# Clinical And Pathological Prognosis Factors Found In Renal Cell Carcinoma

B. Ş. Sandu [1,2], Ş. Raşcu [1,2], M. Costache [1,3], D. Bădescu [1,2], D. Rădăvoi [1,2], S. Costache [1,3], A. Sin [2], I. Dragomirişteanu [2], S. Nedelea [4], R. Borcăiaş [1,2], P. Călinoiu [1,2], I. P. Ionel [1,2], V. Jinga [1,2]

[1] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2] *"Prof. Dr. Th. Burghele" Clinical Hospital, Urology Department, Bucharest, Romania*
[3] *Bucharest Emergency University Hospital, Pathology Department, Bucharest, Romania*
[4] *"Prof. Dr. Agrippa Ionescu" Emergency Clinical Hospital*

**Abstract**

**Introduction and objectives.** Renal cell carcinoma (RCC) is one of the most important urological pathologies, being correlated with high morbidity, poor prognosis and outcome. Kidney tumors can be heterogeneous comprehending several histological types. Diagnosis of RCC usually results in most cases from incidental findings, although in some cases, due to paraneoplastic syndromes, patients present with symptoms caused by hormones or cytokines excreted by the tumor cells or by a systemic immune response against the tumor. The treatment of choice for RCC is mainly surgical, involving partial or radical nephrectomy, either open or laparoscopic, while the oncological results depend on a series of prognostic factors among which the tumor pathological stage, the presence of lymphovascular or perineural invasion, presence of tumor necrosis or sarcomatoid and rhabdoid changes. The objective of our study was to try and determine correlations between the clinical and the histopathological aspects of renal cell carcinoma patients that might be used as prognostic factors for the evolution of the disease.

**Materials and Methods.** We conducted a retrospective study involving 50 patients treated for renal cell carcinoma, who underwent radical or partial nephrectomy in 2019 in a urology tertiary care center. The demographic data, clinical and histopathological data were gathered into a database for the study group. Our goal was to determine key prognostic factors that could be related to the oncological outcomes and the surgical results for patients with renal cell carcinoma who underwent curative intent treatment.

**Results.** The mean patient's age was 65 years, ranging from 46 to 81 years. In the study groups, there were 32 laparoscopic nephrectomies and 18 through an open approach. In most of the cases the tumor size varied between 4 and 7 cm. In terms of pathological prognosis factors, tumor necrosis was found in 21 cases, 14 of them had Fuhrman grade 3 and 5 cases presented with Fuhrman grade 4. Only 2 cases found to have low Fuhrman grade (2) associated with tumoral necrosis. Patients with larger tumors tended to present with a higher Fuhrman grade. Fatty tissue involvement was found in 15 cases, from which 12 presented with Fuhrman grade 3 and 3 cases with grade 4. Capsular invasion was found in 9 cases and 7 cases had positive lymph nodes. Only one case presented sarcomatoid changes. In terms of intraoperative surgical decision making out of 24 cases of tumors measuring 7 cm or less, 15 of them had the tumor situated at one of the poles, 12 of them without touching the renal collecting system feasible for partial nephrectomy.

Corresponding author: Ștefan Raşcu., M.D, PhD
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
"Prof. Dr. Th. Burghele" Clinical Hospital, Urology Department
20 Panduri Str., Bucharest, Romania
Phone: +40 21 410 69 10
E-mail: stefanrascu.sr@gmail.com

Due to intraoperative complications and aspects, regarding the surgical dissection and the increased bleeding, in seven of these cases, the surgeon's decision was towards radical nephrectomy. Out of these seven cases the histopathological report following radical nephrectomy revealed a Fuhrman grade 3, with five tumors with a diameter of less than 5.5 cm and two cases with tumor dimensions below 4 cm, all situated at one of the poles.

**Conclusion.** Patients with larger tumors presented with higher Fuhrman grades and more tumor necrosis, most of them invading the collecting system ($p<0,05$). Small tumors, less than 4 cm, were more likely to be feasible for nephron sparing surgery. Although 15 cases in our study were suitable for partial nephrectomy, in 7 cases the decision of radical nephrectomy was made intra-operatively and found to have Fuhrman grade 3 and tumor necrosis, in three cases the renal collective system was involved.

Modern approach regarding surgical treatment of RCC depends on the tumor location, size, the relationship with urinary tract, blood vessels and the surrounding organs. Although novel oncologic markers emerge every year and become available for RCC patients, the use of predictive biomarkers for clinical stratification and management still awaits validation studies.

**Keywords:** Fuhrman grade, lymphovascular involvement, partial nephrecomy, radical nephrectomy, renal cell carcinoma, tumor necrosis

## Introduction

Renal cell carcinoma (RCC) is one of the most important urological pathologies, being correlated with high morbidity, poor prognosis and outcome. It represents nearly 3% of all adult malignancies and it is the most lethal cancer in the uro-oncological filed with over 140.000 deaths every year [1].

Its incidence kept on rising since the year 1970, with nearly 3% every year, mostly because of the more frequent and better use of the imaging diagnostic techniques. This trend led to proportional growth of incidental findings of localized tumors and a higher 5-year survival rate for localized RCC [2,3].

Kidney tumors can be heterogeneous comprehending several histological types. The most common are, beside the benign tumors, are the clear cell type RCC, papillary RCC (type 1 and 2), chromophobe RCC and collecting duct RCC. Each type has different molecular and genetic characteristics. By convention, the term RCC – is used usually to refer to clear cell carcinoma type, due to being the most common histological type of RCC and standings for 75-80% of primary renal epithelial tumors. It is followed by papillary (10-15%), chromophobe (5%) and collecting duct carcinoma (<1%) [4].

The incidence of clear cell carcinoma increases with age and it is higher in the male gender. In 2012, it was the ninth most common cancer in men (214,000 cases) and fourteenth most common in women (124,000) [5]. With male: female ratio of 2:1, clear cell carcinoma occurs mostly in countries with high socio-economic development, in the United States there are each year approximately 64,000 new cases diagnosed and nearly 14,000 death associated with clear cell carcinoma [6]. The median age at presentation is 66 years and most cases are present in patients between the fifth and seventh decades of life [7]. The most important risk factors known for RCC include excess body weight (an indirect relationship between obesity and RCC has been described due to an increase in estrogen production, the rate of this neoplasm is almost double in the obese population compared to the normal-weight population [7]), arterial hypertension and cigarette smoking, acquired cystic kidney disease due to end stage renal disease, occupational exposure to trichloroethylene and neuroblastoma [8]. Moreover, recently, other comorbidities have also been associated with RCC, including chronic kidney disease, hemodialysis, kidney transplantation, previous renal carcinoma and diabetes mellitus [9].

Diagnosis of RCC usually results in most cases from incidental findings, although in some cases, due to paraneoplastic syndromes, patients present with symptoms caused by hormones or cytokines excreted by the tumor cells or by a systemic immune response against the tumor [10]. These symptoms and syndromes include hypercalcemia, fever and erythrocytosis, usually reversed after the tumor is resected [11]. The classic triad of hematuria, pain and flank mass is now seen

much less frequently than in the past due to the improvements in imaging techniques [12].

Usually, clear cell renal cell carcinomas are solitary and randomly distributed throughout the renal cortex. It is known that both kidneys are equally affected. Bilateral lesions are less common, accounting for 0.5% to 3% of cases, but these findings should rise the suspicion of a familial condition (the most common one is the Von Hippel-Lindau disease-associated clear cell RCC). [12]

The treatment of choice for RCC is nephrectomy, partial or radical, that can be performed either open or laparoscopic. Besides clinical and epidemiological aspects, in terms of prognostic factors regarding RCC, pathological stage of the tumor is the most accurate one [13], other prognostic parameters among tumors of the same stage, are the tumor grade, presence of micro-invasion, lymphovascular or perineural invasion, presence of necrosis (>15%) or sarcomatoid and rhabdoid changes [14]; also preoperative blood parameters are known to have potential prognostic for kidney cancer as the level of hemoglobin, neutrophils and platelets.

Survival rates for patients with lymph node involvement are known to be between 5 and 30% at 5 years and 0% to 5% at 10 years. [15]

The Fuhrman nuclear grade, for clear cell and papillary RCC, has been based primarily on nuclear size and shape, and the presence or absence of prominent nucleoli.

Grade 1: nucleoli inconspicuous or absent at 400x

Grade 2: nucleoli prominent at 400x

Grade 3: nucleoli prominent at 100x magnification

Grade 4: extreme nuclear pleomorphism, multinucleated giant cells, sarcomatoid or rhabdoid change. [8]

Sarcomatoid differentiation in not very common, found in less than 5% of all RCC, most frequent in cases of clear cell carcinoma. Different variants of it, have been described for other subtypes of RCC [16]. Histologically it is characterized by spindle cells that are positive for vimentin, with an infiltrative growth pattern, locally aggressive and metastatic, and with poor prognosis. [17]

## Materials and Methods

The objective of our study was to try and determine correlations between the clinical and the histopathological aspects of renal cell carcinoma patients that might be used as prognostic factors for the evolution of the disease. Key prognostic factors have been identified, including performance status, time from diagnosis to surgery, the levels of hemoglobin, neutrophils and platelets levels. We also wanted to investigate the association between intraoperative decision making regarding partial or radical nephrectomy and the later obtained histopathological parameters that are known to determine RCC aggressiveness, like high Fuhrman grade, tumor necrosis, vascular and fat tissue invasion and sarcomatoid transformation. Therefore, we conducted a retrospective study, on 50 patients treated for renal cell carcinoma, who underwent radical or partial nephrectomy in 2019, in a urology tertiary care center – the Urology Department of the „Prof. Dr. Th. Burghele" Clinical Hospital, in Bucharest, Romania. The demographic data, such as age and gender, smoking habits, alcohol consumption patterns, other present comorbidities present, imaging aspects, clinical and histopathological data were gathered into a database for the study group. Concerning the histopathological (HP) aspects, following the surgery, the specimen was sent to the Laboratory of Pathology for HP examination. Paraffin-embedding histological technique was used for processing the kidney fragments. The obtained sections were stained with Hematoxylin-Eosin (H&E) and Van Gieson.

## Results

All 50 cases have been diagnosed with Computer tomography (CT) and all tumor masses enhanced more than 20 Hounsfield Units; diagnosis of clear cell carcinoma was established after surgery. In the study group, nephrectomy was performed to all the patients, 32 subjects underwent nephrectomy (radical or partial) through a laparoscopic procedure, while 18 subjects through an open approach. The mean age for patients with laparoscopic nephrectomy was 59.39±12 years and 63.31±11 years for the open approach sub-group. The male patients were statistically significantly older than the female patients from the study group.

The mean age of the patients was 65 years (table 1), the youngest one had 46 years old and the oldest 81 years. (table 2)

*Table 1: Age distribution*

| Age category | No. of Cases | Percent |
|---|---|---|
| 40-49 | 5 | 10% |
| 50-59 | 11 | 22% |
| 60-69 | 23 | 46% |
| 70-79 | 10 | 10% |
| 80-89 | 1 | 2% |

*Table 2: Sex distribution*

| Sex | No. of Cases | Percent |
|---|---|---|
| Female | 17 | 34% |
| Male | 33 | 66% |

At the moment of diagnosis only 4 patients had significant weight loss (>10% of body wight) and 2 patients had cachexia and poor performance status.

Regarding the comorbidities found in the study group and also associated risk factors, most of the patients had hypertension, diabetes mellitus and smoking habits (figure 1).

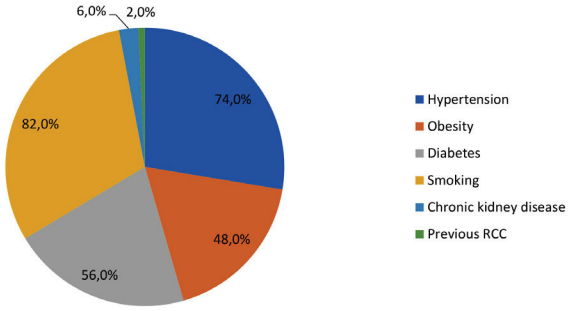



*Figure 1: Frequent comorbidities encountered in the study group*

On gross examination, on most of the tumors, the cut surface revealed a round shape, well defined tumor, with pseudo capsule (created by the surrounding tissue compressed by the growth of the tumor) and with no adjacent renal parenchymal infiltration; just in 2 cases the tumor was poorly circumscribed (figure 2). All tumors had the same golden-yellowish color, some of them with grey areas of necrosis, hemorrhagic zones, small areas of cystic change and occasionally areas of calcification (figure 3). It should be noted that in higher-grade lesions, usually with a sarcomatoid component, the golden yellow areas tend to be less evident (having low levels of lipid and glycogen) and appear embedded within a fleshy, gray to tan-white fibrous appearing mass.

Microscopically, RCC normally consists of tumor cells with clear cytoplasm (they reflect the amount of lipid and glycogen contained) arranged in nests or tubules, even a solid growth pattern, surrounded by a rich, but usually delicate, vascular network having a „chicken wire" appearance or a sinusoidal pattern (figure 4). Using the usual histologic preparation methods, the lipid content of tumor cells is dissolved away, leaving behind an empty cytoplasm, so called „clear cell", surrounded by a distinct cell membrane (figure 5). Nevertheless, these lipids can be identified using oil Red O and Sudan IV reaction. To demonstrate the glycogen content, we can use Periodic acid-Schiff (PAS). It is important to note that cells having granular or eosinophilic cytoplasm are more frequently encountered in higher grade carcinomas. Findings of sarcomatoid transformation, having pleomorphic and spindle cell growth, tend to be more common in larger tumors (figure 6).

The most widely used grading system for clear cell carcinoma is the Fuhrman grading system, which defines four nuclear grades (1-4), by the nuclear size, irregularity and nucleolar prominence. The nuclear Fuhrman grade has shown to have prognostic value in clear cell carcinomas. [18]

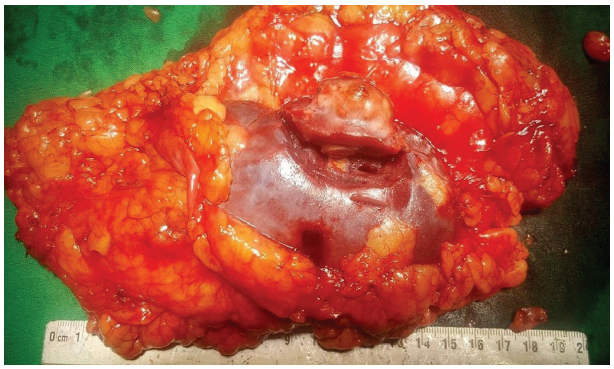


*Figure 2. Postoperative macroscopic aspect of renal tumor*

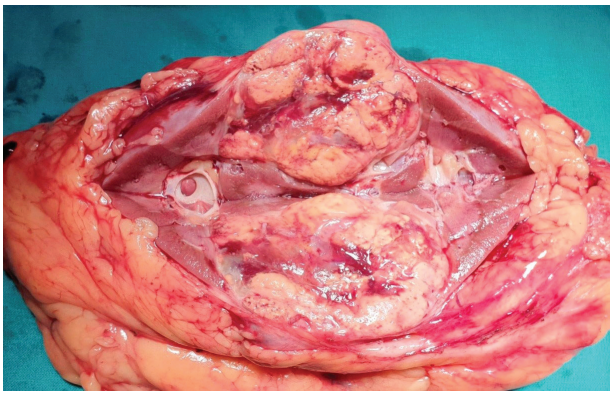


*Figure 3. Postoperative macroscopic aspect of renal tumor*

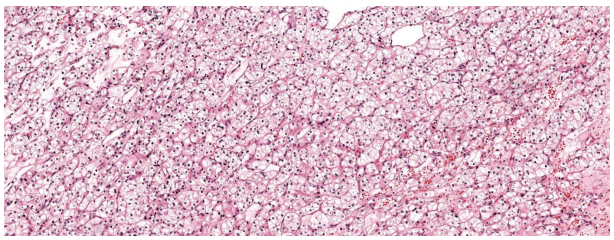


*Figure 4. Renal cell carcinoma, clear type with well-differentiated morphology (H&E, 100x)*

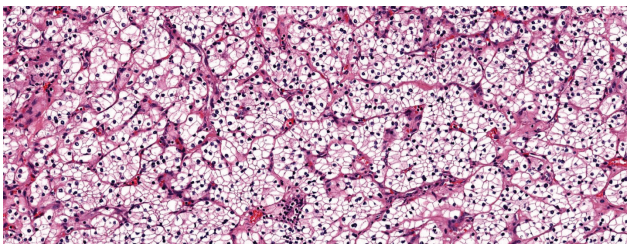


*Figure 5. Renal cell carcinoma, clear type (H&E, 200x)*

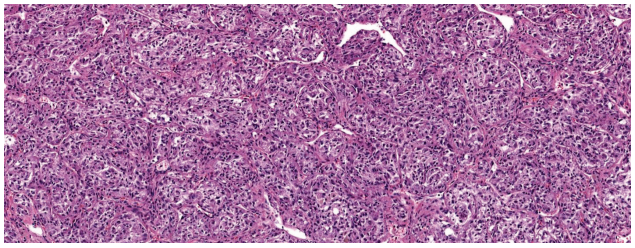


*Figure 6. Sarcomatoid type component of renal cell carcinoma (H&E, 100x)*

In most of the cases the tumor size varied between 4 and 7 cm. A total number of 15 cases had tumors below 4 cm, out of which 8 patients underwent partial nephrectomy.

*Table 3: Cases distribution by tumor size*

| Dimensions | No. of Cases | Percent |
|---|---|---|
| ≤4cm | 15 | 30% |
| >4 - ≤7cm | 24 | 42% |
| >7 - ≤10cm | 7 | 18% |
| >10cm | 4 | 10% |

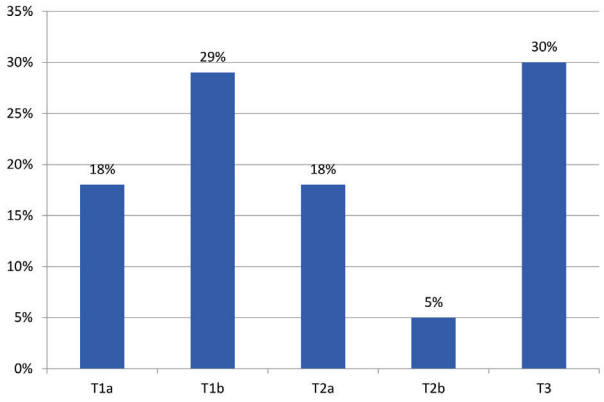



*Figure 7: Case distribution by TNM*

Regarding morphologic prognosis, the main tool is the Fuhrman grade.

*Table 4: Case distribution by Fuhrman grade*

| Fuhrman Grade | | Nr. Cases | Percent |
|---|---|---|---|
| Low | 1 | 2 | 4% |
| | 2 | 26 | 52% |
| High | 3 | 17 | 34% |
| | 4 | 5 | 10% |

Tumor necrosis was found in 21 cases. 14 of them had Fuhrman grade 3 and 5 cases presented with Fuhrman grade 4. Only 2 cases found to have low Fuhrman grade (2) associated with tumoral necrosis.

| Fuhrman Grade No. of Cases | | Present | | Absent | |
|---|---|---|---|---|---|
| | | Percent | No. of Cases | Percent | |
| Low | 1 | 0 | 0% | 2 | 4% |
| | 2 | 2 | 4% | 24 | 48% |
| High | 3 | 14 | 28% | 3 | 6% |
| | 4 | 5 | 10% | 0 | 0% |

*Table 5: Cases distribution by tumor necrosis and Fuhrman grade*

Lymphovascular invasion was found in 22 cases, 13 of them had Fuhrman grade 3.

*Table 6: Case distribution by lymphovascular invasion and Fuhrman grade*

| Fuhrman Grade No. of Cases | | Present | | Absent | |
|---|---|---|---|---|---|
| | | Percent | No. of Cases | Percent | |
| Low | 1 | 0 | 0% | 2 | 4% |
| | 2 | 4 | 8% | 22 | 44% |
| High | 3 | 13 | 26% | 4 | 8% |
| | 4 | 5 | 10% | 0 | 0% |

We found a significant association between Fuhrman nuclear grade and tumor necrosis, vascular invasion, tumor stage and lymph nodes involvement.

| Studied parameters | Fuhrman Grade | Tumor Stage |
|---|---|---|
| Age | p>0.05 | p>0.05 |
| Sex | p>0.05 | p>0.05 |
| Tumor size | p>0.05 | p>0.05 |
| Necrosis | p=0.03 | p>0.05 |
| Vascular invasion | p=0.02 | p=0.006 |
| Capsular invasion | p>0.05 | p>0.05 |
| Positive lymph nodes | p.0.05 | p>0.05 |

*Table 7: Statistical correlation between Fuhrman Grade, tumor stage and studied parameters.*

Fatty tissue involvement was found in 15 cases, from which 12 presented with Fuhrman grade 3 and 3 cases with grade 4. Capsular invasion was found in 9 cases and 7 cases had positive lymph nodes. Only one case presented sarcomatoid changes (figure 6).

There were 5 cases with Fuhrman grade 4 and 7 other cases with Fuhrman grade 3, who presented with preoperative anemia. All 12 patients had microvascular invasion and tumoral necrosis. There were also 15 cases with microscopic hematuria by the time they were hospitalized.

Partial nephrectomy is the preferred surgical procedure in treating patients with pT1a renal cancer over radical nephrectomy. Furthermore, there is a trend to extend the indication of partial nephrectomy to tumors exceeding 4 cm in diameter, if feasible. In our study 24 cases presented with tumors measuring 7 cm or less, 15 of them had the tumor situated at one of the poles, 12 of them without touching the renal collecting system and with a tumor size below 5.5 cm in larger diameter, that were thought to be suitable for undergoing partial nephrectomy pre-operatively. Even so, only 8 of these cases ended up with partial nephrectomy. In most of the cases, the Fuhrman grade was 2 and there were one case with grade 1 and one case with grade 3.

Due to intraoperative complications and aspects, regarding the surgical dissection and the increased bleeding, in the remaining 7 cases, the surgeon's decision was towards radical nephrectomy, although the preoperative surgical decision was towards partial nephrectomy. Out of the 7 afore mentioned cases that resulted in radical nephrectomy, the histopathological report revealed a Fuhrman grade 3, with five tumors with a diameter of less than 5.5 cm and two cases with tumor dimensions below 4 cm, all situated at one of the poles.

## Discussion

Modern approach regarding surgical treatment of RCC depends on the tumor location, size and also the relationship with urinary tract, blood vessels and the surrounding organs. The prognostic significance of morphologic parameters is used in the postoperative management and the Fuhrman grade has been shown to have an important prognostic value in clear cell carcinoma. Although novel oncologic markers emerge every year and become available for RCC patients, the use of predictive biomarkers for clinical stratification and management still awaits validation studies.

## Conclusion

Patients with larger tumors tended to exhibit higher Fuhrman grades and also presented more tumor necrosis, most of them were found to invade the collecting system ($p<0,05$). Small tumors, less than 4 cm, were more likely to be amenable to nephron sparing surgery although 15 cases in our study were suitable for partial nephrectomy, in 7 cases the decision of radical nephrectomy was made intra-operatively and found to have Fuhrman grade 3 and tumor necrosis, in 3 cases the renal collective system was involved.

After the whole data was analyzed, we observed a strong association between Fuhrman grade and tumor necrosis, lymphovascular invasion and tumor stage ($p<0,05$). Another important conclusion was the relationship between tumor necrosis, vascular invasion and fatty tissue extension: out of 15 cases classified as stage III, 12 of them had vascular invasion. A recent study reports that Fuhrman grade, tumor necrosis and vascular microinvasion are independent prognostic factors in a multivariate analysis [19].

Laboratory prognostic factors that are normally linked to the evolution of RCC are hemoglobin, leukocytes, platelet counts, serum calcium and lactate dehydrogenase levels. In our study we found a strong link between preoperative anemia and high Fuhrman grade.

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