Chromophobe RCC was associated with a low rate of cancer-specific death and sarcomatoid differentiation. Both FNG and CTG were associated with overall survival.

**Keywords:** Chromophobe renal cell carcinoma; Nuclear grading system; Fuhrman nuclear grade; Chromophobe tumor grade

## 1 Introduction

Renal cell carcinoma (RCC) was diagnosed in 350,000 people worldwide in 2013 [1]. In the United States of America, about 65,000 new patients are diagnosed with RCC and almost 15,000 patients die each year [2]. Improvements in diagnostic tools have led to earlier diagnosis of RCC in recent years. Clear cell RCC is the most common type of RCC, and chromophobe RCC (chRCC) only accounts for 5% of all cases of RCC [3]. Use of the Fuhrman nuclear grade (FNG) is worldwide, and it categorizes tumors as grade 1 to grade 4 according to nuclei size, shape, presence of nucleoli, and nuclear pleomorphism [4]. However, new subtypes of RCC were defined by the World Health Organization (WHO) in 2016, and the FNG has not yet been validated for these subtypes of RCC, and a proposed four-tier World Health Organization /International Society of Urological Pathology grading system is only applicable for clear cell RCC and papillary RCC [5].

Chromophobe RCC has a better prognostic outcome than clear cell RCC, with a 10-year survival rate of more than 80% [6, 7]. However, due to irregular nuclei and nuclear pleomorphism, chRCC's high FNG can confuse physicians because of the inconsistency of a favorable prognosis and high grade. Delahunt et al. concluded that FNG was not suitable for chRCC [8], and {Delahunt, 2007 #7} Paner et al. proposed a three-tier grading scheme that was strongly associated with pathologic stage and was shown to be an independent predictive factor of outcomes [9]. This grading system has not been applied globally

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due to controversial conclusions between studies. In this study, we re-evaluated patients with chRCC at our hospital using the two grading systems and patient clinical outcomes.

## 2 Materials and methods

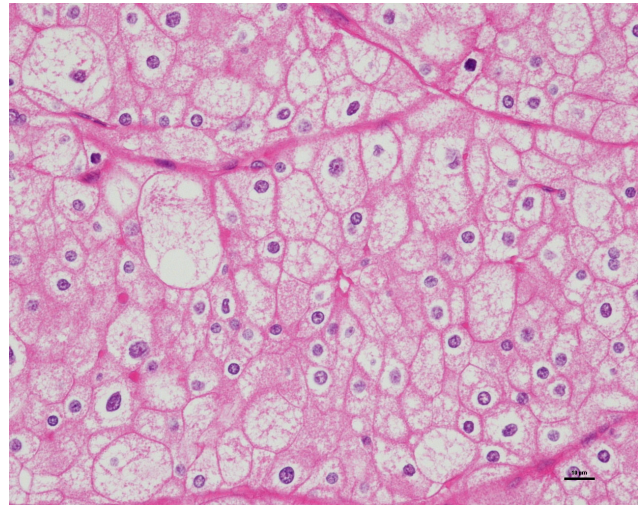
After institutional review board approval, charts of all patients with chRCC from January 2000 to May 2017 were reviewed retrospectively. Patients who did not receive surgical resection and those with no available pathologic slide reviews were excluded. Informed consent has been obtained from all individuals included in this study.

Clinical features included age at surgery, sex, laterality, location, symptoms at presentation, treatment methods, and performance status according to the American Society of Anesthesiologists (ASA) class at surgery. The vital signs of each patient were also reviewed. Image surveys including computed tomography and ultrasound performed 3-6 months after surgery and then annually during follow-up. Adverse events including local recurrence, distance metastasis, and death owing to disease were recorded by clinic visit or telephone interview. Follow-up ended on September 30, 2017.

Pathologic features included tumor size, margin status, neurovascular invasion, lymph node status, cell type (classic or pale, eosinophilic, mixed cell types), broad alveolar growth, sarcomatoid change, necrosis, and pathologic TNM stage according to the 2016 American Joint Committee on Cancer (AJCC 8<sup>th</sup> edition, 2016). The nuclear characteristics were evaluated by FNG (grades 1, 2, 3, and 4) and the chromophobe tumor grade (CTG) three-tier grading system described by Paner et al. [9] (Table 1) The novel CTG system is based on nuclear crowding and anaplasia. Tumor slides were assessed at 100x

and 400x magnification. Nuclear crowding was defined as high nuclear/cytoplasmic density at 100x magnification and some nuclei contact at 400x magnification. Anaplasia was defined as a  $\geq$  three-fold variation in nuclear size and distinct nuclear chromatin irregularities. At least two areas were graded, and the highest grade was assigned to the tumor. A grade 1 tumor was defined as a classic chRCC pattern without nuclear crowding and anaplasia (Figure 1); grade 2 was defined as nuclear crowding and nuclear pleomorphism (Figure 2); and grade 3 was defined as frank anaplasia or sarcomatoid change (Figure 3). All pathologic features and tumor grading were reviewed by one pathologist (SHD).

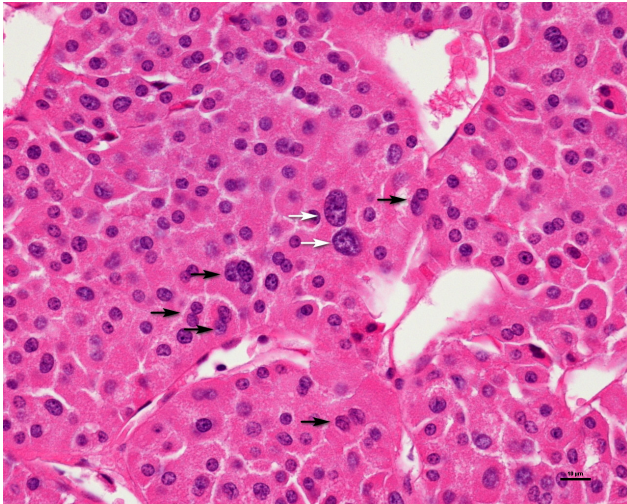
Descriptive and analytic statistics of the data were computed using SPSS (version 21.0; IBM SPSS Statistics, IBM Corporation, Chicago, IL) for Windows. All tests were two-tailed, and the level of significance was set at  $p < 0.05$ . Fisher's exact test and the t-test were used for compari-



**Figure 1:** Classical chromophobe renal cell carcinoma pattern with wide constitutive nuclear range, without nuclear crowding and anaplasia (400x), CTG 1, FNG 3

**Table 1:** The criteria of two tumor grading system for chromophobe RCC

Grade	Fuhrman nuclear grading	Chromophobe tumor grading
Grade 1	Nucleoli are absent or inconspicuous and basophilic at 400x	Wide constitutive nuclear range but without nuclear crowding and anaplasia
Grade 2	Nucleoli are conspicuous and eosinophilic at 400x and visible but not prominent at 100x	Geographic nuclear crowding and the presence of nuclear pleomorphism
Grade 3	Nucleoli are conspicuous and eosinophilic at 100x	Presence of frank anaplasia (nuclear polylobation, tumor giant cells) or sarcomatoid change
Grade 4	Extreme nuclear pleomorphism, multinucleate giant cells, and/or rhabdoid, sarcomatoid differentiation	

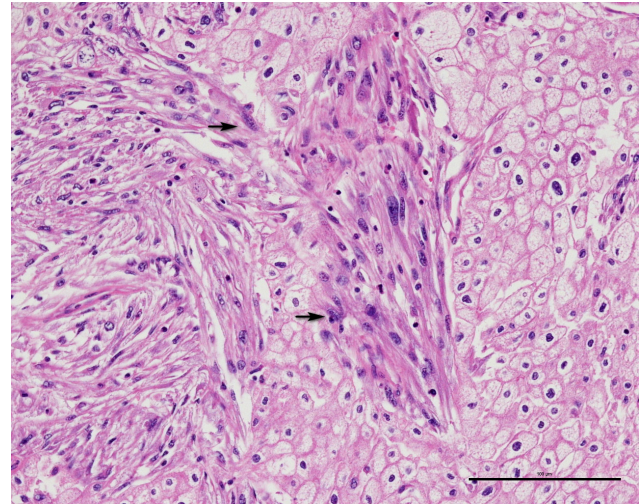


**Figure 2:** Nuclear crowding (black arrow) with pleomorphism (white arrow, three-fold variation in nuclear size and distinct nuclear chromatin irregularities) (400x), CTG 2, FNG 3

sons of demographics including pathologic parameters and survival status. Associations between nuclear grade and pathologic stage were evaluated using Fisher's exact test.

### 3 Results

A total of 20 patients were identified, of whom two were excluded due to having both clear cell and chromophobe cell types. The remaining 18 patients (eight men and ten women; median age 51.7 years, range 35 – 74 years) were enrolled into the analysis. The clinicopathologic and demographic characteristics are illustrated in Table 2. Fourteen patients received radical nephrectomy, and four patients received partial nephrectomy. Neither lymph node dissection nor venous thrombectomy was performed as there was no obvious lymph node enlargement or tumor thrombus. The patients' performance status was assessed by ASA class; two cases were class I, eleven cases were class II, and five were class III. The average tumor size was 7.2 cm (range 2.5 – 14 cm), and 84% of the patients had a low stage (stage I – II) and 16% had a high stage (stage III – IV). Pathology showed that 44% of the cases were mixed type (classic and eosinophilic types) and 44% had tumor necrosis. One case had sarcomatoid change, and another case had neurovascular invasion. All of the cases had a broad alveolar growth pattern. The nuclear grading was as follows: FNG 2, 56%; FNG 3, 39%; FNG 4, 5%; CTG 1, 78%; CTG 2, 17%; and CTG 3, 6%. None of the cases had FNG 1 in this study. 9 cases in FNG 2 and 5 cases in FNG 3 downgrade to CTG 1, 2 cases in FNG 3 downgrade to CTG



**Figure 3:** Tumor cells with sarcomatoid change (black arrow) (200x), CTG 3, FNG 4

2, and one case remained grade 2 in two grading systems. One case remained in the highest grade in pathologic finding.

The mean follow-up period was 70.6 months (range 3 – 205 months). Two patients died. One of the patients died due to recurrence of colorectal cancer with multiple metastases, and the other died of chRCC. This patient had a tumor of 9.5 cm in size with adrenal gland invasion and lung metastasis and died 3 months after nephrectomy. Pathology revealed a pale cell type, sarcomatoid change, and tumor necrosis. The tumor grade was FNG 4 and CTG 3. None of the other patients had local recurrence or distant metastasis. The adverse event rate was 5.56%.

Risk factor analysis showed that neither FNG nor CTG were significantly associated with patient age, sex, surgical margin, cell type, neurovascular invasion, sarcomatoid change, or necrosis. Both FNG and CTG were significantly associated with overall survival (Table 2), however there was no association with cancer-specific survival. In addition, there were no significant associations between survival and age, sex, tumor size, stage or other pathologic factors. There was also no significant relationship between overall survival with FNG ( $p=0.142$ ) and CTG ( $p=0.176$ ) in the nonsarcomatoid chRCC cohort. Pathologic stage was significantly associated with FNG ( $p = 0.005$ ), but not with CTG ( $p = 0.064$ ) (Table 3).

### 4 Discussion

Previous studies have demonstrated the nuclear characteristics of chRCC according to FNG and CTG (Figure



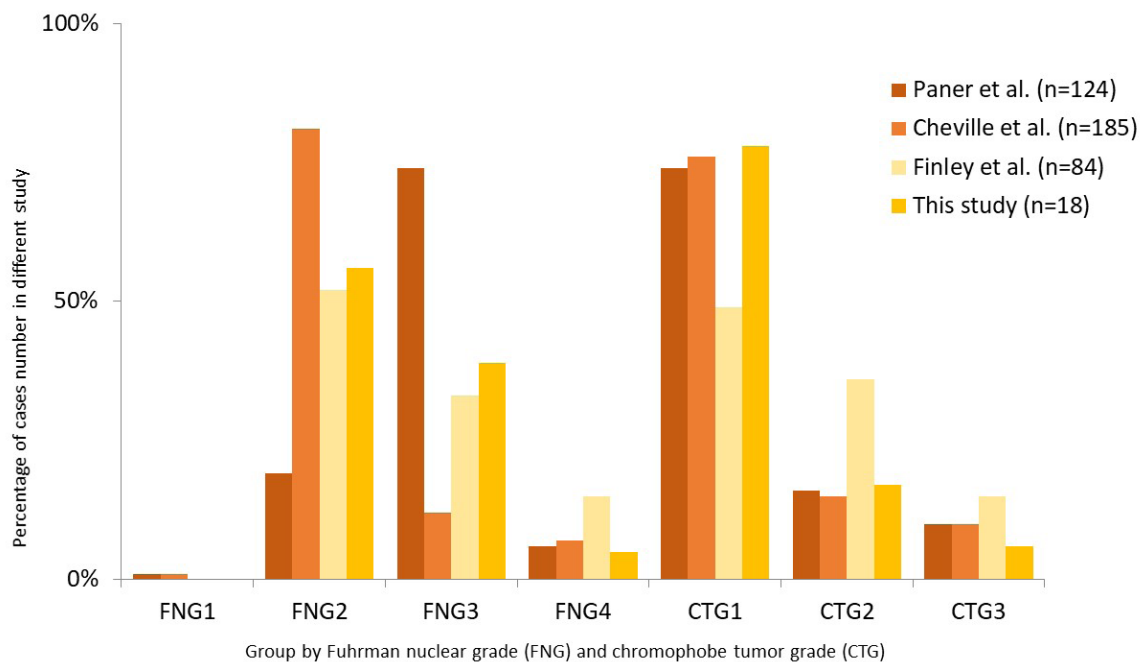
**Table 2:** Clinicopathologic and demographic characteristics of patients. Associations between survival and parameters

		Mean (range)			p value
Age at surgery (years)		51.7 (35-74)			0.609
Maximum tumor size (cm)		7.2 (2.5-14)			0.888
Follow up time (months)		70.6 (3-205)			
		Number (%)	Survival (%)	Death (%)	p value
Sex	Female	10 (56)	10 (100)	0 (0)	0.183
	Male	8 (44)	6 (89)	2 (11)*	
ASA	I	2 (11)	2 (100)	0 (0)	0.137
	II	11 (61)	11 (100)	0 (0)	
	III	5 (28)	3 (60)	2 (40)*	
Stage	I	10 (56)	9 (90)	1 (10)	0.379
	II	5 (28)	5 (100)	0 (0)	
	III	1 (5)	1 (100)	0 (0)	
	IV	2 (11)	1 (50)	1 (50)*	
Margin free status					0.111
	Yes	17 (94)	16 (94)	1 (6)	
	No	1 (6)	0 (0)	1 (100)*	
Neurovascular invasion					>0.999
	Yes	1 (6)	1 (100)	0 (0)	
	No	17 (94)	15 (88)	2 (12)*	
Cell type	1. classic (pale)	1 (5)	0 (0)	1 (100)*	0.176
	2. eosinophilic	5 (28)	5 (100)	0 (0)	
	3. mixed cell types	12 (67)	11 (92)	1 (8)	
Sarcomatoid	Yes	1 (6)	0 (0)	1 (100)*	0.111
	No	17 (94)	16 (94)	1 (6)	
Necrosis	Yes	8 (44)	8 (80)	2 (20)*	0.477
	No	10 (56)	8 (100)	0 (0)	
Fuhrman nuclear grade					0.046
	2	10 (56)	10 (100)	0 (0)	
	3	7 (39)	6 (86)	1 (14)	
	4	1 (5)	0 (0)	1 (100)*	
Chromophobe tumor grade					0.039
	1	14 (78)	14 (100)	0 (0)	
	2	3 (17)	2 (67)	1 (33)	
	3	1 (6)	0 (0)	1 (100)*	

\* represents the patient's clinicopathologic characteristics who died due to chromophobe RCC

**Table 3:** Associations between TNM stage and nuclear grade

	Stage I (%)	Stage II (%)	Stage III (%)	Stage IV (%)	Total n	p value
Fuhrman nuclear grade 2	30	50	10	10	10	0.005
Fuhrman nuclear grade 3	100	0	0	0	7	
Fuhrman nuclear grade 4	0	0	0	100	1	
Chromophobe tumor grade 1	57	36	0	7	14	0.064
Chromophobe tumor grade 2	67	0	33	0	3	
Chromophobe tumor grade 3	0	0	0	100	1	

**Figure 4:** Comparison of FNG and CTG distributions in different studies Only two studies had 1% cases classified as FNG 1. Most cases were classified as FNG 2 or 3 and were classified as CTG 1

4) [9-11]. All of these studies and our data showed that approximately 0 to 1% of all cases were classified as FNG 1. Most cases were classified as FNG 2 or 3, and there were noticeable differences in each study. Most cases were classified as CTG 1, and it seemed to be more consistent in these four studies. As no lowest FNG grade is associated with a good prognosis, Finley et al. suggested that FNG cannot be used for chRCC [10]. Delahunt et al. reviewed 87 cases with chRCC and reported no associations between whole tumor and focal Fuhrman grade and adverse events. They suggested that chRCC often have an insignificant nucleolus, and unusual nuclear pattern. Because FNG relies on individual human observation of nuclear size, shape, and nucleolar prominence, interobserver error may have occurred and caused variations in previous studies. Delahunt concluded that the Fuhrman grading system is not

appropriate for chRCC [8]. The fourth edition of the WHO classification also suggests that the Fuhrman system should not be used for chRCC, and that a new grading system for chRCC may be internationally accepted in the future [5]. In this study, FNG was significantly associated with overall survival, but not cancer-specific survival. This is consistent with previous studies in that the FNG system is not suitable for chRCC.

Paner and colleagues first proposed the three-tier CTG tumor grading system for chRCC. In their study, all 12 CTG 3 tumors showed sarcomatoid changes, and tumors with sarcomatoid differentiation were excluded from their analysis. The pathologic stage was strongly positively associated with CTG, and according to multivariate Cox regression models, CTG and necrosis were independent predictors of adverse events [9]. Finley et al. reported a

strong association between pathologic T stage and both grading systems. In ROC curve analysis, for RFS and OS, CTG provided slightly higher accuracy than FNG for the overall and non-sarcomatoid cohorts [10]. However, Chevillie and colleagues reported different results. They collected data from only non-sarcomatoid and stage I and II cohorts, and found no association between CTG or FNG with cancer-specific survival. Therefore, they suggested that CTG did not provide more prognostic information [11]. In this study, pathologic stage was significantly associated with FNG, and tended to be associated with CTG in the patients overall. However, the number of cases was small.

Previous studies have reported that sarcomatoid differentiation ranges from 2% to 13% of all chRCC [7, 9-13]. {Finley, 2011 #3} However, the number of cases varied greatly between these studies. Sarcomatoid differentiation was associated with adverse outcomes and the highest grade. The number of cases may have influenced the number of adverse events. In our study, only one tumor presented with sarcomatoid differentiation, and the patient died. There were no other cases of local recurrence or metastasis. Therefore, the association between survival and grading system may be affected by the small numbers of cases overall and those with sarcomatoid differentiation.

Weinzierl and colleagues reported that only pathologic stage CTG 3 was significantly associated with adverse events, and that CTG 1 and 2 did not have this association [12]. Xie et al reported 209 Chinese patients with chRCC, in whom multivariate Cox regression analysis showed that tumor stage and CTG were independent predictors of disease-free survival. They also compared CTG 1+2 with CTG 3 and reported that CTG3 was associated with significantly worse disease-free survival, however, they did not find a significant difference between CTG 1 and 2 [7]. Chevillie et al analyzed 185 patients with chRCC adjusted by TNM stage, and found that cancer-specific death was associated with CTG. With the reference set as CTG 1 compared with CTG 2, the p value was 0.13. This indicated that only CTG 3 compared with CTG 1 showed a significant difference in cancer-specific death [11]. In our study, nonsarcomatoid chRCC was also analyzed. Therefore, only CTG 1 and 2 were analyzed. FNG and CTG failed to show a significant relationship between the overall survival rate in the nonsarcomatoid chRCC cohort. This result is consistent with previous studies. As CTG 3 represents sarcomatoid change which in turn indicates poor survival, the authors concluded that CTG 3 may be an independent prognostic factor. However, the predictive value of CTG 1 and 2 was

relatively weak, and further variables may be needed in this grading system to increase prognostic accuracy.

There are several limitations to this study. First, this was a retrospective study from a single center. Therefore, observation bias may be present. Second, the number of cases was small, and only one adverse event was found during a mean follow-up period of 70.6 months. Our study had relatively longer follow-up times than previous studies that compared both FNG and CTG. The only study that had a longer follow up time (126 months) was written by Chevillie and college [11]. The other studies had follow up times shorter than 60 months. We reviewed all suspected cases, of which only 18 were compatible with chRCC, and we reviewed adverse events according to imaging findings and telephone interviews. Multivariate analysis cannot apply in our study due to fewer adverse events. The largest study of chRCC was by Volpe and colleagues, in which only 8.6% of the patients had disease recurrence and 6.2% of the patients died of the disease [6]. This shows that chRCC has a relatively good prognosis and low adverse event rate. Third, only one pathologist reviewed all pathological features in our study. Perez-Pedrosa et al. evaluated interobserver reproducibility of CTG, and found moderate discrete agreement between six participating observers [14]. Therefore, observer bias may have occurred in our study.

In conclusion, chRCC had low rates of cancer-specific death and sarcomatoid differentiation. Both FNG and CTG were associated with overall survival. Further studies are needed to evaluate the value of this system.

### Abbreviations

Chromophobe renal cell carcinoma (chRCC)  
Fuhrman nuclear grade (FNG)  
Chromophobe tumor grade (CTG)

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**Conflicts of interest:** The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

### References

- [1] Capitanio U, Montorsi F. Renal cancer. *Lancet* (London, England). 2016;387(10021):894-906; DOI: 10.1016/s0140-6736(15)00046-x

- [2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA: a cancer journal for clinicians*. 2018;68(1):7-30; DOI: 10.3322/caac.21442
- [3] Frees S, Kamal MM, Knoechlein L, Bell R, Ziesel C, Neisius A, et al. Differences in Overall and Cancer-specific Survival of Patients Presenting With Chromophobe Versus Clear Cell Renal Cell Carcinoma: A Propensity Score Matched Analysis. *Urology*. 2016;98:81-7; DOI: 10.1016/j.urology.2016.05.048
- [4] Fuhrman SA, Lasky LC, Limas C. Prognostic significance of morphologic parameters in renal cell carcinoma. *The American journal of surgical pathology*. 1982;6(7):655-663
- [5] Moch H, Cubilla AL, Humphrey PA, Reuter VE, Ulbright TM. The 2016 WHO Classification of Tumours of the Urinary System and Male Genital Organs-Part A: Renal, Penile, and Testicular Tumours. *European urology*. 2016;70(1):93-105; DOI: 10.1016/j.eururo.2016.02.029
- [6] Volpe A, Novara G, Antonelli A, Bertini R, Billia M, Carmignani G, et al. Chromophobe renal cell carcinoma (RCC): oncological outcomes and prognostic factors in a large multicentre series. *BJU international*. 2012;110(1):76-83; DOI: 10.1111/j.1464-410X.2011.10690.x
- [7] Xie Y, Ma X, Li H, Gao Y, Gu L, Chen L, et al. Prognostic Value of Clinical and Pathological Features in Chinese Patients with Chromophobe Renal Cell Carcinoma: A 10-Year Single-Center Study. *Journal of Cancer*. 2017;8(17):3474-9; DOI: 10.7150/jca.19953
- [8] Delahunt B, Sika-Paotonu D, Bethwaite PB, McCredie MR, Martignoni G, Eble JN, et al. Fuhrman grading is not appropriate for chromophobe renal cell carcinoma. *The American journal of surgical pathology*. 2007;31(6):957-60; DOI: 10.1097/01.pas.0000249446.28713.53
- [9] Paner GP, Amin MB, Alvarado-Cabrero I, Young AN, Stricker HJ, Moch H, et al. A novel tumor grading scheme for chromophobe renal cell carcinoma: prognostic utility and comparison with Fuhrman nuclear grade. *The American journal of surgical pathology*. 2010;34(9):1233-40; DOI: 10.1097/PAS.0b013e3181e96f2a
- [10] Finley DS, Shuch B, Said JW, Galliano G, Jeffries RA, Afifi AA, et al. The chromophobe tumor grading system is the preferred grading scheme for chromophobe renal cell carcinoma. *The Journal of urology*. 2011;186(6):2168-74; DOI: 10.1016/j.juro.2011.07.068
- [11] Cheville JC, Lohse CM, Sukov WR, Thompson RH, Leibovich BC. Chromophobe renal cell carcinoma: the impact of tumor grade on outcome. *The American journal of surgical pathology*. 2012;36(6):851-6; DOI: 10.1097/PAS.0b013e3182496895
- [12] Weinzierl EP, Thong AE, McKenney JK, Jeon SH, Chung BI. Relating prognosis in chromophobe renal cell carcinoma to the chromophobe tumor grading system. *Korean journal of urology*. 2014;55(4):239-44; DOI: 10.4111/kju.2014.55.4.239
- [13] Przybycin CG, Cronin AM, Darvishian F, Gopalan A, Al-Ahmadie HA, Fine SW, et al. Chromophobe renal cell carcinoma: a clinicopathologic study of 203 tumors in 200 patients with primary resection at a single institution. *The American journal of surgical pathology*. 2011;35(7):962-70; DOI: 10.1097/PAS.0b013e31821a455d
- [14] Perez-Pedrosa A, Ortiz-Rey JA, Lorenzo-Mahia Y, Iglesias-Rodríguez B, Peteiro-Cancelo A, Gonzalez-Carrero J. Interobserver reproducibility of a grading system for chromophobe renal cell carcinoma. *Actas urológicas españolas*. 2013;37(6):338-41; DOI: 10.1016/j.acuro.2012.04.005