Original Paper

Histopathological Prognostic Factors in Clear Cell Renal Cell Carcinoma

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ABSTRACT: Clear cell renal cell carcinoma (CCRCC) is the most frequent type of renal cell carcinoma. Fuhrman grade and tumor stage are prognostic factors with great importance in survival rate. This study was performed on 75 cases of CCRCC diagnosed in the Anatomical Pathology Laboratory of the County Clinical Emergency Hospital of Craiova between 2014 and 2017. The biological material was represented by pieces of nephrectomy. The cases were analyzed on two criteria: epidemiology (age, sex) and histopathology (Fuhrman grade, tumor stage, architectural pattern, sarcomatoid transformation, and necrosis). Statistical analysis was done using Chi Square tests. Average diagnosis age of CCRCC was 58.8±10.2 years, predominantly in male patients (66.7%). Tumor sizes were between 2 and 14cm, with an average of 6.7±2.9cm. Most cases were determined to be tumor stage III (60%) and Fuhrman grade 2 (56%), followed, in order of frequency, by tumor stages I and II (28% and 10.7%) and Fuhrman grades 3 and 1 (21.3% and 20%). High Fuhrman grade CCRCC were significantly associated with advanced tumor stage (p<0.05, χ2 test). Most cases presented a mixed pattern, significantly associated with advanced tumor stages (p<0.05, χ2 test). Even though the presence of sarcomatoid transformation was more frequent in advanced tumor stages, it wasn't significantly linked to them (p<0.05, χ2 test). Conclusions: Analyzed histopathological parameters are useful for determining CCRCC aggressiveness. CCRCC in advanced tumor stages is associated with high Fuhrman grade and mixed architectural pattern.

KEYWORDS: Clear cell renal cell carcinoma, Fuhrman grade, tumor stage, architectural pattern.

Introduction

Clear cell renal cell carcinoma (CCRCC) is the most common histological subtype of renal cell carcinoma, representing around 70% of renal malignancies [1]. CCRCC affects most frequently male patients (male:female-2:1) with an incidence spike in the 6-7 decade of life [1]. CCRCC is mostly sporadic and only 5% of occurrences are associated with genetic cancer syndromes [2], such as von Hippel-Lindau Syndrome.

Tumor stage, Fuhrman grade, tumor necrosis, sarcomatoid transformation, fat and vascular invasion, all presented significant correlations with the progression and metastasis of CCRCC [3,4].

Fuhrman nuclear grade is the most used scale in CCRCC classification. Low grade CCRCC (Fuhrman 1 and 2) are associated with better prognosis, unlike high grade (Fuhrman 3 and 4) CCRCC which are correlated with bad prognosis and high morbidity [5,6].

Tumor stage is another important prognosis factor in CCRCC, which correlates with tumor size, vascular invasion, tumor necrosis and the 5-year survival rate [7]. Even though there is a powerful association between pathological stage and death risk, the pathological stage is not enough to offer prognosis information for most patients [5].

The presence of sarcomatoid transformation or tumor necrosis, even in focal form, was associated with bad prognosis [8].

The purpose of the study was to determine the incidence and relation between prognosis factors (pattern, Fuhrman grade, tumor stage, vascular invasion, necrosis, sarcomatoid transformation) in patients with clear cell renal cell carcinoma.

Materials and Methods

The study included 75 cases of CCRCC diagnosed in the Anatomical Pathology Laboratory of the County Clinical Emergency Hospital of Craiova between 2014 and 2017.

The biological material was represented by pieces of nephrectomy that were processed using the classic method represented by paraffin inclusion and hematoxylin-eosin staining after fixation in 10% buffered formalin.

Lesions classification was done according to latest OMS recommendation [2].

We performed an epidemiological (age, sex) and histopathological (tumor size, Fuhrman grade, tumor stage, architectural pattern, sarcomatoid transformation, fat and vascular invasion) analysis of the cases. Statistical analysis was done using Chi Square (χ^2) tests in SPSS software. The study was approved by the local ethics committee (no.41/27.03.2018).

Results

The study included 75 cases of CCRCC and it indicated an average age of diagnosis of 59.8±10.2 years with variation between 33 and 80 years. Most CCRCC were identified in male patients, 50 cases (66.7%). Tumor sizes were between 2 and 14cm, with an average of 6.7±2.9cm.

Histopathological analysis of the 75 cases of CCRCC showed that more than half of them were grade Fuhrman 2 (42 cases=56%) and tumor stage III (45 cases=60%), followed, in order of frequency, by Fuhrman grades 3 (21.3%) and 1 (20%) and tumor stages I (28%) and II (10.7%) (Table 1, Fig.1).

Out of the 75 analyzed cases, 30 presented a mixed pattern (40%) (Fig. 1), 20 showed cystic pattern (26.7%), 18 showed solid pattern (24%), 5 showed papillary pattern (6.7%) and 2 cases showed alveolar pattern (2.7%). Fat invasion was present in 46 cases (61.3%) and vascular invasion was present in 13 cases (17.3%) (Table 1, Fig.1).

Table 1. Histopathological and clinical parameters of CCRCC

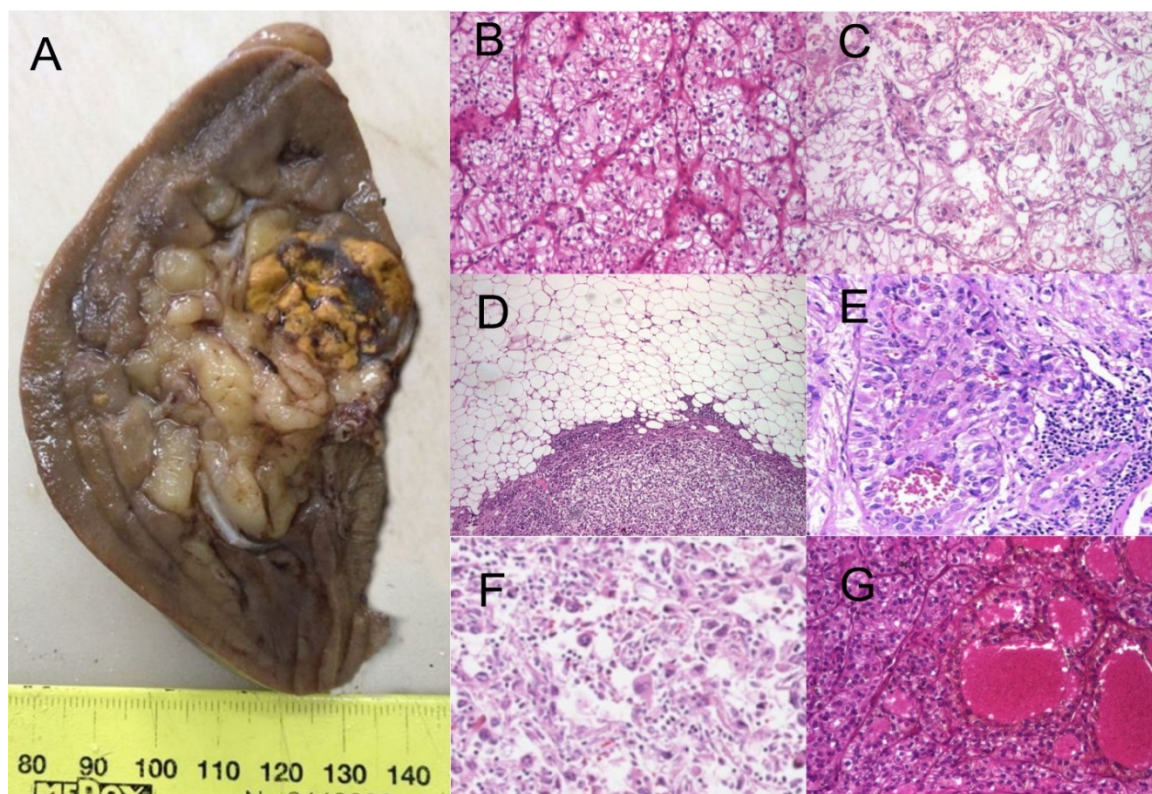| Characteristics	Parameters	Number of cases	Percent %
Gender	Male	50	66.7
	Female	25	33.3
Fuhrman grade	1	15	20.0
	2	42	56.0
	3	16	21.3
	4	2	2.7
Pathological T stage	I	21	2.7
	II	8	28.0
	III	45	10.7
	IV	1	60.0
Patterns	Alveolar	2	2.7
	Cystic	20	26.7
	Mixt	30	40.0
	Papillary	5	6.7
	Solid	18	24.0
Fat invasion	Present	46	61.3
	Absent	29	38.7
Microscopic vascular invasion	Present	13	17.3
	Absent	62	82.7

Fig.1. Macroscopic (A) and histopathological aspect of clear cell renal cell carcinoma (B, C, D, E, F, G). A. Macroscopic aspect of CCRCC; B. Fuhrman grade 1 CCRCC, HE-ob. 10x;C. Fuhrman grade 1 CCRCC, HE-ob. 10x; D. CCRCC with fat invasion, HE-ob. 10x; E. CCRCC with vascular invasion, HE-ob. 10x; F. CCRCC with sarcomatoid transformation, HE-ob. 10x; G. CCRCC with mixed pattern, HE-ob. 10x

We noticed significant associations between Fuhrman grade and tumor stage ($p<0.05$, χ^2 test), and also between Fuhrman grade and vascular invasion ($p<0.05$, χ^2 test) (Table 2) (Fig.2). The associations between Fuhrman grade and pattern and tumor necrosis were not significant.

There were also significant associations between tumor stage and tumor necrosis ($p=0.022$), architectural pattern ($p=0.010$) and vascular invasion ($p=0.015$) (Table 2) (Fig.2).

Most cases presented mixed pattern, which is significantly associated with advanced tumor stages ($p<0.05$, χ^2 test).

Even though sarcomatoid transformation was more frequent in advanced tumor stages, this association was not significant ($p>0.05$, χ^2 test) (Table 2) (Fig.2).

Table 2. Statistic associations between the studied parameters

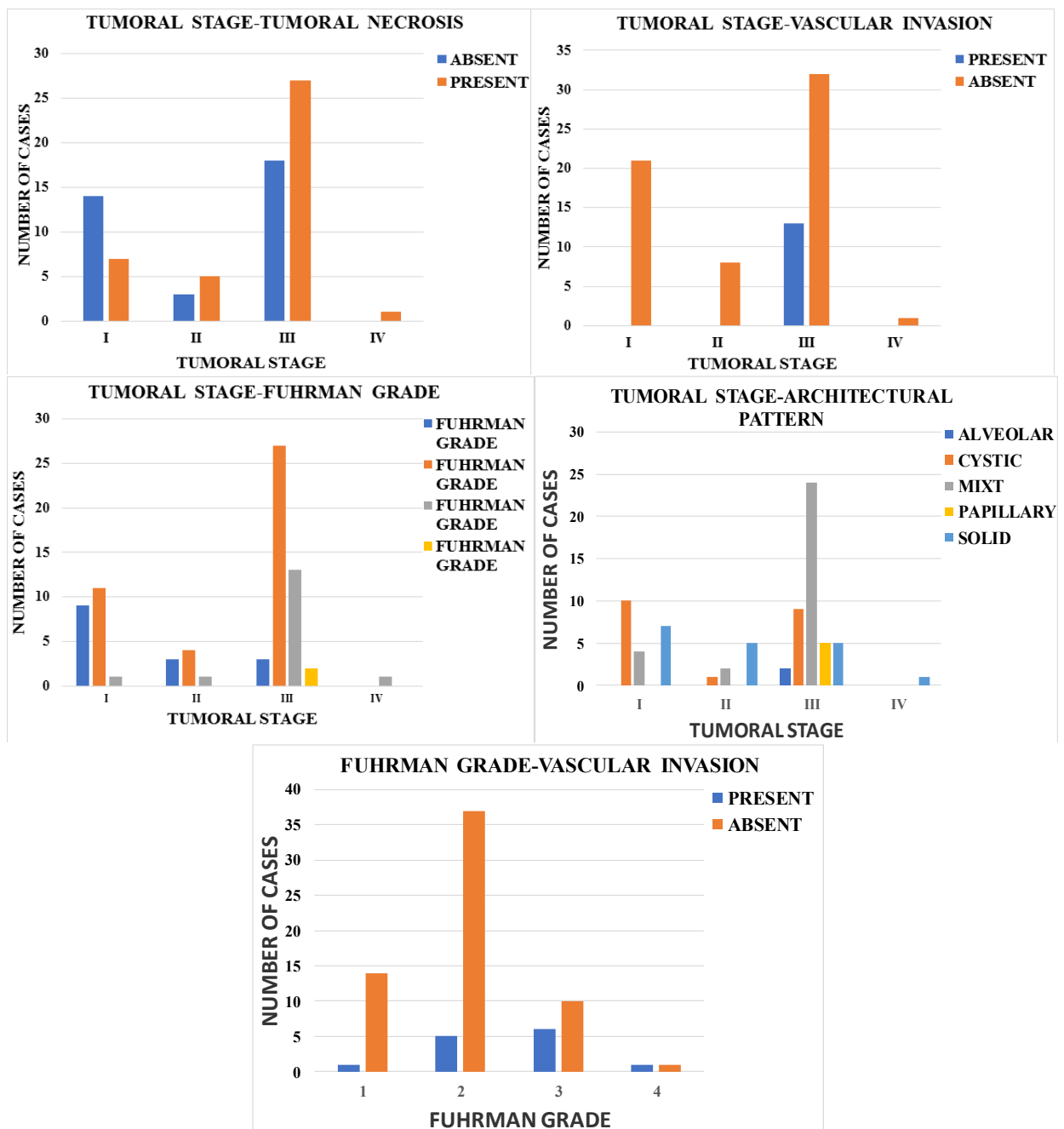| Analyzed parameters	Fuhrman Grade	Pathological T Stage
MICROSCOPIC VASCULAR INVASION	P=0,044	P=0,015
TUMORAL NECROSIS	P=0.079	P=0,022
PATTERN	P=0,055	P=0,010
SARCOMATOID TRANSFORMATION	P=0,98	P=0,55

Fig.2. Statistical associations between the studied parameters

Discussion

Clear cell renal cell carcinoma are the most frequent malignant renal neoplasms. These originate in the renal tube epithelia and most of them show an invasive growth pattern [2].

Important prognostic factors in CCRCC are Fuhrman grade, tumor stage, vascular invasion, sarcomatoid transformation and fat invasion [6].

All these factors were studied in multiple papers and correlated with disease prognostic and survival rate [3].

In the present study, most CCRCC were identified in male patients (66.6%). The average diagnosis age was 59.8±10.2 years, extreme ages being 33 and 80 years. Literature data shows that this malignant neoplasm affects mostly men, with a maximum incidence in the 6th or 7th life decade. This data is supported by Cheville JC et al. [1], but also newer studies, such as Hakushi Kim et al. [6], where the average diagnosis age was 62 years, with extreme ages of 25 and 85 years, most patients being male (309 men out of 406 cases). Similar data was obtained by Damien Ambrosetti et al. in 2018 [9], and S. Chaves Portela et al. in 2011 [10].

Architectural pattern was only significantly associated with tumor stage. There is very scarce literature data about this. Jérôme Verine et al. shows, in an article published in 2018, that the score based on the architectural pattern of CCRCC is better than all other morphological classification systems and it represents an independent predictor for disease-free survival [11].

Fuhrman grade and tumor stage are considered to be the most important prognostic factors in CCRCC, multiple studies indicate Fuhrman grade as a prognostic factor for survival, independent from pathologic stage [12,13].

In Tahir Qayyum's article from 2013, he shows a significant correlation between Fuhrman grade and tumor stage (p=0.001) [14].

Our study also shows a significant association between Fuhrman grade and tumor stage (p<0,05, χ^2 test). Similar statistical data was found in the 2017 study by Shao-Hao Chen et al. [5].

Similar to our study, most CCRCC were found to be Fuhrman grade 2.

In our study, we didn't find a significant association between Fuhrman grade, vascular invasion and tumor necrosis. A recent study reports that Fuhrman grade, tumor necrosis and vascular microinvasion are independent prognostic factors in a multivariate analysis [6].

Another significant correlation was found between tumor stage and vascular invasion, similar data found in the article published by Hai Huang in 2015 [15], where increased incidence of vascular invasion is associated with advanced tumor stages.

Sarcomatoid transformation is considered a factor of bad prognostic, being associated with advanced stages [8].

Even though our study also noted that the presence of sarcomatoid transformation is more frequent in advanced tumor stages, the association was not significant (p>0.05, χ^2 test).

Conclusion

The results of this study underline the importance of histopathological parameters as prognostic factors in CCRCC. They prove useful in determining the aggressiveness of the carcinoma.

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