Prognostic factors in renal cell carcinoma: A single-center study

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Abstract. Renal cell carcinoma (RCC) is a heterogeneous and complex disease with numerous pathophysiologic variants. ~40% of patients succumb due to the progression of the disease, making RCC the most fatal of the common urologic malignancies. Prognostic factors are indicators of the progression of the disease, and the precise determination of these factors is important for evaluating and managing RCC. In the present study, it was aimed to determine and find associations among the histopathological features of RCCs and their impact on survival and metastasis. This is a cross-sectional study of RCC cases who have undergone partial or radical nephrectomy from March 2008 to October 2021 and have been pathologically reviewed at Shorsh General Teaching Hospital in Sulaimani, Iraq. The data in the pathology studies were supplemented by follow-up of the patients to obtain information about survival, recurrence and metastasis. In total, 228 cases of RCC were identified, among whom 60.5% were men and 39.5% were women, with a median age of 51 years. The main tumor types were clear cell RCC (71.1%), papillary RCC (13.6%), and chromophobe RCC (11%). Various measures of aggressiveness, including tumor necrosis, sarcomatoid change, microvascular invasion, and parameters of invasiveness (invasion of the renal sinus and other structures), were significantly correlated with each other, and they were also associated with reduced overall survival and an increased risk of metastasis on univariate analysis. However, on multivariate analysis, only tumor size and grade, and microvascular invasion retained statistical significance and were associated with a lower survival rate. In conclusion, pathological parameters have an impact on prognosis in RCC. The most consistent prognostic factors can be tumor size and grade, and microvascular invasion.

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Introduction

Renal cell carcinoma (RCC) is a heterogeneous and complex disease with numerous pathophysiological variants. Despite the fact that it is the most common type of renal cancer, it comprises only ~3% of malignant tumors in adults (1,2). RCC develops from the renal ductal epithelium and is classified into four major subtypes: i) clear cell RCC, ii) papillary RCC, iii) chromophobe RCC and iv) collecting duct carcinoma (1,3). This type of cancer can be associated with several localized and systemic symptoms, including an abdominal mass, pain, hematuria, anorexia, weight loss and several paraneoplastic syndromes, but the symptoms may arise in the late stages of the disease. ~50 to 60% of the cases are at risk of distant metastasis, with a quarter of them being detected at presentation (4,5). Despite the various treatment options, surgery remains the most effective curative modality. Partial nephrectomy is the standard option to manage T1a tumors and achieve cancer control while preserving optimal renal function, whereas total nephrectomy is the benchmark treatment for T1b-T4 tumors (6). Because ~40% of the cases succumb due to cancer progression, RCC has become the most fatal of the common urologic malignancies (7). Prognostic factors are markers of disease progression, and the precise determination of these factors is important for evaluating and managing patients with RCC (8). Various prognostic factors for RCC have been discussed in the literature, including clinical, anatomical, and molecular parameters, but none have been successfully validated so far (1,9). Pathological stage, lymph node status and histological grade are the prognostic factors that currently attract the attention of scholars in this field (10). The present study aimed to determine and find associations

among the histopathologic features of RCCs and their impact on survival and metastasis.

Patients and methods

Study design. This is a cross-sectional study of patients with RCC whose surgical specimens were evaluated at the pathology laboratory of the Shorsh General Teaching Hospital in Sulaimani, Iraq, from March 2008 to October 2021. Written informed consent was obtained from the patients, and the study was approved (approval no. 130/2021) by the ethical committee of the University of Sulaimani.

Inclusion criteria. The study included all the cases that met the following criteria: Kidneys affected by any subtype of RCC (including clear cell RCC, papillary RCC, chromophobe RCC and collecting duct carcinoma); underwent partial or radical nephrectomy; availability of nephrectomy specimens with detailed clinical and histopathological reports.

Exclusion criteria. Cases that were excluded included those in which the pathology report did not specify whether the specimen was a nephrectomy or a core biopsy and those in which the excision was for tumor recurrence if the primary excision report was already included in the study sample.

Data collection. The data on the cases of RCC were collected from the digital archive of the pathology laboratory of the Shorsh General Teaching Hospital using a custom-built application that allowed searching of the entire content of all the reports. The main keyword for searching was 'RCC,' supplemented by searches for specific tumor types ('chromophobe', 'mucinous', 'tubular' and 'collecting duct'). A total of 228 eligible cases were identified, which included both in-house and consult cases. The available data from the studies on demographics and clinical and pathological parameters were collected and tabulated into a spreadsheet. Information regarding survival, recurrence, metastasis, and time and presumed cause of death (for the cases that had passed away) was obtained by contacting the patients via telephone and reviewing their records at the Hiwa Cancer Hospital. The data were classified into four major categories including demographic data, clinical and gross parameters (procedure, laterality, site, focality, and size of tumor), histopathological parameters (morphologic subtype, grade, the presence of necrosis, sarcomatoid change, rhabdoid change, and microvascular invasion, invasion of the renal capsule, renal sinus, perinephric fat, Gerota's fascia, pelvicalyceal system, renal vein, status of ureteric, vascular, parenchymal margins and tumor stage) and follow-up information (survival, recurrence, metastasis and the time and cause of death). The tumors were graded according to the Fuhrman and International Society of Urological Pathology (ISUP) grading systems and were staged according to the American Joint Committee on Cancer (AJCC) and Tumor, Node and Metastasis (TNM) staging systems (11-13).

Statistical analysis. The obtained data were entered into the Statistical Package for the Social Sciences (v.25; IBM Corp.), and the variables were optimized for analysis. Descriptive statistics were generated, followed by correlation testing; the Chi-squared (X^2) and Fisher's exact tests were used to find correlations among the various parameters. Kaplan-Meier analysis was used to identify the relationship of the different parameters with survival and Cox regression analysis was used to determine the relationship of the parameters with the risk of metastasis as well as for multivariate analysis. $P \leq 0.05$ was considered to indicate a statistically significant difference.

Results

The age of the patients ranged from 4 to 90 years old, with a mean and median of 51 years each. The majority of the cases (43.9%) were between the ages of 45 and 64. The sex distribution was skewed towards men (60.5%), with a men-to-women ratio of 1.5:1. Almost 58% of the cases had a radical nephrectomy, with the right-side tumors predominating (Table I). The tumors in most of the cases (98.7%) were unifocal, with sizes ranging from 1.0 to 22.5 cm (mean=6.4 cm). The major histologic type was clear cell RCC (71.1%), followed by papillary RCC (13.6%) and chromophobe RCC (11%) (Table I). More than half (50.9%) of them were classified as grade II tumors. Necrosis, as the most common aggressive factor, was found in 30.7% of the cases, followed by renal capsule invasion (14.9%) and renal sinus invasion (14.9%). Out of the partial nephrectomies, seven cases (8.1%) had an involved parenchymal margin, and five cases (3.8%) of radical nephrectomies had an involved renal vein margin (data not shown). In 10 cases, the margin status was unclear because the procedure type was not specified (Table I). TNM stage was determined for all the tumors except three cases in which the tumor size was missing from the reports and there was no invasion of the renal sinus or other structures to upgrade them to a T3 or T4 stage.

Follow-up data. A total of 187 cases (82%) could be reached when contacted to obtain information about survival. Data about recurrence, metastasis, and time and cause of death (if applicable) were retrieved in 186 cases (81.6%). The follow-up data for the remaining cases were missing as the patients were lost to follow-up (Table I). The duration of follow-up in patients with retrieved data ranged from 21 days to 13.1 years, with a mean of 3.9 years. Among the cases, 33 were deceased; 23 cases (69.7%) succumbed to cancer-related complications (metastasis), nine cases (27.3%) succumbed to unrelated causes (other malignancies or chronic illnesses), and the cause was unknown in one patient (3%).

Correlation of histologic parameters. Out of all the gross and histological parameters studied, sex showed a significant association with tumor necrosis (P=0.002), with tumors in males revealing a higher association with tumor necrosis. Tumors removed with a radical nephrectomy were more significantly associated with all the markers of aggressiveness and invasion (MAI) than those removed with a partial nephrectomy ($P<0.05$). Out of all MAI, laterality was only significantly correlated with renal sinus invasion (P=0.024), with the latter being more common in right-sided tumors (data not shown). Tumor size and tumor grade were both significantly correlated with each other and with all MAI and tumor stage (Tables II, III). There was a significant bidirectional association

Table I. Baseline characteristics.

Variables	Percentages/ Frequency
Age	
≤18 years	1.8%
>18 and ≤44 years	32%
>44 and ≤64 years	43.9%
>64 and ≤84 years	21.1%
>84 years	1.3%
Mean and median age (min-max)	51 (4-90 years)
Sex	
Male	138 (60.5%)
Female	90 (39.5%)
Clinical and gross parameters	
Procedure	
Partial nephrectomy	86 (37.7%)
Radical nephrectomy	132 (57.9%)
N/A	10 (4.4%)
Laterality	
Right side	115 (50.4%)
Left side	99 (43.4%)
N/A	14 (6.2%)
Site	
Upper	59 (25.9%)
Lower	69 (30.3%)
Middle	33 (14.5%)
Pan (Entire Kidney)	7 (3.1%)
N/A	60 (26.2%)
Focality	
Unifocal	225 (98.7%)
Multifocal	2 (0.9%)
N/A	1 (0.4%)
Tumor size	
≤4 cm	83 (36.4%)
>4 and ≤7 cm	63 (27.6%)
>7 and ≤10 cm	46 (20.2%)
>10 cm	30 (13.2%)
N/A	6 (2.6%)
Histopathologic parameters	
Tumor morphotypes	
Clear cell RCC	162 (71.1%)
Papillary RCC	31 (13.6%)
Papillary RCC, type 1	11 (4.8%)
Papillary RCC, type 2	9 (3.9%)
Papillary RCC, not specified	11 (4.8%)
Chromophobe RCC	25 (11.0%)
Translocation RCC	3 (1.3%)
Clear cell papillary RCC	2 (0.9%)
RCC, unclassified	2 (0.9%)
Collecting duct carcinoma	1 (0.4%)
Fumarate hydratase-deficient RCC	1 (0.4%)
Mucinous, tubular, and spindle cell RCC	1 (0.4%)
Histopathologic grade	
1	50 (21.9%)
2	116 (50.9%)
3	23 (10.1%)
4	17 (7.5%)
N/A	22 (9.6%)
Markers of Aggressiveness and Invasiveness	
Necrosis	70 (30.7%)
Sarcomatoid change	15 (6.6%)
Rhabdoid change	10 (4.4%)
Microvascular invasion	33 (14.5%)
Renal sinus invasion	34 (14.9%)
Renal capsule invasion	34 (14.9%)
Perinephric fat invasion	27 (11.8%)
Gerota's fascia invasion	9 (3.9%)
Pelvicalyceal invasion	22 (9.6%)
Renal vein invasion	20 (8.8%)
TNM staging	
T1	121 (53.0%)
T1a	81 (35.5%)
T1b	40 (17.5%)
T2	46 (20.2%)
T2a	29 (12.7%)
T2b	17 (7.5%)
T3a	48 (21.1%)
T4	10 (4.4%)
N/A	3 (1.3%)
Follow-up outcomes	
Survival status	
Deceased	33 (14.5%)
Cancer-related complication	23 (69.7%)
Unrelated cancer cause	9 (27.3%)
Unknown	1 (3%)
Alive	154 (67.5%)
N/A	41 (18.0%)
Recurrence status	
Recurrence	6 (2.6%)
No recurrence	180 (78.9%)
N/A	42 (18.5%)
Metastasis status	
Metastasis	36 (15.8%)
No metastasis	150 (65.8%)
N/A	42 (18.4%)

N/A, Non-available; RCC, renal cell carcinoma; TNM, tumor, node and metastasis.

Table II. Correlation of tumor size with parameters of aggressiveness and invasiveness, tumor grade, and TNM stage.

		Tumor size				
Variables	Total	≤4 cm	>4 and ≤7 cm	>7 and ≤10 cm	>10 cm	P-value
Necrosis						<0.001
No	154	73	48	25	8	
Yes	68	10	15	21	22	
Sarcomatoid change						<0.001
No	207	83	60	41	23	
Yes	15	0	3	5	7	
Rhabdoid change						0.012
No	213	83	61	43	26	
Yes	9	0	2	3	4	
Microvascular invasion						<0.001
No	192	82	54	36	20	
Yes	30	1	9	10	10	
Renal sinus invasion						<0.001
No	189	82	50	34	23	
Yes	33	1	13	12	7	
Renal capsule invasion						<0.001
No	192	79	57	37	19	
Yes	30	4	6	9	11	
Perinephric fat invasion						<0.001
No	198	81	57	39	21	
Yes	24	2	6	7	9	
Gerota fascia invasion						0.037
No	213	82	61	44	26	
Yes	9	1	2	2	4	
Pelvicalyceal invasion						0.017
No	200	81	56	39	24	
Yes	22	2	7	7	6	
Renal vein invasion						0.002
No	203	81	58	36	28	
Yes	19	2	5	10	2	
Tumor Grade						<0.001
Low-grade (1 and 2)	164	79	42	27	16	
High-grade (3 and 4)	37	2	10	13	12	
TNM stage						<0.001
≤T2a	150	78	45	27	0	
≥T2b	72	5	18	19	30	

TNM, tumor, node and metastasis.

among numerous histological parameters, including necrosis, sarcomatoid change, rhabdoid change, microvascular invasion, renal sinus invasion, pelvicalyceal system invasion, renal capsule invasion, and perinephric fat invasion (P≤0.05). Most of these factors also had a significant association with Gerota fascia invasion and renal vein invasion. Moreover, all MAI, except rhabdoid change, were significantly associated with increasing tumor stage (Table IV).

Survival, recurrence, and metastasis. Survival analysis using a life table showed overall survival rates at one, five, and ten-year intervals of 87, 79, and 55%, respectively. Sex did not influence survival using log-rank analysis (P=0.726) (data not shown). Age had a significant impact on survival (P<0.001) when divided into four age groups (≤18, >18 and ≤64, >64 and ≤84, and >84 years), with patients in the groups of ≤18 and >84 years having the worst survival rate, followed by those

Table III. Correlation of tumor grade with parameters of aggressiveness and invasiveness, tumor size, and TNM stage.

Parameters of aggressiveness and invasiveness	Total	Tumor grade				P-value
		1	2	3	4	
Necrosis						<0.001
No	140	43	84	10	3	
Yes	66	7	32	13	14	
Sarcomatoid change						<0.001
No	192	50	115	22	5	
Yes	14	0	1	1	12	
Rhabdoid change						<0.001
No	196	50	116	21	9	
Yes	10	0	0	2	8	
Microvascular invasion						<0.001
No	176	50	106	16	4	
Yes	30	0	10	7	13	
Renal sinus invasion						<0.001
No	176	49	103	14	10	
Yes	30	1	13	9	7	
Renal capsule invasion						<0.001
No	176	48	108	15	5	
Yes	30	2	8	8	12	
Perinephric fat invasion						<0.001
No	182	49	111	16	6	
Yes	24	1	5	7	11	
Gerota fascia invasion						0.006
No	198	50	113	21	14	
Yes	8	0	3	2	3	
Pelvicalyceal invasion						0.047
No	185	47	105	21	12	
Yes	21	3	11	2	5	
Renal vein invasion						<0.001
No	188	50	108	16	14	
Yes	18	0	8	7	3	
TNM stage						<0.001
T1a	76	34	41	1	0	
T1b	35	7	25	1	2	
T2a	25	3	16	5	1	
T2b	15	2	9	3	1	
T3a	44	3	21	10	10	
T4	9	0	3	3	3	

TNM, tumor, node and metastasis.

in the >64 and ≤84 years group. The patients in the group of >18 and ≤64 years had the best survival rate (Fig. 1). Similar to its association with MAI, radical nephrectomy had a negative impact on survival (P=0.003) (data not shown).

Tumor laterality had no impact on survival (P=0.523) (data not shown). Tumor size had an impact on survival only when divided into two groups of tumors with the sizes of ≤10 and >10 cm, in which patients with a tumor size of >10 cm had poorer survival (P<0.001) (Fig. 2). Tumor grade also affected survival when it was divided into low-grade (grades 1 and 2 in the ISUP grading scheme) and high-grade (grades 3 and 4 in the ISUP grading scheme) tumors, with high-grade tumors having an adverse impact on survival (P<0.001) (Fig. 3). Tumor size and tumor grade had a significant impact on survival in univariate analysis and retained their individual significance when combined in multivariate regression

Table IV. Correlation among the parameters of aggressiveness and invasiveness and with TNM stage.

Part A.

	Sarcomatoid change			Rhabdoid change			Microvascular invasion			Renal sinus invasion			Renal capsule invasion		
Variables	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value
Necrosis			<0.001			<0.001			<0.001			0.003			0.009
No	155	3		157	1		145	13		142	16		141	17	
Yes	58	12		61	9		50	20		52	18		53	17	
Sarcomatoid change						<0.001			<0.001			0.013			<0.001
No				209	4		189	24		185	28		188	25	
Yes				9	6		6	9		9	6		6	9	
Rhabdoid change									<0.001			0.045			0.008
No							192	26		188	30		189	29	
Yes							3	7		6	4		5	5	
Microvascular invasion												<0.001			<0.001
No										182	13		179	16	
Yes										12	21		15	18	
Renal sinus invasion															<0.001
No													174	20	
Yes													20	14	

Part B.

	Perinephric fat invasion			Gerota fascia invasion			Pelvicalyceal invasion			Renal vein invasion			TNM stage						
Variables	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	T1a	T1b	T2a	T2b	T3a	T4	P-value
Necrosis			0.004			0.284			0.004			0.048							<0.001
No	146	12		153	5		149	9		148	10		70	31	19	6	24	5	
Yes	55	15		66	4		57	13		60	10		8	11	11	11	24	5	
Sarcomatoid change			<0.001			0.015			0.008			0.387							0.003
No	194	19		207	6		196	17		195	18		78	40	29	15	40	8	
Yes	7	8		12	3		10	5		13	2		0	2	1	2	8	2	
Rhabdoid change			0.020			0.663			0.060			0.215							0.128
No	195	23		209	9		199	19		200	18		78	40	29	16	43	9	
Yes	6	4		10	0		7	3		8	2		0	2	1	1	5	1	

Table IV. Continued.

Part B.

	Perinephric fat invasion			Gerota fascia invasion			Pelvicalyceal invasion			Renal vein invasion			TNM stage						
Variables	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	No	Yes	P-value	T1a	T1b	T2a	T2b	T3a	T4	P-value
Microvascular invasion			<0.001			0.004			0.001			0.001							<0.001
No	184	11		191	4		182	13		184	11		78	40	29	15	24	6	
Yes	17	16		28	5		24	9		24	9		0	2	1	2	24	4	
Renal sinus invasion			<0.001			0.030			<0.001			<0.001							<0.001
No	180	14		189	5		182	12		186	8		78	41	30	17	18	7	
Yes	21	13		30	4		24	10		22	12		0	1	0	0	30	3	
Renal capsule invasion			<0.001			<0.001			0.028			0.004							<0.001
No				194	0		179	15		182	12		76	42	28	17	28	1	
Yes				25	9		27	7		26	8		2	0	2	0	20	9	
Perinephric fat invasion						<0.001			0.007			0.001							<0.001
No				201	0		186	15		189	12		78	42	30	17	30	1	
Yes				18	9		20	7		19	8		0	0	0	0	18	9	
Gerota fascia invasion									0.606			0.181							<0.001
No							198	21		201	18		78	42	30	17	46	3	
Yes							8	1		7	2		0	0	0	0	2	7	
Pelvicalyceal invasion												0.006							<0.001
No										192	14		78	42	28	17	29	9	
Yes										16	6		0	0	2	0	19	1	
Renal vein invasion																			<0.001
No													78	41	30	16	33	7	
Yes													0	1	0	1	15	3	

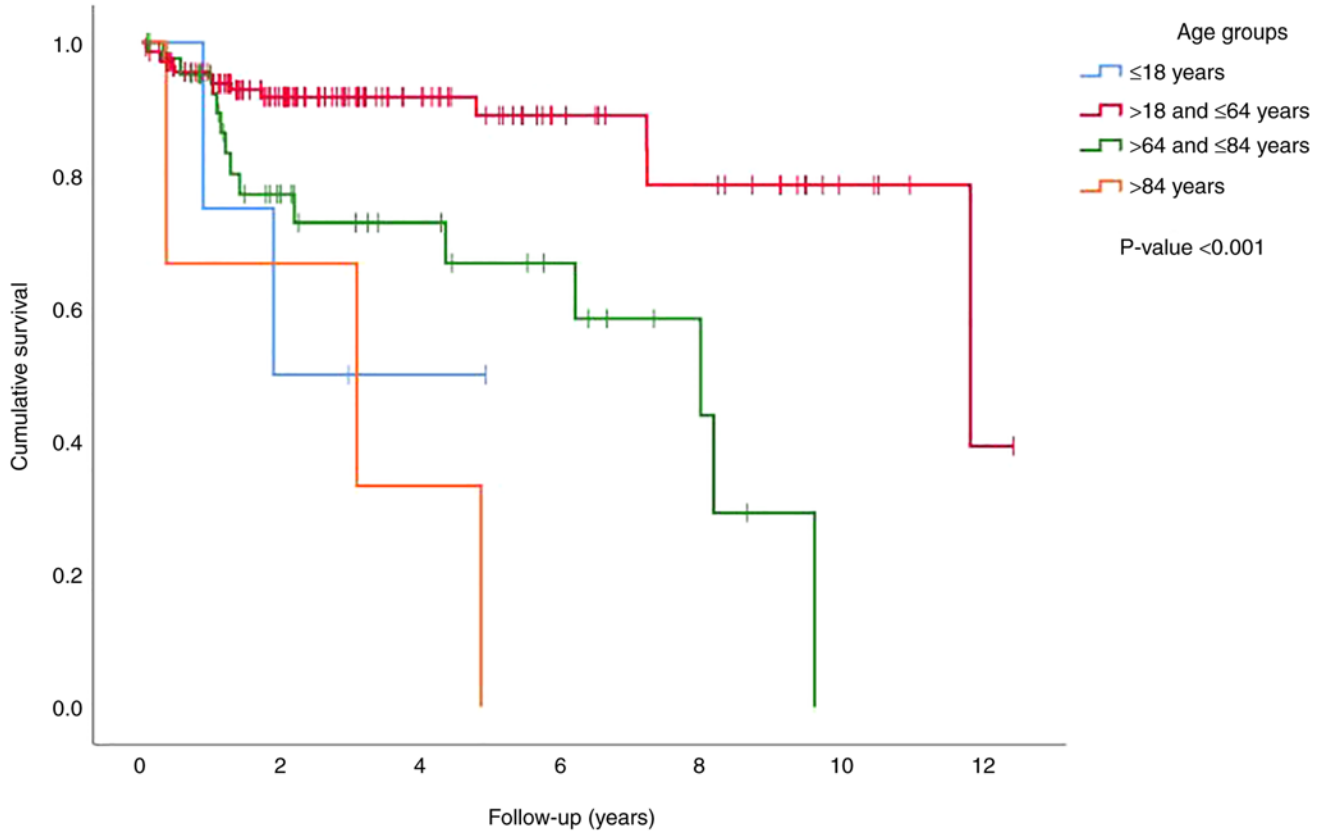

Figure 1. Univariate analysis of survival correlation with age.

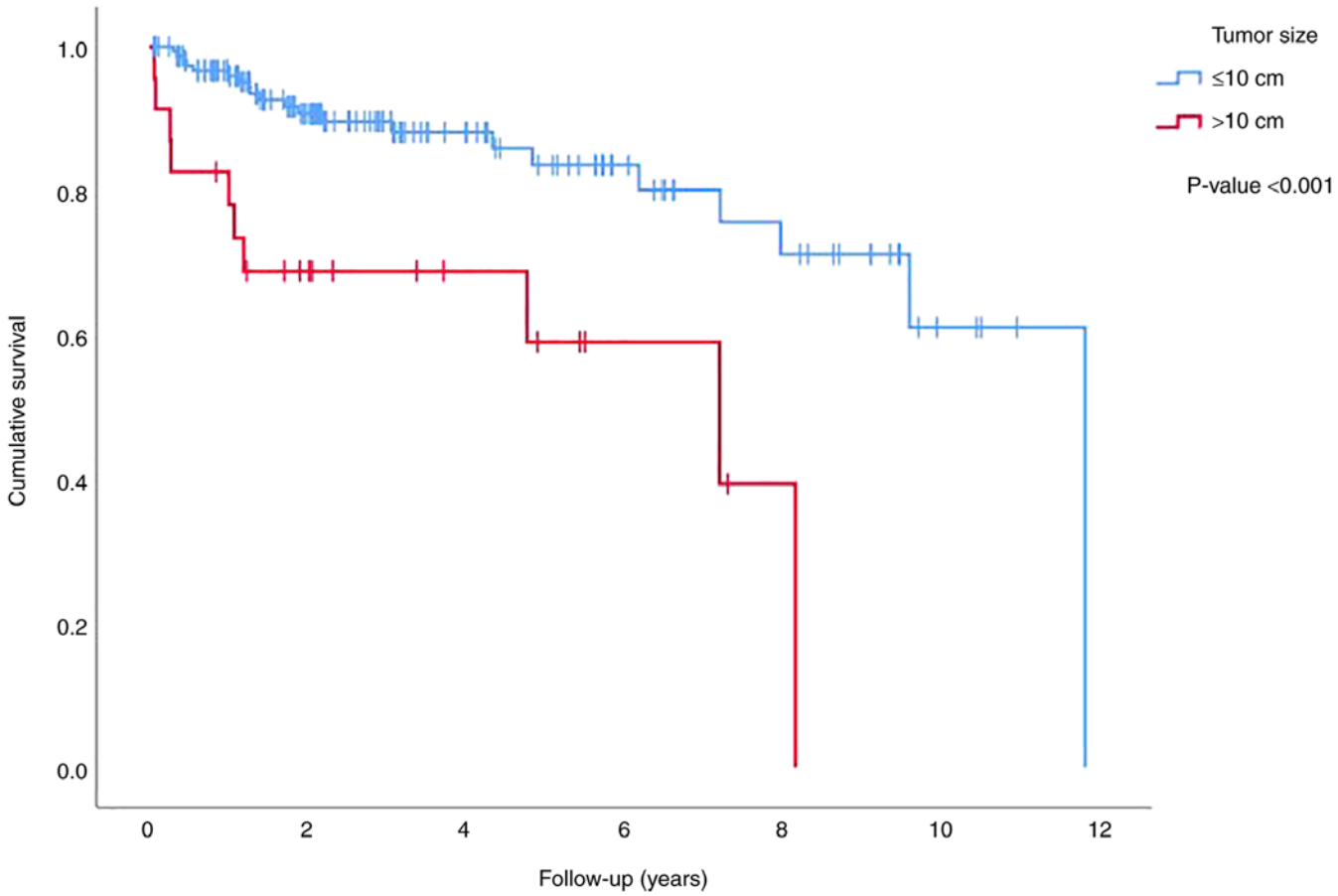

Figure 2. Univariate analysis of survival correlation with tumor size.

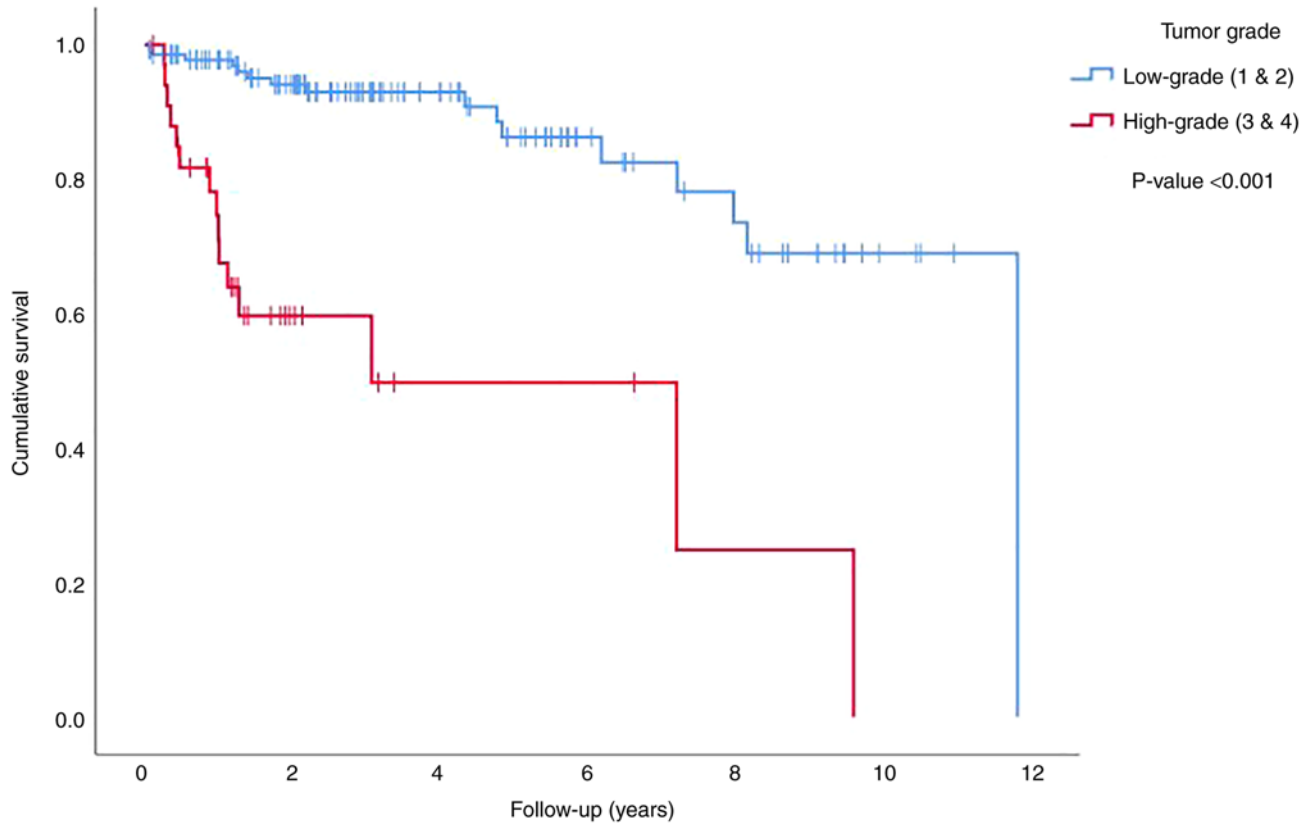

Figure 3. Univariate analysis of survival correlation with tumor grade.

analysis (Tables V and VI). Analysis of survival by tumor type revealed no significant difference among clear cell RCC, papillary RCC and chromophobe RCC. The only significant difference pertained to the worse outcome for the remaining histologic types grouped together as compared with clear cell carcinoma (P=0.034) and chromophobe carcinoma (P<0.001) (Fig. 4).

Regarding the effects of MAI on survival, necrosis had a significant impact only in patients with clear cell RCC (P=0.026) (data not shown). In addition, univariate analysis demonstrated a significant impact on survival in the presence of sarcomatoid change (P<0.001), rhabdoid change (P=0.037), and microvascular invasion (P<0.001) (Table V). However, on multivariate analysis, when these three factors, along with tumor necrosis, were stratified for tumor grade, only microvascular invasion retained a significant impact (P=0.008) (Table VI). On univariate analysis, there was, likewise, a significant impact on survival in the presence of invasion of the renal sinus (P=0.001), renal capsule (P=0.001), perinephric fat (P<0.001), Gerota fascia (P=0.024), pelvicalyceal system (P=0.042), and renal vein (P=0.046) (Table V). However, multivariate analysis for all of these parameters, combined and stratified against tumor grade and tumor size, revealed no significant impact for any individual parameter (Table VI). Analysis of the effect of tumor stage on survival only showed a significant difference between tumors that were at stage T2a or lower and tumors that were at stage T2b or higher (P<0.001) (Fig. 5).

Using Cox regression analysis, the rate of metastasis was demonstrated to be significantly increased (P<0.001) with a higher tumor size (Fig. 6), grade (Fig. 7) and stage (data not shown) using the two-tiered groupings mentioned previously for each parameter. Furthermore, all MAI significantly increased the risk of metastasis (Table VII).

Discussion

In the Surveillance, Epidemiology, and End Results (SEER) data, the most frequent age group for all cases of kidney and pelvis cancer was the 65-74 age group, with a median age of 64 years (14). In the present study, the most frequent group was the 45-64 age group, with a mean age of 51 years, which is in line with a previous local study that reported mean age of 54.3 in patients with metastatic RCC (15). This difference regarding the aforementioned study and the present study compared with SEER data may reflect the difference in life expectancy between the studied populations as well as the differences in risk factor exposure.

The sex distribution in the incidence of RCC was positively skewed towards males, with a male-to-female ratio of 1.8:1 in the SEER data (14), although, a previous study revealed female preponderance in West Africa (16). The findings of the present study were concordant with the results of the SEER data (14) and the aforementioned local study (15), with a male-to-female ratio of 1.5:1.

Aron *et al* (17) also reported significant sex differences in other parameters, including larger tumor size, higher grade, higher incidence of metastasis, and shorter overall survival for males. However, in the data of the present study, there was no significant sex difference in tumor size and grade, or overall survival. More studies are required to determine whether there

Table V. Univariate analysis of survival correlation with tumor size, tumor grade, aggressiveness, and invasiveness parameters.

	Correlation with survival							
							95.0% CI for Exp(B)	
Variables in the equation	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Necrosis	0.616	0.360	2.923	1	0.087	1.851	0.914	3.748
Sarcomatoid change	2.146	0.427	25.231	1	<0.001	8.552	3.702	19.759
Rhabdoid change	1.297	0.622	4.345	1	0.037	3.658	1.081	12.380
Microvascular invasion	2.163	0.393	30.213	1	<0.001	8.694	4.021	18.797
Renal sinus invasion	1.281	0.385	11.094	1	0.001	3.602	1.694	7.656
Renal capsule invasion	1.190	0.368	10.479	1	0.001	3.288	1.599	6.761
Perinephric fat invasion	1.953	0.387	25.469	1	<0.001	7.047	3.301	15.044
Gerota fascia invasion	1.226	0.541	5.131	1	0.024	3.409	1.180	9.849
Pelvicalyceal invasion	1.021	0.501	4.152	1	0.042	2.775	1.040	7.406
Renal vein invasion	0.991	0.497	3.986	1	0.046	2.695	1.018	7.132
Tumor grade [Low-grade (1 and 2) and High-grade (3 and 4)]	1.962	0.376	27.267	1	<0.001	7.117	3.407	14.865
Tumor size (≤10 cm and >10 cm)	1.393	0.393	12.581	1	<0.001	4.027	1.865	8.694

B, coefficient for the constant; SE, standard error; WALD, Wald chi-square test; df, degrees of freedom; Sig, the P-value; Exp(B), exponentiation of the B coefficient; C.I., confidence interval.

are consistent differences between the sex in tumor characteristics and whether there are genetic and biochemical bases for these differences.

Performing radical or partial nephrectomies is based on specific selection criteria for each procedure, and these can be affected by the preference of the surgeon. Partial nephrectomy is usually performed for smaller tumors without invasion of adjacent structures, while radical nephrectomy is chosen for larger tumors, tumors in the mid portion of the kidney, and tumors that have invaded adjacent structures (6). Kattan *et al* (18) excluded the type of procedure from their postoperative nomogram for RCC due to the lack of agreement on policy and fixed selection criteria for nephron-sparing surgery among their surgeons. These criteria can explain the reason that in the present study, the cases that underwent radical nephrectomy were significantly more likely to have markers of aggressiveness, whereas those for which partial nephrectomy had been performed were less likely to have the histologic parameters of aggressiveness. This simply reflects the fact that the tumors that have a larger size or are determined by imaging to be invading beyond the kidney or into the sinus or other structures are more likely to be removed with a radical nephrectomy. This also explains the worse survival rates observed in patients for whom a radical nephrectomy had been performed, as these tumors were larger and had a significantly higher likelihood of invasion beyond the kidney or into the renal hilum.

A meta-analysis on the long-term outcome of partial and radical nephrectomies for tumors 4-7 cm in size that included sixteen studies with a total of 13,016 patients demonstrated a higher rate of radical nephrectomies (88%) (19). They revealed that the 5- and 10-year cancer-specific survival was improved in the radical nephrectomy group than in the partial nephrectomy group. The present study did not show a significant difference in outcome between radical and partial nephrectomy for any tumor size group in particular. There was only an overall difference in the outcome, with patients who underwent radical nephrectomy having worse survival than those who underwent partial nephrectomy. This is congruent with the fact that radical nephrectomies are performed for higher-stage tumors, and these have a poorer prognosis due to their other histologic parameters of aggressiveness, while the better survival noted by the aforementioned study may be due to performing partial nephrectomies for cases which should have been treated by radical nephrectomy, leading to recurrence and metastasis due to inadequate treatment.

In the present study, 50.4% of the tumors were right-sided, and Guo *et al* (20) reported a similar rate of 50.6% from their analysis of the SEER data, however, a local study reported a higher percentage (64.8%) (15). The present results showed a significantly higher rate of renal sinus invasion in right-sided tumors, while Guo *et al* (20) reported that right-sided tumors were more likely to have favorable pathologic features, including improved cancer-specific survival. Further studies are required to identify consistent differences in tumor characteristics and behavior with regard to sidedness and in identifying an anatomical basis for them.

Different rates of tumor multifocality, including 5 to 25%, have been reported in the literature. Sargin *et al* (21) reported a rate of 13.1% in a total of 122 specimens (21). They revealed

Table VI. Multivariate analysis of survival correlation with tumor size, tumor grade, aggressiveness and invasiveness parameters.

	Correlation with survival								
							95.0% CI for Exp (B)		
Variables	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper	Covariate means
Multivariate Cox regression analysis for tumor size and grade (both two-tiered) as covariates									
Size (≤10 cm and >10 cm)	0.943	0.425	4.917	1	0.027	2.567	1.116	5.907	0.133
Grade [Low-grade (1 and 2) and High-grade (3 and 4)]	1.673	0.401	17.375	1	<0.001	5.330	2.427	11.708	0.188
Multivariate Cox regression analysis stratified for tumor grade (two-tiered)									
Necrosis	-0.031	0.465	0.004	1	0.948	0.970	0.390	2.413	0.320
Sarcomatoid change	0.969	0.641	2.288	1	0.130	2.636	0.751	9.252	0.071
Rhabdoid change	-0.836	0.753	1.233	1	0.267	0.434	0.099	1.895	0.053
Microvascular invasion	1.357	0.515	6.948	1	0.008	3.884	1.416	10.654	0.160
Multivariate Cox regression analysis stratified for tumor grade (two-tiered)									
Renal sinus invasion	0.676	0.498	1.841	1	0.175	1.967	0.740	5.224	0.166
Renal capsule invasion	-9.035	110.183	0.007	1	0.935	0.000	0.000	7.321E+89	0.148
Perinephric fat invasion	10.031	110.185	0.008	1	0.927	22,726.533	0.000	1.400E+98	0.124
Gerota fascia invasion	-0.583	0.766	0.579	1	0.447	0.558	0.125	2.504	0.041
Pelvicalyceal invasion	0.165	0.568	0.085	1	0.771	1.180	0.388	3.591	0.107
Renal vein invasion	-0.498	0.639	0.607	1	0.436	0.608	0.174	2.127	0.089
Multivariate Cox regression analysis stratified for tumor size (two-tiered)									
Renal sinus invasion	0.884	0.492	3.226	1	0.072	2.420	0.923	6.348	0.181
Renal capsule invasion	-9.096	105.708	0.007	1	0.931	0.000	0.000	1.068E+86	0.147
Perinephric fat invasion	10.407	105.709	0.010	1	0.922	33,076.445	0.000	3.159E+94	0.124
Gerota fascia invasion	-0.564	0.694	0.662	1	0.416	0.569	0.146	2.215	0.045
Pelvicalyceal invasion	0.214	0.576	0.138	1	0.710	1.238	0.400	3.831	0.107
Renal vein invasion	-0.108	0.643	0.028	1	0.866	0.897	0.254	3.164	0.090

B, coefficient for the constant; SE, standard error; WALD, Wald chi-square test; df, degrees of freedom; Sig, the P-value; Exp(B), exponentiation of the B coefficient; C.I., confidence interval.

a significant association of multifocality with tumor stage and grade but not with tumor morphotype or other parameters. In the present study, only 0.9% of the tumors were multifocal, preventing firm conclusions from being drawn about their significance. Variations in the rates of multifocality are partly explained by differences in the meticulousness of grossing technique, partly by differences in early detection of cancer due to more frequent usage of abdominal imaging techniques, and partly due to regional differences in the rates of papillary RCC and other aggressive histological subtypes that may more frequently be presented as multiple masses.

With regards to tumor size, Zhang *et al* (22) reported frequencies of tumor size according to the AJCC staging cut-offs of 49, 33.5, 12.9, and 4.6% for the group sizes of ≤4 cm, 4.1-7 cm, 7.1-10 cm, and >10 cm, respectively (22). This demonstrated a higher proportion of tumors in the ≤4 cm category compared with the results of the present study, which demonstrated 36.4, 27.6, 20.2 and 13.2% for the respective categories, indicating a higher proportion of tumors >7 cm in size in the current cases. They also revealed a significant association between increasing tumor size and tumor grade, stage, and invasiveness, similar to the findings of the present

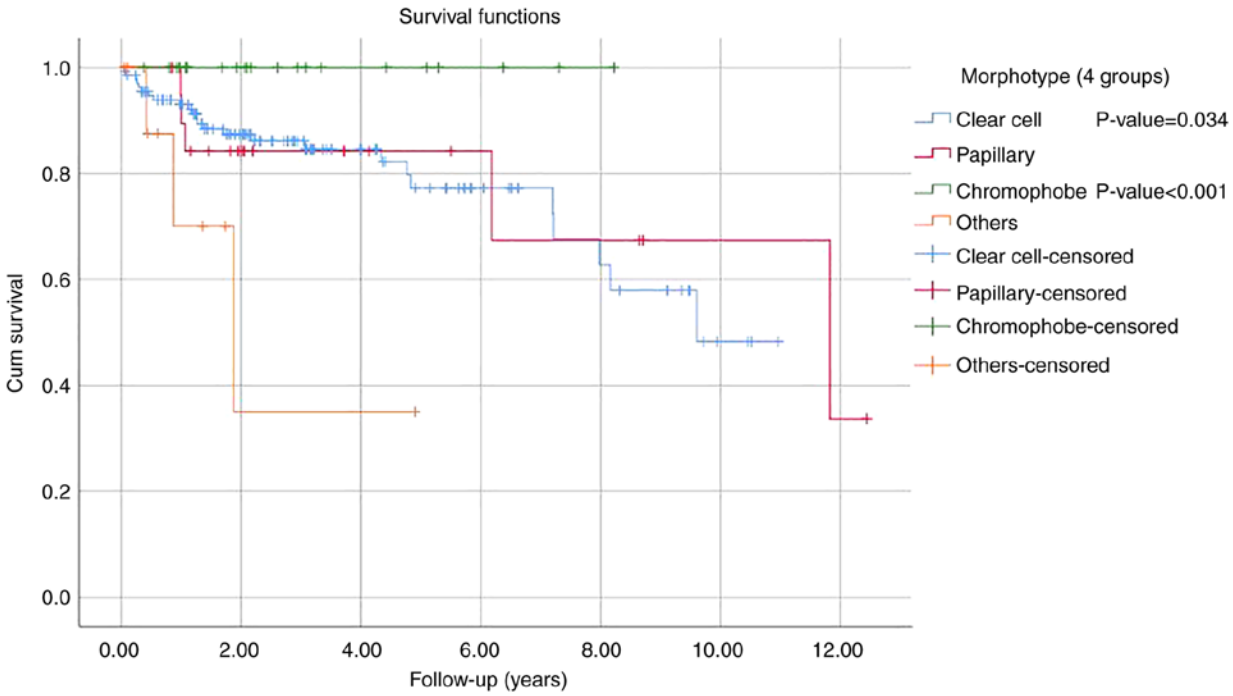

Figure 4. Univariate analysis of survival correlation with histologic morphotypes.

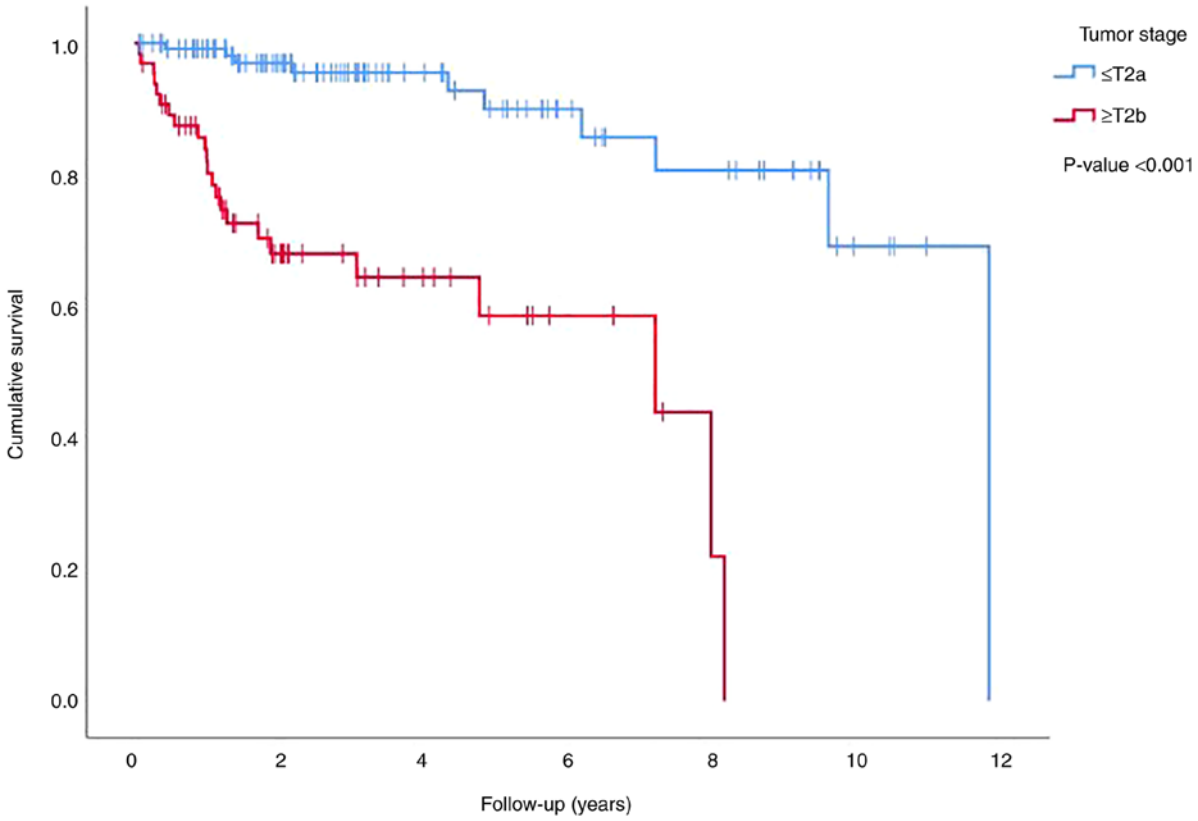

Figure 5. Univariate analysis of survival correlation with tumor stage.

study. Zhang *et al* (22) also revealed in their study that the probability of clear cell carcinoma increased as the tumor size increased, unfortunately, a significant relationship between tumor size and morphotype could not be demonstrated in the present study.

The three most common histologic types of RCC are clear cell, papillary and chromophobe in decreasing order of frequency, but the exact percentages vary among the different studies (23,24). The findings of the present study were concordant with the ordering of these three types, with frequencies

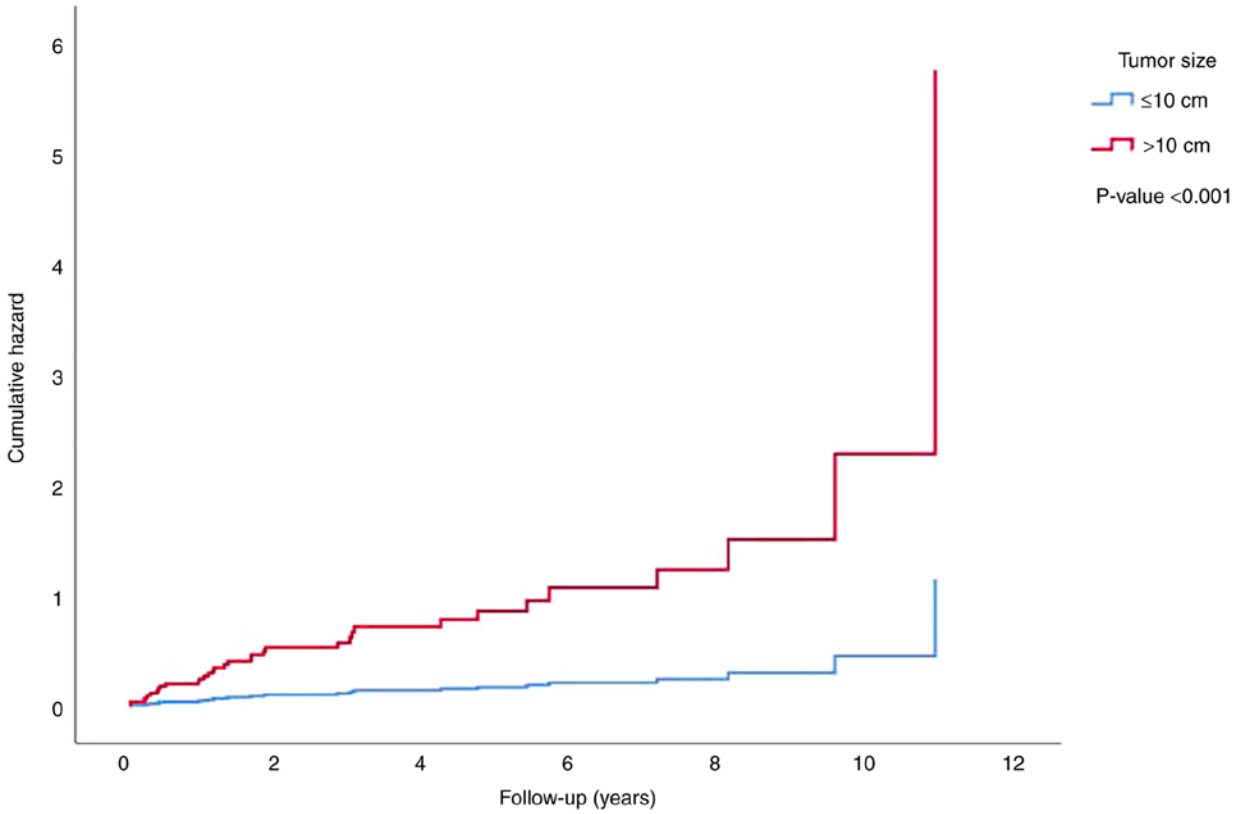

Figure 6. Univariate analysis of metastatic correlation with tumor size.

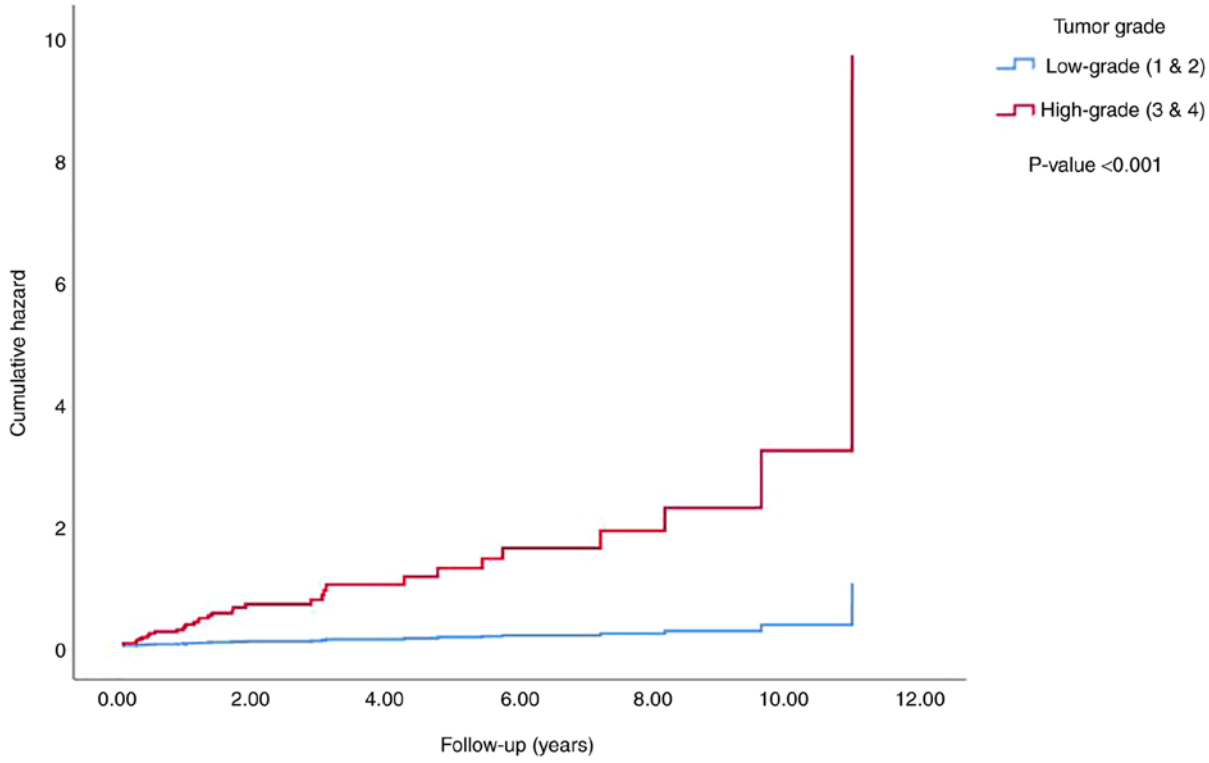

Figure 7. Univariate analysis of metastatic correlation with tumor grade.

of 71.1, 13.6 and 11% respectively. Patard *et al* (25) reported frequencies of 87.7, 9.7 and 2.5%, while Cheville *et al* (23) reported frequencies of 83.2, 11.3 and 4.3% for the three types (23), highlighting a lower rate of the chromophobe subtype and a higher rate of the clear cell subtype compared with the findings of the present study.

Table VII. Univariate analysis of metastasis correlation with tumor stage and aggressiveness and invasiveness parameters.

	Correlation with metastasis							
							95.0% CI for Exp (B)	
Variables in the Equation	B	SE	Wald	df	Sig.	Exp (B)	Lower	Upper
Necrosis	0.933	0.336	7.699	1	0.006	2.542	1.315	4.914
Sarcomatoid change	2.301	0.389	35.057	1	<0.001	9.982	4.661	21.379
Rhabdoid change	1.967	0.465	17.869	1	<0.001	7.151	2.872	17.802
Microvascular invasion	2.304	0.363	40.232	1	<0.001	10.010	4.912	20.397
Renal sinus invasion	1.342	0.359	13.948	1	<0.001	3.828	1.893	7.745
Renal capsule invasion	1.390	0.344	16.330	1	<0.001	4.013	2.045	7.874
Perinephric fat invasion	1.944	0.356	29.733	1	<0.001	6.984	3.473	14.045
Gerota fascia invasion	1.272	0.487	6.825	1	0.009	3.567	1.374	9.261
Pelvicalyceal invasion	1.062	0.457	5.400	1	0.020	2.892	1.181	7.083
Renal vein invasion	1.368	0.410	11.164	1	0.001	3.929	1.761	8.766
Tumor Stage	2.298	0.432	28.250	1	<0.001	9.952	4.265	23.222

B, coefficient for the constant; SE, standard error; WALD, Wald chi-square test; df, degrees of freedom; Sig, the P-value; Exp(B), exponentiation of the B coefficient; C.I., confidence interval.

Patard *et al* (25) observed a significant survival difference among the three histologic types only on univariate analysis, with chromophobe carcinoma having a more favorable outcome. Cheville *et al* (23) demonstrated a significant difference in the outcome of the three types on both univariate and multivariate analysis, with clear cell RCC having a worse outcome than papillary RCC and chromophobe RCC. The results of the present study revealed no significant survival difference between patients with clear cell RCC and papillary RCC. The only significant observation was that the remaining tumor types as a group had a worse outcome than each of clear cell RCC and chromophobe RCC. There was a trend toward better survival in type 1 papillary RCC compared with type 2 papillary RCC, but this did not reach statistical significance. It is difficult to draw conclusions from this since a large proportion of the papillary tumors in the present study were neither specified as type 1 nor type 2, and the difficulties in making this assignment are also recognized in the literature by the wide variation in the proportions of the two tumor types (26). Any attempt to compare the survival outcomes of the two types requires accurate assignment to the appropriate category. This distinction also affects the survival properties of papillary RCC, as some of the tumors previously designated as type 2 papillary RCC are now reclassified as other subtypes based on immunohistochemical findings, and this partly explains the lack of a significant difference in survival between papillary RCC and the other subtypes in the data of the present study.

Grading of RCC was largely based on the Fuhrman system until it was superseded by the ISUP grading scheme (12,13). Considering the period in which the tumors in the present study were reported, some have been graded using the Fuhrman system, while the more recent tumors were graded using the ISUP system. However, there is a close similarity between the two systems, particularly in the first three grades, thus no attempt was made to distinguish between them. The relative frequencies for the 4 grades in the data of the present study were, in order, 21.9, 50.9, 10.1 and 7.5%. In a previous study by Dagher *et al* (24) regarding 374 tumors, the frequencies of the 4 grades consecutively were 9.3, 50.3, 24.1 and 16.3%, highlighting a lower rate of grade 1 tumors and higher rates of grade 3 and 4 tumors compared with the findings of the present study. This difference in the frequency of the nuclear grades can partly be explained by interobserver variation in assigning a nuclear grade and partly by selection bias (later detection of renal cancer has been observed in the aforementioned studies due to differences in risk factors and less liberal use of imaging modalities for abdominal symptoms).

Delahunt *et al* (27), in a study of 121 cases, also reported frequencies of 14, 74.3 and 11.6% for the first 3 grades based on nucleolar prominence (27). In another study conducted on 125 patients with papillary RCC of both types, rates of 31, 36, 32, and 1% for the 4 grades in order were observed. These two studies show the differences in the relative frequencies of the four grades when tumors are selected by histological type (28).

The prognostic significance of these various grades has been presented in several studies to various degrees (24,27,29). Delahunt *et al* (27) identified a statistically significant difference in survival between grades 2 and 3 based on the worst nucleolar grade in both univariate and multivariate analyses.

Khor *et al* demonstrated no significant difference in outcome among grades 1, 2 and 3, but the difference for grade 4 was significant (29). Dagher *et al* (24) showed significant differences in cancer-free survival among grades 2, 3, and 4. In the results of the present study, the impact of tumor grade on survival was only significant when the tumors were grouped into a low-grade tier (ISUP grades 1 and 2) and a high-grade tier (ISUP grades 3 and 4), negating the significance of any difference between grades 1 and 2 on the one hand and grades

3 and 4 on the other hand. These differences may pertain to the accuracy of nuclear grading in these various studies and the lack of a significant difference in behavior and outcome between grades 1 and 2 on the one hand and between grades 3 and 4 on the other hand.

Tumor necrosis was present in 30.7% of the cases of the present study, and this is comparable to what others have reported, including 30% by Katz *et al* (30), 30.4% by Sengupta *et al* (31), 27% by Lee *et al* (32) and 37.2% by Zhang *et al* (22). Lee *et al* (32) revealed that the presence of tumor necrosis was more likely to be associated with increasing tumor size, higher tumor stage, higher tumor grade, microvascular invasion, and the presence of sarcomatoid change (32). The present study also demonstrated a significant association between tumor necrosis and tumor size, stage, grade and MAI.

With regards to its impact on survival, Lee *et al* (32) showed that the presence of necrosis had a significant impact on non-metastatic, clear cell RCC that persisted even on multivariate analysis, while the effect was lost for metastatic tumors as well as for non-clear cell tumors (32). Katz *et al* (30) revealed that the presence of tumor necrosis associated with survival on a univariate, but not a multivariate, analysis. Sengupta *et al* (31) observed that necrosis significantly affected survival for all three major tumor types in both univariate and multivariate analyses. In the present study, tumor necrosis did not significantly affect survival when analyzed for all the tumor types combined, but it did significantly reduce survival for clear cell RCC in particular when the analysis was stratified for tumor morphotype.

Sarcomatoid change was present in 5% of the tumors studied by Cheville *et al* (33). On both univariate and multivariate analysis, the authors observed a significant decrease in survival in the presence of sarcomatoid change, regardless of the type of RCC or tumor grade. In their study of 101 RCCs with sarcomatoid change, De Peralta-Venturina *et al* (34) identified worse survival on both univariate and multivariate analysis. The findings of the present study were mostly concordant with the aforementioned studies, with 6.6% of the tumors in the present study having sarcomatoid change, and this revealed a significant impact on survival on univariate analysis but not on multivariate analysis when compared with the presence of necrosis, rhabdoid change and microvascular invasion. Sarcomatoid change was also associated with a higher rate of metastasis.

Rhabdoid change has been reported with a frequency of 4.7% by Gökden *et al* (35) and 4.5% by Leroy *et al* (36). They both identified a significant impact of rhabdoid change on the rate of survival and metastasis. In the present study, 4.4% of the tumors demonstrated rhabdoid change, and this was associated with a significant decrease in survival and an increase in the rate of metastasis only in univariate analysis.

Microvascular invasion has been reported at a wide range of frequencies, with Kroeger *et al* (37) reported it in 18% of their cases and demonstrating a strong association with increasing tumor size, tumor grade and tumor stage. In the present study, the incidence of microvascular invasion was 14.5%, with a similarly strong association with tumor size, tumor grade and tumor stage, as well as with MAI. Kroeger *et al* (37) demonstrated a higher rate of metastasis and lower survival in the presence of microvascular invasion, but the effect on survival was lost on multivariate analysis. The present study showed similar findings, but the significance was retained even on multivariate analysis with necrosis, sarcomatoid change, and rhabdoid change.

In the present study, tumor invasion into the renal sinus, pelvicalyceal system, renal capsule, perinephric fat, Gerota fascia and the renal vein was significantly associated with decreased survival and an increased risk of metastasis, in consistency with previous studies (38-40). Shah *et al* (41), however, showed no significant impact on survival for isolated perinephric fat invasion, renal sinus invasion, or renal vein invasion, but there was decreased overall survival for patients with multiple patterns of extrarenal extension.

Most of these invasion patterns, except that of the renal capsule, are included in the TNM staging system, and they raise the tumor stage to T3a or T4 accordingly (11). Tsui *et al* (42) demonstrated that as the overall TNM stage increased, cancer-specific survival decreased, although there was no independent effect for the tumor stage. The findings of the present study also showed no independent effect of the tumor stage on overall survival beyond the effect of tumor size, as there was a significant difference in the outcome between tumors of stage T2a or lower (which are ≤10 cm in size) and tumors of stage T2b or higher (which are >10 cm), but there was no significant difference between T2b tumors and tumors that were T3a or higher. These findings demonstrated that tumor size had an independent impact on survival, while tumor stage and invasion parameters did not.

The value of these prognostic indicators can be further refined by performing additional, functional studies on similar datasets. These can include immunohistochemical testing for the expression level and localization of various proteins, including tumor suppressors, cell cycle regulators, and angiogenic factors, and the association of these with the histopathologic parameters that have been outlined in this study as well as with survival and risk of metastasis. Other study designs of interest can include tissue microarray testing for protein expression patterns and mutation analysis to identify differences in the genetic makeup of these tumors and how they associate with differences in aggressiveness, survival, and metastasis. The small sample size and data from a single center were the limitations to the present study.

In conclusion, accurate assessment of the gross and histologic parameters of RCC is essential for tumor prognostication, as numerous of these histological features significantly impact the overall survival and the risk of metastasis. The most important of these parameters are tumor size, grade, and microvascular invasion.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RA and DM are pathologists who examined the specimens and contributed majorly in the conception of the study, data analysis, as well as for the literature search for related studies. RA and DM confirm the authenticity of all the raw data. RB, SF, BA and SM were involved in literature review, data collection and organization. FK and HA contributed in the literature review, acquisition and interpretation of data and the writing of the manuscript. ST, RR, CO and HR were involved in the literature review, the design of the study and the critical revision of the manuscript. FA and MK contributed in the processing of the figures and the critical revision of the manuscript. All the authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved (approval no. 130/2021) by the ethical committee of the University of Sulaimani (Sulaymaniyah, Iraq). Written informed consent was obtained from all patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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