

RENAL HÜCRELİ KARSİNOMLARDA FUHRMAN NÜKLEER DERECE, EVRE VE SARKOMATOİD DİFERANSİYASYONUN SAĞKALIM İLE İLİŞKİSİ

ÖZET

Amaç: Renal hücrelikarsinom, böbrek tubulepitelinden kaynaklanan malign bir tümördür. Çalışmamızda bu tümörlerin histolojik özellikleri, boyutu, evrelendirme, nükleer derecelendirme ve sarkomatoid diferansiyasyon parametreleri ile sağkalım arasındaki ilişki araştırıldı.

HastalarveYöntemler: 2000-2008 yılları arasında renal hücreli karsinom tanısı almış 78 nefrektomi olgusunun histolojik kesitleri 2004 Dünya Sağlık Örgütü sınıflamasına göre yeniden değerlendirildi. Beş histolojik alt tipte sınıflandırılan olguların Fuhrman Nükleer Dereceleri, evreleri,sarkomatoid diferansiyasyon varlığı ve sağkalım oranları kaydedildi. Tüm parametrelerin birbirleriyle ilişkileri istatistiksel yöntemlerle değerlendirildi.

Bulgular: Çalışmamızda yüksek nükleer derece, ileri evre ve sarkomatoid diferansiyasyon gösteren olgularda sağkalım süreleri kısaydı ($p<0,05$). Sonuç olarak, renal hücreli karsinomlarda prognostic değeri olan histopatolojik parametreler ile sağkalım arasında literatürle uyumlu olarak anlamlı ilişki saptandı.

Sonuç: Renal Hücreli Karsinomların değerlendirilmesinde kullanılan Fuhrman nükleer dereceleme, evre ve sarkomatoid diferansiyasyon sağkalım ile ilişkili önemli parametrelerdir. Fuhrman nükleer dereceleminin mutlaka doğru yapılması ve tumor içinde izlenen en yüksek derecenin raporlanması uygundur. Literatürde çok sayıda çalışma yapılmamış olmakla birlikte tümörde sarkomatoid diferansiyasyon varlığı sağkalım oranlarını anlamlı ölçüde azaltmaktadır. Sarkomatoid diferansiyasyonu da içeren histopatolojik parametrelerin doğru değerlendirilmesi ve patoloji raporunda bildirilmesi çok önemlidir.

Anahtar kelimeler: Renal hücrelikarsinom, Prognoz, Anjiyogenez

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THE RELATIONSHIP OF FUHRMAN NUCLEAR GRADE, TUMOR STAGE AND SARCOMATOID DIFFERENTIATION WITH SURVIVE IN RENAL CELL CARCINOMAS

ABSTRACT

Objectives:Renal cell carcinoma derived from tubular epithelium is one of the malign tumors of the kidney. We have investigated histological features, pathological stage, nuclear grade and sarcomatoid differentiation of thesetumors.

Patients and methods:Histological slides from seventy-eight nephrectomy specimens diagnosed as renal cell carcinoma between 2000 and 2008 were reevaluated according to the 2004 World Health Organization classification system of kidney tumors. Reclassified cases were collected in five groups and were scored for Fuhrman nuclear grading, stage, sarcomatoid differentiation and survival rate.

Results:In our study, cases with high nuclear grade, advanced stage andsarcomatoid differentiation revealed pure survival rates ($p<0.05$). In conclusion, the correlation between prognostic histopathological parameters and survival rates was consistent with literature findings.

Conclusion: Fuhrman nuclear grading, stage and sarcomatoid differentiation are important parameters and are related factors with survive when investigating renal cell carcinomas. Fuhrman nuclear grading must be evaluatedcorrectly and the highest grade should be reported. Although there aren'tenough studies about sarcomatoid differentiation, its presence significantly decreases survival rates. It's very important to state histopathological parameters including sarcomatoid differentiation exactly on the pathology report.

Keywords: Renal cell carcinoma, Prognosis, Angiogenesis

65 **INTRODUCTION**

66 Renal cell carcinoma (RCC) is an important health problem of the adults which
67 constitutes 80-85% of the renal tumors and 2% all of malignancies. The incidence
68 increases on the world and 100.000 with RCC patients die per year (1).

69 Metastasis is frequent because the symptoms reveal quite late and treatment
70 can be started on late stages. Approximately 1/3 of the patients have metastases and
71 five year survival rate is under 5% in this group on the patients (1).

72 Many factors have impact on survival duration in RCC. All of these
73 factors affect the course of the disease as dependent (tumor related) and
74 independent prognostic factors. Tumor related factors are known as parameters
75 which determined by tumor stage (tumor size, local tumor spread, adrenal gland,
76 large vessels, lymphatic nodes involved, far metastasis), histologic subtype, nuclear
77 grade, sarcomatoid differentiation and histological tumor necrosis (2).

78 There are various clinical trials which focus on factors affecting life duration
79 and determination of survival duration in RCC. The aim of our study is to investigate
80 the relation between life duration and tumor related factors which can effect survival.

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91 **METHODS**

92 The surgical pathology reports of all patients who underwent nephrectomy for
93 RCC between 1998 and 2008 in our hospital were reviewed. Histological slides from
94 seventy eight nephrectomy specimens with RCC and were re-evaluated
95 retrospectively to study a consistent set of pathologic features. In case of
96 requirement new sections from the blocks of nephrectomy specimens were cut. All
97 histological sections were stained with Hematoxylin and Eosin. The histologic subtype,
98 Fuhrman Nuclear Grading (FNG), stage and sarcomatoid differentiation (SD) of all
99 patients was reviewed by two pathologists who were blind to the clinical features and
100 outcome of the patients. The size of each neoplasm and macroscopic renal vein
101 involvement and other macroscopical findings were extracted from the pathology
102 reports. The pathological findings (histologic subtype, stage, FNG and
103 sarcomatoid differentiation) were re-classified according to new evaluation results.

104 For classification of renal tumors, World Health Organization (WHO) 2004
105 classification was used (3).

106 Nuclear grade was determined using the criteria proposed by Fuhrman et al.
107 (4). FNG-1 tumors are composed of cells with small (approximately 10 μm), round,
108 uniform nuclei and inconspicuous or absent nucleoli; FNG-2 tumor cells have larger
109 (approximately 15 μm) nuclei with irregular outlines and nucleoli that are visible under
110 high-power (400X) microscopy; FNG-3 tumor cells have even larger nuclei
111 (approximately 20 μm) with obviously irregular outlines and prominent nucleoli even
112 under low-power (100X) microscopy; and FNG-4 tumors exhibit features similar to
113 those of FNG-3 tumors but also have bizarre, often multilobed nuclei and heavy
114 chromatin clumps.

115 The tumors were staged according to the 2002 TNM classification system
116 using the AJCC stage grouping; tumor 4 cm or less in greatest dimension, limited to
117 the kidney; Stage 1a, tumor more than 4 cm but not more than 7 cm in greatest
118 dimension, limited to the kidney; stage 1b, tumor more than 7 cm in greatest
119 dimension, limited to the kidney stage 2, tumor extends into major veins or invades
120 adrenal glands or perinephric tissue but not beyond Gerato's fascia stage 3, tumor
121 invades beyond Gerato's fascia; stage 4(5). Stage 1a and 1b were unified into a
122 single group in order to make statistical comparisons. Sarcomatoid differentiation was

123 assessed on histologic sections and was graded into two categories, present or
124 absent.

125 Survival information was obtained from patient follow-up unit of the university
126 or by phone from the patients themselves or relatives. The local ethics committee
127 approved the study design (...University No.64/2008-10/18).

128 Statistical analysis was performed using the Statistica 7.0 (License number:
129 31N6YUCV38) software package. The data were analyzed using descriptive analysis
130 and the survival calculations were illustrated with Kaplan–Meier Curves. The power of
131 the results of survival analysis was assessed according to sarcomatoid
132 differentiation and 3 years survival rates were found to be as % 88.3 and % 58.3
133 for cases with and without sarcomatoid differentiation, respectively. The power was
134 0.98 if "n" value was 78 and $\alpha = 0.05$.

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149 **RESULTS**

150 According to final evaluation 48 (61.5%) of the patients had clear cell RCC.
151 The final diagnosis of other patients were as follows; 10 (12.8%) papillary RCC, 10
152 (12.8%) unclassified type RCC, 5 (6.4%) chromofob RCC and 5 (6.4%)
153 multiloculecystic RCC (MLC-RCC). Macroscopic and microscopic appearances of
154 histological subtypes can be seen in Figure 1-2.

155 The study group consisted of 50 (64.1%) patients for male and 28 (35.9%) for
156 female (Table 1). Age interval changes were between 26 and 80. The means age
157 were 60.25 ± 10.20 in patients with clear cell RCC; 64.10 ± 10.00 in papillary RCC,
158 54.00 ± 17.00 in chromofob RCC, 40.40 ± 14.20 MLC-RCC, 58.80 ± 13.70 in unclassified
159 RCC (Table 2). Tumor localization was right kidney in 40 (51.3%) of the patients and
160 left kidney in 38 (48.7%).

161 Survival evaluation revealed a general survival rate of 78.21% and a mean
162 survive duration of 86,6 months ($86,59 \pm 4,8$) in RCC (Figure 3). Among histological
163 subtype groups the survival rates was 81.25% and mean survival duration 88.14
164 months in clear cell RCC. The same values were 70% and 62.03 months in papillary
165 RCC, respectively. All the patients with chromofob RCC and MLC-RCC were alive.
166 Survival rate was 50% and mean survival duration was 55.2 months in unclassified
167 RCC. The longest survival duration and highest survival rates were in patients with
168 clear cell RCC when chromofob RCC and MLC-RCC patients were excluded. Both
169 parameters were low in unclassified RCC patients. However no significant difference
170 in terms of survival duration was found among histological subtypes on statistical
171 evaluation (Figure 4).

172 The distribution of FNG, stage, size and SD properties of the patients in
173 histological subtype groups were shown in Table 3. Fourteen of the patient (17.9%)
174 were in FNG-1; 32 (41.0%) in FNG-2; 20 (25.6%) in FNG-3; 12(14.1%) in FNG-4. While
175 the survival rates were 78.57% and 93.75% in FNG-1 and FNG-2, the rates degrees to
176 65% in FNG-3 and 58.33% in FNG-4, respectively. The comparison of survival rates
177 in FNGs revealed that survival rates and survival durations decreased as FNG
178 grades increased. The difference of these parameters among FNG groups were
179 found to be statistically significant (**p: 0.021**)(Figure 5).

180 Of all the patients 31 were in stage 1(39.75%); 17 in stage 2(21.9%),
181 26(33.33%) in stage 3, 4 (5.12%) in stage 4. When stage groups were compared with
182 the survival rates and mean survival durations, higher stage correlates with lower
183 values of survival rates and mean survival durations. There was statistically
184 significance among pathological stages and survival duration and rates (**p: 0.001**)
185 (Figure6).

186 When evaluating SD, 11 of 78 RCC patients (14%) exhibited this finding and 8
187 (72.7%) of these patients had clear cell RCC while 3 (27.3%) had unclassified RCC
188 (Figure 7). SD was observed more frequently in large size tumors as a remarkable
189 finding. The diameter of these tumors was larger than 7 cm in 81.8% of the patients.
190 When the relationship was evaluated between SD and survives, it was observed that
191 RCC patients with SD had a survival rate of 54.55% and survival duration of 28.18
192 months, while patients without SD had a survival rate of 82.09% and survival duration
193 of 90.5 months. This difference was statistically significant (**p: 0.018**) (Figure 8).

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215 **DISCUSSION**

216 As renal tumors cause late symptoms due to their retroperitoneal localizations
217 they are generally diagnosed on advanced stage they. Early diagnosis is sometimes
218 possible when local symptoms and paraneoplastic signs appear earlier
219 (6,7). Although surgical approach is possible, metastasis is frequent and prognosis is
220 poor on advanced stages. Thus, optimal determination of prognostic factors is vitally
221 important on the treatment of renal tumors and survival of the patients.

222 It has been reported that five years survival rates of the patients with RCC is
223 30-60%. The longest follow up duration among our patients was 10 years and the
224 shortest was 1 year with a general survival rate of 78.21% and mean survival duration
225 of 86.6 months. However, it has been reported that there are important differences
226 among histological subtypes. The 5-year disease-specific survival for chromophobe
227 RCC, papillary RCC, clear cell RCC, and unclassified RCC was 100%, 86%, 76%, and
228 24%, respectively (8). Cheville et al. (9) and Patard et al. (10) showed that prognosis
229 is the best in chromophobe type and worst in clear cell type. Similarly, we found that the
230 best prognosis appeared in patients with chromophobe RCC and MLC-RCC. However,
231 different from this study, the longest survival duration and highest survival rate were
232 in patients with clear cell RCC following chromophobe RCC and MLC-RCC. The shortest
233 survival duration and the lowest survival rate were found in patients with unclassified
234 RCC. As great amount of patients had clear cell RCC and the number of patients
235 were low in other subtype groups, no statistically significant difference could be
236 obtained between survival rate and histological subtypes.

237 The most important predictor of prognosis in RCC patients is accepted to be
238 the histopathological stage (7). Survival rates decrease with increasing stage (11,12).
239 Recent studies revealed that five years survival is 90-100% in stage 1 tumors, 75-
240 90% in stage 2, 60-70% in stage 3 and 15-30% in stage 4 (10). General survival
241 rates in our study were found to be 96.7%, 82.35%, 57.69% and 29.75%,
242 respectively; these findings are parallel to the findings of the former studies.

243 Evaluation criteria used in tumor grading is subjective and evaluation
244 discordance is possible for all grading systems. Despite this nuclear grading is the
245 most important prognostic parameter for almost all malignant tumors. While
246 differentiation (morphologic and/or functional) and anaplasia are generally used for
247 grading of tumors, only nucleus and nucleolus features (size and morphology) are

248 evaluated in RCC (12). FNG system is the most frequent evaluation method
249 nowadays used in RCC (13).In this system, four groups are constituted in terms of
250 nucleus contour, size and nucleolus intensity. According to Delahunt et al. (13) the
251 subjectivity of the criteria and variation in tissue fixing methods can cause
252 interpretation differences in FNG system. Nucleolus are not visible in poorly fixed
253 tissues, thus tumors might have been classified as low grade. Besides, the same
254 investigators pointed FNG system as being insignificant in subtypes other than clear
255 cell RCC and stated that this system should not be used in papillary and chromophob
256 RCC. They claim FNG distribution is unstable in chromophob RCC and this leads to
257 discordance in grading among the observers. In Delahunt and al.'s study eighty-seven
258 cases of chromophob renal cell carcinoma were investigated. Authors emphasized that
259 the fact all 8 dead chromophob RCC patients had FNG-2, supports this opinion (13-
260 17). According to our observations, tissue fixing is a misleading factor that
261 complicates the evaluation. Sometimes, nucleus structure in chromophob RCC can
262 cause higher interpretation degree of FNG. All of the chromophob RCC were FNG-1
263 and FNG-2 on our study and no FNG-3 and FNG-4 patient existed. In addition to
264 recommendation of Delahunt et al. (13), we advise mutual evaluation of FNG by two
265 different pathologists for an objective evaluation and to decrease error probability. We
266 also recommend that careful screening of tumor areas with worst nuclear grading
267 should be the focus of the evaluation. Though the number of patients with chromophob
268 RCC is insufficient on our study, it is not convenient to use FNG system on chromophob
269 RCC cases. Kus et al. (18) found that survival rate decreased as FNG increased.
270 Gelb et al., (19) performed on their study among 82 patients with grade 1 RCC,
271 showed nuclear grading and tumor size are to be independent factors for survival.
272 Similarly survival rate and duration decreased significantly as FNG increased in our
273 study.

274 In Goldstein et al.'s study (20), while FNG-1 and FNG-2 showed similar
275 prognostic features, FNG-3 and FNG-4 showed same similarity among these. The
276 survival rates of our patients are in concordance with that. Although it was not
277 possible to perform statistical analysis due to the insufficient number of patients in
278 some groups, advanced stages with FNG increase and diameters being greater than
279 7 cm. in 91.7% of FNG-4 tumors are striking findings.

280 SD is an important finding that accompanies many tumors (21-22). It can be
281 shown in many types of RCC. SD is much more evaluated in FNG-4 group tumors. De
282 Peralta-Venturina et al. (22) investigated 101 cases with SD and reported that SD
283 was observed in 8% of clear cell RCC, 9% of chromofob RCC, and 11% of
284 unclassified RCC. Our cases showed SD in 16.7% of clear cell RCC, and 30% of
285 unclassified-RCC. This sign was absent in chromofobRCC. In De Peralta-Venturina et
286 al's (22) studies, while 63% of patients with SD were in stage 3 and 25% in stage 4,
287 mean survival duration were 19 months. Similarly in our study, 50% of cases were in
288 stage 3, 50% in stage 4 and the mean survival duration was 28.8 months. Five of 11
289 cases with SD are not alive. The presence of SD decreases survival rate and
290 duration. These group tumors have markedly worse prognosis and most of them die
291 in one year (21). Therefore SD should be searched and their presence should be
292 indicated in pathological reports.

293 Some factors limited our statistical analysis and a better discussion of our data.
294 Though ten years of experience was evaluated low number of patients in some
295 groups was an important limitation.

296 There are important markers in determining prognosis of renal tumors showing
297 quite late symptoms and being diagnosed late advanced stage. We investigated the
298 presence of the most important parameters which should be used to determine the
299 survival durations and rates in these cases. Despite low numbers of patients in some
300 groups, we have achieved significant results associated with survival.

301 According to the statistical analysis results of our study showed important
302 relations of histological subtype, FNG, stage, SD with survival. We think that FNG
303 classification should be performed by two different pathologists for enhancing the
304 accuracy of the evaluation and the worst grade should be reported after scanning of
305 many various areas. While there are many studies investigating the relation among
306 FNG, tumor stage and survival, the number of studies about the relation of SD and
307 survival is limited. Yet, according to our results the presence of SD decrease the
308 survival rates significantly. We thus think that accurate evaluation and clear definition
309 of these parameters by pathologists affect the quality of clinical approach and
310 consequently survival and life quality.

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			Histologicaltype					Total
			CC-RCC	P-RCC	C-RCC	MLC-RCC	Un-RCC	
GENDER	MALE	Count	30	9	2	2	7	50
		% withingender	60,0	18,0	4,0	4,0	14,0	100,0
		% withinhistologicaltype	62,5	90,0	40,0	40,0	70,0	64,1

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373 **Table 1**-Gender-Histological TypeCrosstabulation

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	FEMALE	Count	18	1	3	3	3	28
% withingender		64,3	3,6	10,7	10,7	10,7	100,0	
% withinhistologicaltype		37,5	10,0	60,0	60,0	30,0	35,9	

375 **CC-RCC:** Clear cell renal cell carcinoma; **P-RCC:** Papillary renal cell carcinoma; **C-RCC:** Chromofob renal cell carcinoma;
376 **MLC-RCC:** Multiloculecyclic renal cell carcinoma; **Un-RCC:** Unclassified renal cell carcinoma.
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378 Patientnumbersarelow in somegroups. Forthisreason, thestatisticalanalysiscould not
379 be performed.

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388 Table 2- Age distribution of patients

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	n	Meanage±SD	Minimum	Maximum
CC-RCC	48	60,25±10,24	37,00	80,00
P-RCC	10	64,10±10,00	45,00	78,00
C-RCC	5	54,00±17,04	26,00	72,00
MLC-RCC	5	40,40±14,18	24,00	53,00
Un-RCC	10	58,90±13,69	36,00	80,00
Total	78	58,89±12,31	24,00	80,00

390 **CC-RCC:** Clear cell renal cell carcinoma; **P-RCC:** Papillary renal cell carcinoma;**C-**
391 **RCC:**Chromofob renal cell carcinoma; **MLC-RCC:**Multiloculecystic renal cell
392 carcinoma; **Un--RCC:** Unclassified renal cell carcinoma
393 P= 0.004 (Kruskal Wallis Analysis of variance)

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Table3:The distribution of Fuhrman Nuclear Grading (FNG), stage, size and Sarcomatoid differentiation (SD) properties of the 40: patients in histological subtypes

HISTOLOGICAL SUBTYPE	FNG (n,%)				Stage (n,%)				Size (n,%)			Sarcomatoid Differentiation (n,%)	
	1	2	3	4	1	2	3	4	<4 cm	≥4-7 cm	>7 cm	(+)	(-)
CC- RCC (n=48)	7 14.6%	21 43.8%	11 22.9%	9 18.8%	19 39.6%	9 18.8%	16 33.3%	4 8.3%	10 20.8%	18 37.5%	20 41.7%	40 83.3%	8 16.7%
P-RCC (n=10)	2 20%	5 50%	3 30%	0 0%	4 40%	3 30%	3 30%	0 0%	2 20%	3 30%	5 50%	10 100%	0
C-RCC (n=5)	1 20%	4 80%	0 0%	0 0%	2 40%	2 40%	1 20%	0 0%	0 0%	2 40%	3 60%	5 100%	0
MLC-RCC (n=5)	4 80%	1 20%	0 0%	0 0%	4 80%	1 20%	0 0%	0 0%	1 20%	3 60%	1 20%	5 100%	0
Un-RCC (n=10)	0 0%	1 10%	6 60%	3 30%	2 20%	2 20%	6 40%	0 0%	2 20%	3 30%	5 50%	7 70%	3 30%
Total (n=78)	14	32	20	12	31	17	26	4	15	29	34	67	11

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FNG: Fuhrman Nuclear Grading **CC-RCC:**Clear cell renal cell carcinoma; **P-RCC:** Papillary renal cell carcinoma; **C-RCC:**Chromofob renal cell carcinoma; **MLC-RCC:**Multiloculecyctic renal cell carcinoma; **Un-RCC:** Unclassified renal cell carcinoma.

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FIGURE LEGENDS:

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450 **Figure 1:** The macroscopic appearances of histological subtypes in renal cell
451 carcinoma patients. **A:** Clear cell renal cell carcinoma; **B:** Papillary renal cell
452 carcinoma; **C:**Chromofob renal cell carcinoma; **D:**Multilocule-cystic renal cell
453 carcinoma

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455 **Figure 2:** The microscopic appearances of histological subtypes in renal cell
456 carcinoma patients. **A:** Clear cell renal cell carcinoma (HE X 10),

457 **B:** Papillary renal cell carcinoma (HE X 10), **C:**Chromofob renal cell carcinoma (HE X
458 10), **D:**Multilocule-cystic renal cell carcinoma (HE X 1,25)

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461 **Figure3.** The survival rates of the renal cell carcinoma patients

462 **Cum Survival:** Cumulative survive **Survive:** Life duration (month).

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466 **Figure4.**The survival rates of the histological types in renal cell carcinomapatients

467 **Cum Survival:** Cumulative survive **Survive:** Life duration (month).

468 **Histological Type:**1:Clear cell renal cell carcinoma; 2: Papillary renal cell carcinoma;

469 3:Chromofob renal cell carcinoma; 4:Multilocule-cystic renal cell carcinoma;

470 5: Unclassified renal cell carcinoma

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473 **Figure5.**The survival rates of the Fuhrman Nuclear Grading groups in renal cell
474 carcinoma patients

475 **Cum Survival:** Cumulative survive **Survive:** Life duration (month).

476 1:Fuhrmann Nuclear Grade-1; 2:Fuhrmann Nuclear Grade-2;

477 3:Fuhrmann Nuclear Grade-3; 4:Fuhrmann Nuclear Grade-4.

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480 **Figure6.**The survival rates of the stage groups in renal cell carcinoma patients.

481 **Cum Survival:** Cumulative survive **Survive:** Life duration (month).
482 1: Stage 1, 2: Stage 2, 3: Stage 3, 4: Stage 4.

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484 **Figure 7:A sample of sarcomatoid differentiation in a renal cell carcinoma**
485 **patient (HE X 10).**

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488 **Figure8.**The survival rates of the sarcomatoid differentiation in renal cell carcinoma
489 patients

490 **Cum Survival:** Cumulative survive **Survive:** Life duration (month).

491 **SARCOMATOID DIFFERENTIATION: 0: Absent, 1: Present**

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