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ORIGINAL ARTICLE

The effect of tumor volume on survival in patients with renal cell carcinoma

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PURPOSE
The aim of this study was to investigate the effect of tumor volume on prognosis and the relation of tumor volume with other prognostic factors in patients with renal cell carcinoma (RCC).

MATERIALS AND METHODS
The study included 46 retrospectively assessed patients with RCC (32 males and 14 females; mean age, 58.13±10.47 years) who underwent surgery between January 2002 and January 2009. Patients were staged according to clinical, radiological, and pathological data. The basic radiological characteristics of tumors and tumor volumes were defined by two observers. The clinical information and the last health status of all patients were recorded. The life duration of the patients after surgery was determined, and cumulative survival rates were calculated.

RESULTS
The survival rates showed no difference between the male and female patients (P = 0.569); the five-year survival was 75.7% and 78.5%, respectively. The survival rates demonstrated differences between groups according to potential prognostic markers such as cell type, Fuhrman's grade, the diameter, invasion of perinephric fat, sinus, or adrenal gland, pathological stage, and presence of metastasis. The inter- and intra-observer reliability of radiological volume measurements were 93.6% and 100%, respectively (P < 0.001). Two groups of tumor volume (i.e., smaller and greater than 110 cm^3) showed statistically significant difference in terms of survival (P < 0.032). In univariate analysis, only Fuhrman's grade and T stage were independent prognostic variables.

CONCLUSION
Tumor volume is predictive of survival in patients with RCC; however, it does not appear to be an independent prognostic factor. The prognostic factors for overall survival are Fuhrman's grade and T stage.

Key words: • *renal cell carcinoma* • *survival analysis* • *tumor volume*

Renal cell carcinoma (RCC) constitutes 85% of all primary malignant tumors arising from kidney and nearly 3% of adult cancers (1–6). Approximately 20%–30% of patients diagnosed with RCC have metastasis at the time of diagnosis (1). In patients with recurrent RCC, progression of the disease, the period of survival, and the disease process can be predicted owing to many morphological, clinical, histological, and molecular parameters (3). The prognostic markers of RCC include tumor node metastasis (TNM) stage as morphological marker; histological type, nuclear grade, tumor necrosis, and sarcomatoid change as histological markers; and factors such as adhesion molecules, molecules stimulating immune response, growth factor receptors, and molecules inducing hypoxia as molecular and genetic markers (3). Clinical and laboratory prognostic factors are represented by the following parameters: patient performance at tumor presentation, the erythrocyte sedimentation rate, thrombocyte count, as well as serum calcium, hemoglobin, and lactate dehydrogenase levels. Among these, tumor stage, grade, and patient performance are the most widely used. Many studies on molecular and cytogenetic markers have been performed but none has been found to be better than tumor stage and nuclear grade to estimate prognosis. For this reason, efforts for determining new prognostic factors that indicate the proliferation and progression of RCC still persist (2–4). Several trials have been conducted concerning the diameter of tumors in RCC; however, few trials exist regarding the tumor volume. Tumor volume calculated using three-dimensional (3D) imaging techniques is accepted as independent marker in predicting the outcome in pharyngolaryngeal, lung, and breast cancers (5). Tumor volume is the basic criterion for deciding the treatment outcome in radiotherapy (7). Measuring the volume of brain tumors allows making decision on the prognosis and treatment of the patient (8).

The aim of our study was to investigate the effect of tumor volume on prognosis and the relation of tumor volume to other prognostic markers in patients with RCC.

Materials and methods

The study included 46 retrospectively assessed patients (32 males and 14 females; mean age, 58.13±10.47 years; age range, 33–81 years) who underwent surgery between January 2002 and January 2009 and received a diagnosis of RCC. Considering January 1, 2009 as the deadline, the clinical information and the last health status of all patients were obtained from the hospital information system and/or by contacting the patients or their relatives who agreed to communicate by phone. The study was approved by the local ethics committee of our institution.

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Imaging parameters

The study protocol included the standard computed tomography (CT) imaging parameters used at our institution during the years 2002–2009. A total maximum dose of 100 mL of nonionic iodinated contrast material (1.5–2 mL/kg) was injected via an automated injector as a bolus with an injection rate of 3 mL/s. The images were obtained during breathhold, using a 4- or 16-detector CT (MX8000 or Brilliance 16, respectively; Philips, Eindhoven, The Netherlands) at the arterial phase (30 s) and at 70 s after the injection. The following parameters were applied: rotation time, 0.5 s; slice thickness, 5 mm; reconstruction interval, 3 mm; tube voltage, 120 kVp; tube current, 200–400 mA.

Clinical and pathological analysis

Clinical characteristics included the basic demographic features and the medical condition of the patients. Pathological characteristics were the tumor cell type, Fuhrman's grade, size of the tumor, invasion of the tumor to perirenal fat, sinus, adrenal or renal vein, and the presence of microvascular invasion. Histopathological data were obtained based on the reports that had been prepared by the pathology department. Patients were staged according to 2002 TNM criteria with cumulative clinical, radiological, and pathological data. Fuhrman's classification was used for histological grading. The life duration of the patients after the operation was determined, cumulative survival rates were calculated, and lifetime curves were compared for different parameters. Independent variables that might have an influence on survival were analyzed.

Radiological analysis

Two independent observers with equal experience (five years in general radiology and one year in abdominal radiology) evaluated the basic radiological characteristics of tumors that included the size, volume, contrast enhancement, and necrosis of the tumors, perirenal heterogeneity, and perirenal vascular heterogeneity. The tumor volumes were measured at a dedicated post-processing workstation (ViewForum, Philips) enabling 3D image processing, including volume analysis. Volume calculations were also performed by the conventional method of multiplication of three sizes of the tumor on CT images by 0.52. To explore the intra-observer variability, the same operations were repeated by the observers leaving a 10-day period between the two evaluations. The two observers were kept unaware of each other's results to prevent inter-observer bias.

At the beginning of the study, a prospective analysis was performed in a group of nine patients other than those in the study group who would undergo surgery to test the validity of the 3D volume measurement method or to obtain a correction factor, if necessary. The volume of tumors in those patients was evaluated by the slice-by-slice pathology volume measurement method. The method was found to be compatible with the pathological method, and no correction factor was needed.

Statistical analysis

All clinical, pathological, and radiological information of the patients were entered into a database generated using a computer software (Statistical Package for Social Sciences version 15.0, SPSS Inc., Chicago, Illinois, USA). The frequency distribution of all variables was calculated. Analyses were performed by generating cross-tables between these variables and death, and by performing chi-square and Mann-Whitney U tests, as appropriate. The relationship between the variables affecting the survival and tumor volume was assessed by the chi-square test. Volume values obtained from the workstation and diameter calculations were compared both in intra-observer and inter-observer fashion using Pearson's correlation test. Additionally, the largest diameters of the tumor measured by each observer were compared with the diameters obtained from pathology. Receiver operating characteristic (ROC) curve analysis was used to identify the most appropriate point reflecting the contribution of the tumor volume and tumor size in pathology to the live and dead patients' last status with the highest sensitivity and specificity rates. Cumulative survival rates were estimated by Kaplan-Meier survival analysis and a log-rank test was used to compare the life curves. For the multiple parameters affecting survival, Cox regression analysis was used to determine the independent variables that had an influence on survival.

Results

Clinical and pathological results

The histological cell types of tumors were clear cell in 25 patients (54.3%), papillary or chromophobe cell in 14 patients (30.4%), and unclassified or sarcomatoid type in seven patients (15.3%). According to Fuhrman's histological grading, 12 patients (26.1%) were Grade 1, 21 patients (45.7%) were Grade 2, six patients (13%) were Grade 3, and seven patients (15.2%) were Grade 4. Patients were divided into two groups: low Fuhrman's Grade 1 and 2, and high Fuhrman's Grade 3 and 4. Thirty-three patients (71.7%) were in the low-grade group and 13 patients (28.3%) were in the high-grade group.

According to the pathology reports, tumor diameters varied between 2 and 13 cm (mean, 6.02 cm). The patients were grouped depending on diameters of the tumors as <4 cm, 4–7 cm, and >7 cm. Sixteen patients (34.8%) were in the first group, 17 patients (37%) were in the second group, and 13 patients (28.3%) were in the third group.

We found invasion of perinephric fat in six patients (13%), invasion of sinus fat in five patients (10.9%), invasion of the renal vein in six (13%) patients, invasion of the adrenal vein in three patients (6.5%), and microvascular invasion in 11 patients (23.9%).

According to TNM staging, 15 patients (32.6%) in were T1a, 12 patients (26.1%) were T1b, seven patients (15.2%) were T2, six patients (13%) were T3a, and six patients (13%) were T3b. When the patients were grouped according to T stage to obtain statistically reliable and measurable numbers, 27 patients (58.7%) were in the first group (T1a+T1b), seven patients (15.2%) were in the second group (T2), and 12 patients (26.1%) were in the third group (T3a+T3b). Lymph node staging was noted as N0 in 44 patients, N1 in one patient, and N2 in one patient. Metastases were found at the time of diagnosis in 10 patients (21.7%). When the patients were divided into two groups according to TNM staging as low and high stages, 30 patients (65.2%) were in the low-stage group (Stage 1+2) and 16 patients (34.8%) were in the high-stage group (Stage 3+4). Surgical margins were free of residual tumor in all patients.

Survival rates and relationship with prognostic markers

The survival rates showed no difference between the male and female patients ($P = 0.569$); the five-year survival was 75.7% and 78.5%, respectively.

The survival rates demonstrated statistically significant differences between groups according to potential prognostic markers such as cell type, Fuhrman's grade, pathological diameter, perinephric fat invasion, sinus fat invasion, adrenal invasion, pathological stage, presence of metastasis, and clinical stage (Table 1).

The survival rate differences between the patients with clear cell carcinoma and those with papillary+chromophobe cell carcinoma were not statistically significant ($P = 0.119$). However, unclassified type+sarcomatoid type tumor patients had a survival disadvantage compared with the clear cell ($P < 0.005$) and papillary+chromophobe cell type groups ($P < 0.001$). According to Fuhrman grading, low-grade patients (Group 1+2) had significantly better survival rates than high-grade patients (Group 3+4) ($P < 0.001$). Grouping the tumor sizes as <4 cm, 4–7 cm, and >7 cm, a survival difference was found between the <4 cm and >7 cm tumor size groups ($P < 0.008$). Survival differences among the other groups were not statistically significant. Patients with perinephric fat, sinus fat, and adrenal invasion had a survival disadvantage compared with the patients without invasion ($P < 0.002$, $P < 0.007$, and $P < 0.001$, respectively). The effect of renal vein and microvascular invasion on survival was not significant ($P = 0.483$ and $P = 0.076$, respectively).

Regarding pathological T stage, T1 tumor patients showed a better survival rate than T3 patients ($P < 0.011$). No significant survival difference was observed between the T1 and T2 ($P = 0.075$), and T2 and T3 ($P = 0.500$) groups. A significant difference was observed concerning the survival rate between the patients with and without metastasis ($P < 0.001$). Low-stage patients (Stage 1+2) had significantly better survival compared with the high-stage patients (Stage 3+4) ($P < 0.001$).

Table 1. Survival rates and their relation with prognostic markers

			Exitus		Alive		
		n	n	%	n	%	*P*
Histological cell type	Clear cell	25	4	16.0	21	84.0	< 0.001
	Papillary+chromophobe	14	0	0.0	14	100	
	Unclassified sarcomatoid	7	5	71.4	2	28.6	
Fuhrman's grade	Low grade (1+2)	33	1	3.0	32	97.0	< 0.001
	High grade (3+4)	13	8	61.5	5	38.5	
Pathological diameters	≤4 cm	16	0	0.0	16	100	< 0.008
	4–7 cm	17	3	17.6	14	82.4	
	>7 cm	13	6	46.2	7	53.8	
Perinephric fat invasion	No	40	5	12.5	35	87.5	< 0.002
	Yes	6	4	66.7	2	33.3	
Sinus fat invasion	No	41	6	14.6	35	85.4	< 0.016
	Yes	5	3	60.0	2	40.0	
Adrenal invasion	No	43	6	14.0	37	86.0	< 0.001
	Yes	3	3	100.0	0	0.0	
Pathological stage	pT1	27	1	3.7	26	96.3	< 0.003
	pT2	7	2	28.6	5	71.4	
	pT3	12	6	50.0	6	50.0	
Metastasis	No	36	1	2.8	35	97.2	< 0.001
	Yes	10	8	80.0	2	20	
Clinical stage	Low (1+2)	30	0	0.0	30	100.0	< 0.001
	High (3+4)	16	9	56.2	7	43.8	
Dimensional parameters	Pathological largest diameters (mm)		84.4±27.9		54.4±28.3		< 0.009
	Largest diameters on CT (mm)		88.3±32.8		58.3±29.2		< 0.009
	Volume measured from three dimensions (cm^3)		319.3±344.0		140.1±229.2		< 0.015
	Volume measured at workstation (cm^3)		349.8±390.8		160.7±258.9		< 0.030

CT, computed tomography.

Volume measurements and relationship of volume with prognostic markers

The inter-observer and intra-observer reliability of volume measurements were 93.6% and 100%, respectively ($P < 0.001$). There was statistically significant difference in terms of survival between tumor volume groups of <110 cm^3 and >110 cm^3 ($P < 0.032$). The tumor volume was >110 cm^3 in 76.9% of the patients with a high Fuhrman's grade, 60% of the patients with sinus fat invasion, 72.7% of the patients with microvascular invasion, 70% of the patients with metastasis, 75% of the patients with a high stage, 55.6% of the patients with tumor necrosis, 75% of the patients with perirenal heterogeneity, 71.4% of the patients with perirenal vascular heterogeneity, and 100% of the patients with perinephric fat invasion, renal vein invasion, and adrenal invasion. Prognostic markers that affected the relation between survival and tumor volume are presented in Table 2.

Independent variables determining the prognosis of the disease were analyzed using multivariate analysis, which was performed using parameters affecting the survival in the univariate analysis (Table 3). Fuhrman's grade and T stage were detected as independent prognostic variables. The tumor volume, despite affecting the prognosis in patients with RCC, was not found to be an independent prognostic marker (Figs. 1–3).

Discussion

Primary tumor size is the key component of the TNM classification system and one of the most important prognostic factors of RCC. Life expectancy has been shown to depend on tumor size, and the survival rates of tumors <5 cm, 5–10 cm, and >10 cm are 84%, 50%, and 0%, respectively (9). In 1997, the cut-off value for tumor size at T1 stage was increased from 2.5 cm to 7 cm (10). Many studies have evaluated the most appropriate tumor size in the T1 stage for the partial or radical nephrectomy criteria and have recommended various sizes as the cut-off points (11). Although previous studies do not agree on the most appropriate cut-off value, they share the same opinion that tumor size is a factor determining the prognosis. Recently, TNM staging has been updated and subgroups of T2 are defined according

Table 2. Prognostic markers affecting survival and their relation with tumor volume

			Tumor volume				
			≤110 cm^3		>110 cm^3		
		n	n	%	n	%	*P*
Complaints on admission	Symptomatic	34	16	47.1	18	52.9	< 0.029
	Co-incidental	12	10	83.3	2	16..7	
Fuhrman's grade	Low grade (1+2)	33	23	69.7	10	30.3	< 0.040
	High grade (3+4)	13	3	23.1	10	76.9	
Perinephric fat invasion	No	40	26	65.0	14	35.0	< 0.030
	Yes	6	0	0.0	6	100.0	
Adrenal invasion	No	43	26	60.5	17	39.5	< 0.040
	Yes	3	0	0.0	3	100.0	
Renal vein invasion	No	40	26	65.0	14	35.0	
	Yes	6	0	0.0	6	100.0	
Microvascular invasion	No	35	23	65.7	12	34.3	< 0.025
	Yes	11	3	27.3	8	72.7	
Metastasis	No	36	23	63.9	13	36.1	< 0.05
	Yes	10	3	30.0	7	70.0	
Clinical stage	Low (1+2)	30	22	73.3	8	26.7	< 0.002
	High (3+4)	16	4	25.0	12	75.0	
Tumor necrosis on CT	No	10	10	100.0	0	0.0	< 0.002
	Yes	36	16	44.4	20	55.6	
Perirenal heterogeneity on CT	No	34	23	67.6	11	32.4	< 0.010
	Yes	12	3	25.0	9	75.0	
Perirenal vascular heterogeneity on CT	No	25	20	80.0	5	20.0	< 0.001
	Yes	21	6	28.6	15	71.4	
Total		46	26	56.5	20	43.5	

CT, computed tomography.

to the diameter of 7–10 cm for T2a and >10 cm for T2b (12). Tumor size is also a parameter that may alter the surgical approach as laparoscopic vs. open nephrectomy, or partial vs. radical nephrectomy (13–15). Because nephron sparing surgery is the main aim and has an increasing popularity in smaller tumors, the T1 cut-off value carries importance not only as a prognostic parameter but also as a parameter of treatment (13). Nephron sparing surgery for large tumors has also been suggested as a feasible method with acceptable pathological results despite prolonged operation times (14). Hafez et al. (11) have attempted to determine the most appropriate cut-off

Table 3. Result of survival analysis (univariate analysis with log-rank rest)

		n	Five-year survival (%)	Mean life expectancy (months)	*P*
Gender	Male	32	75.7±0.081	61±5	0.569
	Female	14	85.7±0.094	66±6	
Complaints	Symptomatic	34	75.0±0.078	61±5	0.356
	Coincidental	12	100.0	69±6	
Cell type	Clear cell	25	82.9±0.078	-	< 0.001
	Papillary+chromophobe	14	100	-	
	Unclassified+sarcomatoid	7	21.4±0.178	13±9	
Fuhrman's grade	Low grade	33	96.7±0.031	76±2	< 0.001
	High grade	13	29.31±0.153	26±7	
Pathological size	≤62.5 mm	27	92.3±0.052	72±4	< 0.02
	>62.5 mm	19	59.9±0.123	51±8	
Pathological size	≤4 cm	16	100	-	< 0.008
	4–7 cm	17	80.2±0.104	-	
	>7 cm	13	53.8±0.138	-	
Perinephric fat invasion	No	40	87.0±0.054	69±4	< 0.002
	Yes	6	25.0±0.204	23±7	
Sinus fat invasion	No	41	83.6±0.062	67±4	< 0.007
	Yes	5	30.0±0.239	10±2	
Adrenal invasion	No	43	85.4±0.055	68±4	< 0.001
	Yes	3	0.0	13±7	
Renal vein invasion	No	39	80.5±0.068	65±5	0.483
	Yes	6	66.7±0.192	55±13	
Microvascular invasion	No	35	83.7±0.068	67±4	0.076
	Yes	11	62.3±0.150	50±10	
Pathological stage	pT1	27	96.2±0.038	75±3	< 0.004
	pT2	7	71.4±0.171	56±12	
	pT3	12	45.7±0.155	42±10	
Metastasis	No	36	97.1±0.029	76±2	< 0.001
	Yes	10	12.5±0.115	14±5	
Clinical stage	Low (1+2)	30	100	-	< 0.001
	High (3+4)	16	37.7±0.135	5±1.3	
Necrosis	No	10	100		0.101
	Yes	36	73.0±0.078		
Tumor volume	≤110 cm^3	26	92.0±0.054	72±4	< 0.032
	>110 cm^3	20	62.2±0.117	52±8	

Data are given as mean±standard deviation.

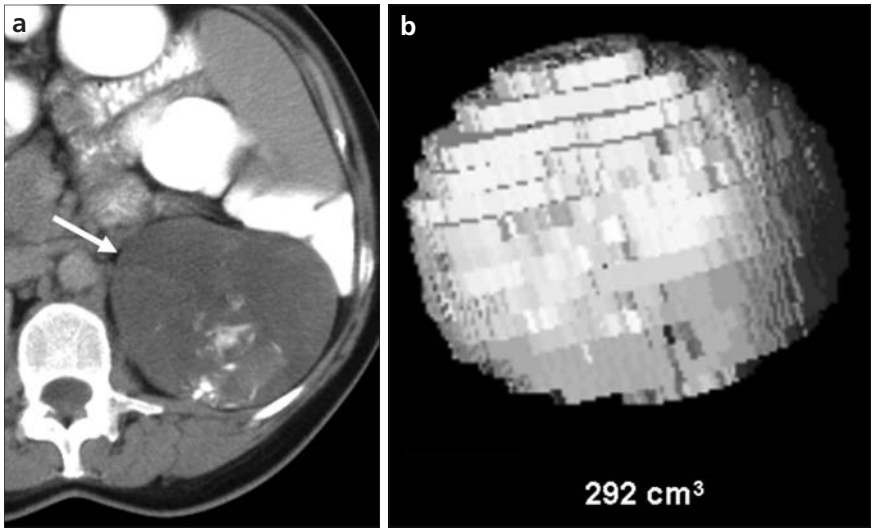

Figure 1. a, b. Tumor with the diagnosis of papillary cell type renal cell carcinoma T2N0M0, Fuhrman Grade 2 **(a**, *arrow***)**. The maximum diameter was 9.3 cm, calculated volume was 292 cm^3 **(b)**. The patient was alive at 76 months.

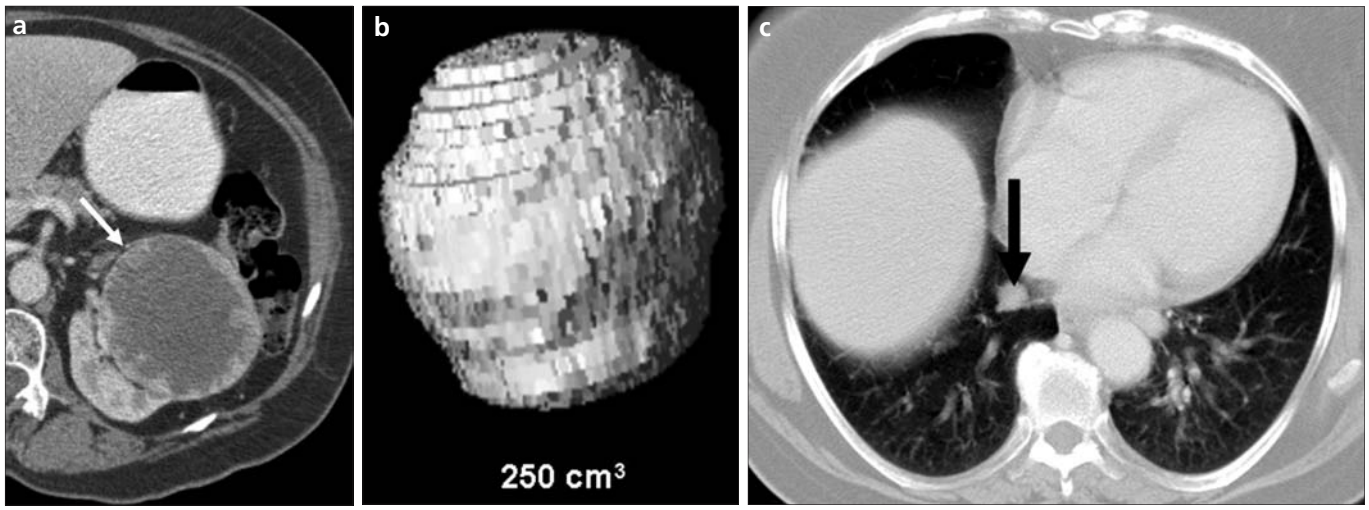

Figure 2. a–c. Tumor with the diagnosis of clear cell type renal cell carcinoma T2N0M1, Fuhrman Grade 2 **(a**, *arrow***)**. The maximum diameter was 8 cm, calculated volume was 250 cm^3 **(b)**. Metastasis was detected in the lung **(c**, *arrow***)**. The patient died at seven months.

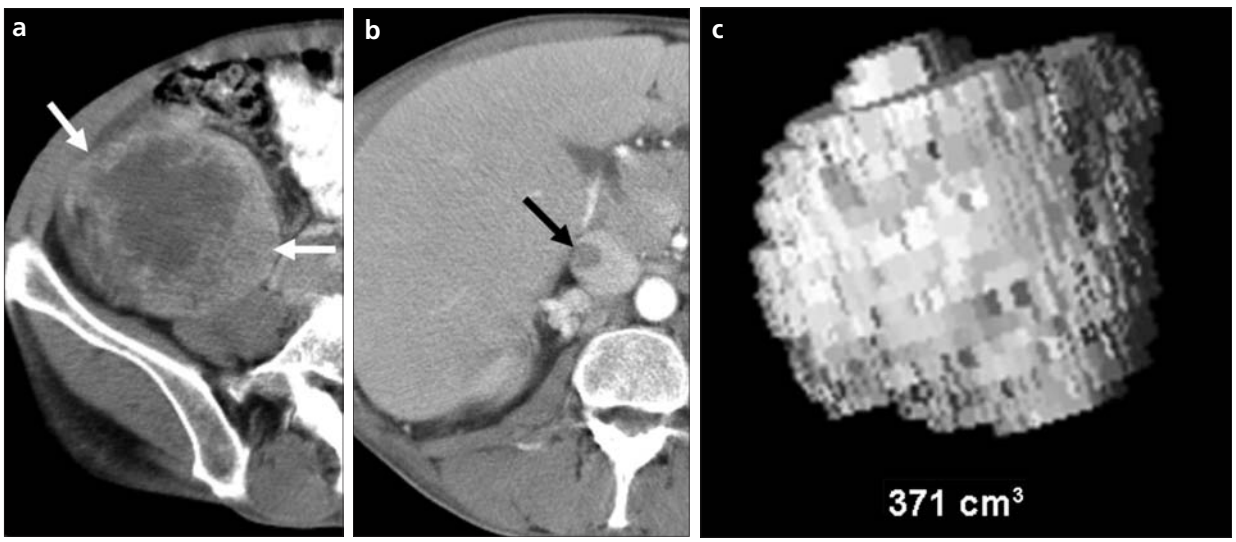

Figure 3. a–c. Tumor with the diagnosis of clear cell type renal cell carcinoma with rhabdoid features **(a**, *arrow***)**. The stage was T3BN0M0 and Fuhrman Grade 3. Tumor thrombus in the vena cava inferior **(b**, *arrow***)** makes the stage T3B. The diameter was 9.6 cm, calculated volume was 371 cm^3 **(c)**. The patient died at 10 months.

value for partial nephrectomy in RCC patients. In their study, they defined patients with a tumor size of ≤4 cm as T1 and suggested that performing partial nephrectomy in those patients resulted in better survival rates than the patients with larger tumors. Many researchers have attempted to improve the classification based on tumor size and the prognostic accuracy of T2 tumors (16, 17). Frank et al. (16) examined 544 patients with T2 tumors and suggested that patients with >10 cm tumors were more aggressive than the patients with tumors of 7–10 cm. In our study, the five-year survival rates for patients with tumor sizes of ≤4 cm, 4–7 cm, and >7 cm were 100%, 80.2%, and 53.8%, respectively. The prognosis of the patients with a tumor size of >7 cm was worse than that for patients with a tumor of ≤4 cm. The survival differences among the patients with a tumor size of ≤4 cm, 4–7 cm, and >7 cm tumor were not statistically significant. In our study, a 62.5 mm tumor size seemed to be the best cut-off point to designate the difference between the live and dead patients in ROC curve. An additional finding of our study related to the parameter of "diameter" is that the pathological tumor size and the size measured by CT are compatible, and the size determined by CT can reliably be used in staging and also planning for nephron sparing surgery. In the literature, controversy exists regarding the relationship between radiological and pathological sizes of renal tumors. Although the aforementioned measurements are generally accepted to be highly correlated (18), some reports have revealed a discrepancy between the two methods (19). The actual size of a renal mass can generally be overestimated by CT images; however, the difference may be minimal and clinically insignificant in most cases (16).

Although many trials have been reported in the literature regarding tumor diameter, few studies exist concerning tumor volume (20–22). However, the tumor volume calculated by 3D imaging techniques has been reported to be an independent marker in predicting the outcome in pharyngolaryngeal, lung, and breast cancers (5). Tumor volume has been the basic criterion for deciding the treatment outcome in radiotherapy (5). Measuring the tumor volume in the brain allows making a decision on the prognosis and treatment of the patient (7). Tumor volume is the best prognostic factor that was confirmed in prostate cancer in a study by Bettendorf et al. (21), in which a significant concordance was found between the tumor volume and prognostic parameters such as pre-operative prostate-specific antigen level, histological grade, lymph node metastasis, and malignant cell differentiation. Because the tumor volume detected in the study by Wagenaar et al. (22) in patients with invasive cervix cancer was only related to deep tumor invasion, a relation with tumor diameter, lymph node involvement, and invasion to deep tissues was also detected. In the univariate analysis, the tumor diameter and volume were found to be related to survival. In one study, in patients with renal cortical tumors, the tumor volume was measured from pre-operative radiological images and post-operative pathological tumor material; the measurements were similar in both (18). Moreover, the tumor volume was determined to be an important independent marker in estimating the patients with renal cortical tumors (18). In a retrospective study of 64 patients with RCC, the authors stated that the tumor size and tumor volume calculated from pathological size were not effective predictors of metastasis and survival (23).

In our study, a statistically significant relationship was found between the tumor volume and survival. Tumor volume was a prognostic marker affecting the survival, but it was not an independent parameter. Additionally, together with the increase in volume, the invasion rates in perinephric fat, adrenal vein, or the renal vein were increasing considerably. The tumor volume was significantly greater than 110 cm^3 in patients within the metastatic and high histological grade group. Tumor necrosis, perirenal heterogeneity, and perirenal vascular heterogeneity identified with CT images significantly increased for tumor volumes above 110 cm^3.

Our study possessed some limitations that should be addressed. First, owing to the design, it is a retrospective study, and CT imaging parameters may have minor variations among the patients. However, patients with unacceptable images in the archive that would have caused a limitation of 3D volume measurements were not included in the study. Second, as in the other survival analysis studies, estimating the nontumoral environmental factors that may have influence on the survival of the patients is very difficult. At least, one may propose that the treatment and follow-up parameters have been maintained at a standard level in that patient group. All advanced stage patients underwent immunotherapy or chemotherapy as appropriate additional treatment after the surgery. Because these treatments were given as a standard protocol and are known to have very low influence on survival, they most likely had limited effect on the study.

As a conclusion, the tumor volume is likely to be a predictive parameter determining the survival in patients with RCC; however, it does not appear to be an independent factor. The most important factors determining the general survival are Fuhrman's grade and TNM stage.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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