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Visceral obesity is associated with better recurrence-free survival after curative surgery for Japanese patients with localized clear cell renal cell carcinoma

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Abstract

Objective: To investigate the prognostic significance of visceral obesity to predict recurrence after curative surgery for Japanese patients with localized renal cell carcinoma.

Methods: The data of 285 patients who underwent curative surgery for localized renal cell carcinoma were retrospectively reviewed. Median follow-up was 36.7 months. The association between visceral obesity and recurrence-free survival rate was evaluated using the Kaplan–Meier method and Cox regression models. Visceral fat area at the level of the umbilicus measured using pre-operative computed tomography was used as an index of visceral obesity.

Results: Twenty-nine patients (10.2%) experienced recurrence. Five-year recurrence-free survival rates were 91.3% in high visceral fat area group ($\geq$120 cm^2) and 76.9% in low visceral fat area group (<120 cm^2) ($P = 0.037$); however, visceral fat area was not an independent predictor of recurrence-free survival in multivariate analysis. In the patients with clear cell renal cell carcinoma, 28 patients (11.6%) experienced recurrence. Five-year recurrence-free survival rates were 88.7% in high visceral fat area group and 71.0% in low visceral fat area group ($P = 0.043$), and visceral fat area was an independent predictor of recurrence-free survival (hazard ratio: 1.974, $P = 0.042$) as well as C-reactive protein, Fuhrman nuclear grade, tumor size and microvascular invasion. In patients with organ confined clear cell renal cell carcinoma in particular, visceral fat area was also a useful and independent predictor of recurrence-free survival (hazard ratio: 2.807, $P = 0.038$). Body mass index was not useful in either cohort.

Conclusions: High visceral fat area was a positive predictive biomarker for better recurrence-free survival after curative surgeries for localized clear cell renal cell carcinomas; however, body mass index was not a predictor.

Key words: visceral obesity, obesity, renal cell carcinoma, clear cell renal cell carcinoma, recurrence-free survival

Introduction

The prevalence of being overweight and obese has been increasing around the world. In Japan, dietary changes favoring more Western eating habits have resulted in a rapid increase in the percentage of obese people in the general population (1), thus, obesity has become a major social and health issue. Obese patients are predisposed to the development of various diseases, such as diabetes mellitus, hypertension, coronary heart disease, airway obstruction and certain types of malignant tumors including renal cell carcinoma (RCC) (2).

Although obesity is an established risk factor implicated in the pathogenesis of RCC (3,4), the association between obesity and the prognosis of RCC patients has been conflicting. Some studies reported better prognosis in overweight or obese patients following surgical therapy (5–9). Furthermore, one study reported being underweight was a significant predictor of poor prognosis for patients in whom RCC was diagnosed and resected (10). However, some studies reported that no association between body weight and a clinical course was found after tumor resection (11,12).

In previous studies, body mass index (BMI) has been widely used as a parameter of obesity. However, BMI is not able to distinguish between fat and muscle weight or between visceral and subcutaneous fat. Visceral fat is thought to be the largest endocrine organ and it produces several hormones and cytokines related to carcinogenesis and tumor progression, therefore, some believe that the true effect of obesity on cancer survival should be evaluated using the degree of visceral obesity instead of BMI. Recently, in several types of malignant tumors, such as colorectal cancer (13,14) and pancreatic adenocarcinoma (15), an association between visceral obesity and survival was reported. Additionally, in metastatic RCC, visceral obesity was reported as a positive predictive biomarker for patients who receive vascular endothelial growth factor targeted therapy as a first-line therapy, and BMI was not a useful predictor (16). However, the association between visceral obesity and survival after curative surgery for localized RCC has not been elucidated.

The aim of the present study was to determine the association between visceral obesity and recurrence-free survival (RFS) after curative surgery for localized RCC.

Patients and methods

After institutional review board approval, we performed a retrospective analysis using the data of patients who underwent surgery for RCC at our institution. A total of 445 surgeries (272 radical nephrectomies and 173 partial nephrectomies) had been performed for RCC between 2005 and 2011. Among them, we excluded 145 patients who preoperative abdominal computed tomography (CT) was performed at another institute because visceral fat area (VFA) could not be measured by the software used at our institute. Additionally, 13 patients who had lymph node metastasis or distant metastasis in pre-operative imaging study were also excluded. Furthermore, two patients with positive surgical margin were also excluded. Therefore, a total of 285 patients who received curative surgery (176 radical nephrectomies and 109 partial nephrectomies) for localized RCC were enrolled in the present study.

Radical and partial nephrectomies were performed by laparotomy or laparoscopy, and a transperitoneal or retroperitoneal approach. A decision concerning operative procedure was made according to the preference of the attending physician and the patient. A dissection of regional lymph nodes was not performed.

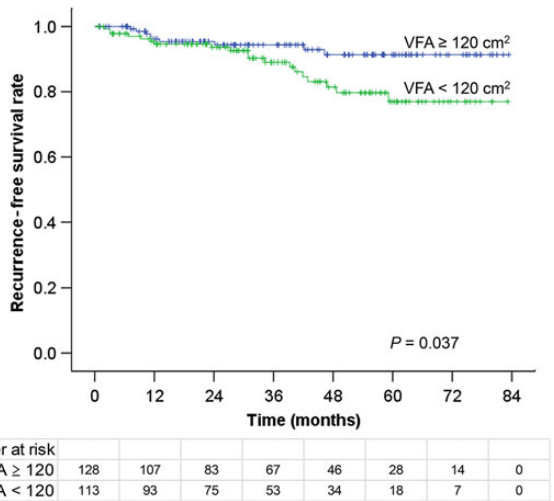
All removed specimens were examined to determine tumor size, histological subtype, Fuhrman nuclear grade, pathological staging and microvascular invasion. Histological subtyping was determined according to the 2004 WHO classification. Pathological staging was performed using the 2009 TNM classification system, and grading was determined according to the Fuhrman nuclear grading system.

VFA was measured at the level of the umbilicus using pre-operative CT performed within 4 weeks prior to surgery because a significant correlation between VFA at that level and the total volume of visceral fat has been reported (17,18). VFA was calculated by measuring pixels with densities in the range of −190 to −30 Hounsfield units as described earlier (19). The border of the intra-abdominal cavity was outlined on the CT image and VFA was then quantified using standard software (Fig. 1). Fat measurements were all carried out by the same radiologist who was blinded to the clinical details.

In addition to VFA, age, sex, BMI, pre-operative C-reactive protein (CRP) and pathological parameters (Histology, Fuhrman nuclear grade, pathological T (pT) stage, tumor size and with or without microvascular invasion) were reviewed from medical records. CRP was measured on the day before the surgery. BMI, as defined by the ratio of the weight of the patient in kilograms divided by the square of the patient's height in meters, was calculated. According to the definition of the Western Pacific Regional Office of WHO, BMI < 18.5kg/m^2, 18.5 kg/m^2 ≤ BMI < 23.0 kg/m^2, 23.0 kg/m^2 ≤ BMI < 25.0kg/m^2 and 25.0 kg/m^2 ≤ BMI was defined as underweight, normal weight, overweight and obese, respectively (20). Since no established cutoff value for VFA existed, VFA was analyzed as dichotomous variables according to approximate optimal cutoff points. The value that best discriminated between good and poor survival, that is with the most significant *P* value according to the log-rank test, was determined by testing all possible cutoffs, and then, 120 cm^2 was defined as the cutoff value of VFA in the present study. Of note, VFA ≥120 cm^2 and <120 cm^2 were defined as high VFA and low VFA, respectively.

All patients were followed every 6 months for the first 3 years and then annually. A history, physical examination, chest and abdominal CT and laboratory studies were performed for follow-up.

Correlations between continuous variables were investigated by Spearman's rank correlation test. The variables of different groups were compared using the χ^2 test or Mann–Whitney *U*-test. The end point of the present study was RFS. Recurrence was defined as any



Number at risk								
VFA ≥ 120	128	107	83	67	46	28	14	0
VFA < 120	113	93	75	53	34	18	7	0

Figure 1. Recurrence-free survival (RFS) estimates according to visceral fat area (VFA) in 285 patients who underwent curative surgery for localized renal cell carcinoma (RCC).

documented recurrence by imaging study, and both local recurrence (a relapse in the operative site and regional lymph nodes) and distant recurrence were included. RFS was defined as the time from the date of surgery to date of recurrence or date of last contact. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. An association between clinicopathologic parameters including VFA and RFS after curative surgery was assessed in multivariate models using Cox proportional hazards regression models with step-wise forward selection. Additional analysis was performed in a subgroup of patients who underwent surgery for localized clear cell RCC. All statistical tests were two-sided, with $P < 0.05$ considered to indicate statistical significance. All data analyses were performed using SPSS statistical software, version 18.0 (SPSS, Chicago, IL, USA).

Results

Relationship between BMI and VFA

The median BMI (interquartile range, IQR) was 23.6 kg/m^2 (21.7–26.2). Ten patients (3.5%), 104 patients (36.5%), 72 patients (25.3%) and 99 patients (34.7%) were underweight, normal weight, overweight and obese, respectively, according to the Western Pacific Regional Office of WHO criteria. Because underweight patients were small, they were grouped together with normal weight patients for further analyses. The median VFA (IQR) was 123.0 cm^2 (72.8–167.7), and 139 patients (48.8%) and 146 patients (51.2%) belonged to the low and high VFA groups, respectively. VFA significantly correlated with BMI ($P < 0.001$, $r = 0.756$); however, a wide range of VFA existed within each BMI class.

Relationship between VFA and the prevalence of other comorbidity (hypertension and hyperlipidemia)

In the present study, the cutoff value of hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg according to The Japanese Society of Hypertension Guidelines for the Management of Hypertension (21). The cutoff value of hyperlipidemia was defined as low-density lipoprotein cholesterol ≥140 mg/dl, high-density lipoprotein <40 mg/dl or triglyceride ≥150 mg/dl according to the Japan Atherosclerosis Society Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases (22). In the present cohort, the prevalence of hypertension and hyperlipidemia in the high VFA group was significantly higher than that in the low VFA group (hypertension: 52.3 vs. 27.4%, $P < 0.001$, and hyperlipidemia: 24.2 vs. 10.6%, $P = 0.006$).

Analyses for the predictors of RFS in all histologies

Table 1 demonstrates the association between clinicopathologic parameters and VFA in 284 patients who underwent curative surgery for localized RCC. The distribution of male patients in the high VFA group was significantly higher compared with the low VFA group. Similarly, the distribution of clear cell RCC in the high VFA group was also significantly higher than that in the low VFA group. There were no significant differences in age, CRP, Fuhrman nuclear grade, pT stage, tumor size and microvascular invasion between the high and low VFA groups.

The median (IQR) follow-up duration was 36.7 (19.5–57.7) months. During follow-up, 28 patients (9.9%) experienced recurrence. Of 28 patients with recurrence, 24 patients (85.7%) developed distant recurrence, 2 patients (7.1%) had both local and distant recurrence and 2 patients (7.1%) had isolated local recurrence. The 5-year RFS rates in obese, overweight and normal weight patients were 94.1, 80.2 and 78.6%, respectively, and the RFS rate in the higher BMI group was slightly better ($P = 0.056$). As shown in Fig. 1, patients in the high VFA group could be predicted to have a lower risk of recurrence, and the 5-year RFS rates were 91.3% in the high VFA group and 76.9% in the normal VFA group ($P = 0.037$). Table 2 summarizes univariate and multivariate analyses for prediction of RFS. In univariate analyses, VFA, Fuhrman nuclear grade, pT stage, tumor size and microvascular invasion were significantly associated with RFS. Multivariate analysis showed that Fuhrman nuclear grade (hazard ratio, HR = 4.642, $P < 0.001$), pT stage (HR = 2.905, $P = 0.025$) and microvascular invasion (HR = 2.939, $P = 0.015$) were independent predictors of RFS, while VFA was not an independent predictor.

Analyses for the predictors of RFS in clear cell RCC

Next we analyzed for risk factors for recurrence in 241 patients who underwent surgery for localized clear cell RCC. Table 1 shows the association between clinicopathologic parameters and VFA. The distribution of male patients in the high VFA group was significantly higher than that in the low VFA group. There were no significant differences in age, CRP, Fuhrman nuclear grade, pT stage, tumor size and microvascular invasion between the high and low VFA groups.

The median (IQR) follow-up duration was 35.6 (19.0–55.5) months. During follow-up, 28 patients (11.6%) experienced recurrence. Of 28 patients with recurrence, 24 patients (85.8%) developed distant recurrence, 2 patients (7.1%) had both local and distant recurrence and 2 patients (7.1%) had isolated local recurrence. The 5-year RFS rates in obese, overweight and normal weight patients were 87.4, 80.3 and 74.0%, respectively ($P = 0.162$). Patients in the high VFA group could be predicted to have a lower risk of disease recurrence, and the 5-year RFS rate was 88.7% in the high VFA group and 71.0% in the low VFA group ($P = 0.043$, Fig. 2).

Univariate and multivariate analyses were performed to determine the predictors of cancer recurrence (Table 2). In univariate analysis, age, VFA, CRP, Fuhrman nuclear grade, pT stage, tumor size and microvascular invasion were significantly associated with RFS. In multivariate analysis, VFA was found to be an independent predictor of recurrence (HR = 1.974, $P = 0.042$), as well as CRP (HR = 1.233, $P = 0.034$), Furman nuclear grade (HR = 2.946, $P = 0.025$), tumor size (HR = 1.242, $P = 0.026$) and microvascular invasion (HR = 2.848, $P = 0.033$); however, high BMI was not an independent predictor.

Subgroup analysis also demonstrated that patients with high VFA could be predicted to have a lower risk of recurrence in cases of organ confined clear cell RCC (pT1 and pT2) ($P = 0.042$). The 5-year RFS rate was 92.0% in the high VFA group and 74.7% in the low VFA group. And a low VFA was an independent predictor of worse RFS in multivariate analysis (HR = 4.281, $P = 0.006$), as well as tumor size (HR = 1.379, $P = 0.005$) and microvascular invasion (HR = 3.988, $P = 0.006$) (Table 2). Meanwhile, there was no significant difference in recurrence between the high and low VFA groups in cases of locally advanced clear cell RCC (pT3 or pT4) ($P = 0.363$).

The VFA of male clear cell RCC patients was significantly different from that of female patients (136.6 ± 66.4 cm^2 vs. 89.9 ± 74.4 cm^2, $P < 0.001$). In the subgroup analysis using the data of male patients, disease recurrence in the high VFA group was significantly lower than that in the low VFA group ($P = 0.014$). The 5-year RFS rate was 88.0% in the high VFA group and 63.9% in the low VFA group. And a low VFA was an independent predictor of worse RFS in multivariate analysis (HR = 3.875, $P = 0.019$), as well as pT stage (HR = 4.094, $P = 0.010$), tumor size (HR = 1.303, $P = 0.008$) and

Table 1. Clinical and pathological characteristics of patients who underwent curative surgery for localized renal cell carcinoma

Variable	All histology ($n = 285$)				Clear cell ($n = 241$)			
		VFA (cm^2)		*P* value		VFA (cm^2)		*P* value
		<120 cm^2 ($n = 139$)	≥120 cm^2 ($n = 146$)			<120 cm^2 ($n = 113$)	≥120 cm^2 ($n = 128$)	
Age (years), (mean (± SD))	59.0 (±12.5)	57.7 (±13.0)	60.3 (±11.9)	0.080	59.1 (±12.6)	57.6 (±13.1)	60.4 (±12.1)	0.086
Sex, (no. (%))				<0.001				<0.001
Male	229 (80.4)	95 (68.3)	134 (91.8)		200 (83.0)	83 (73.5)	117 (91.4)	
Female	56 (19.6)	44 (31.7)	12 (8.2)		41 (17.0)	30 (26.5)	11 (8.6)	
BMI, (no. (%))				<0.001				<0.001
–18.5 kg/m^2	10 (3.5)	10 (7.2)	0 (0)		8 (3.3)	8 (7.1)	0 (0)	
18.5–23 kg/m^2	104 (36.5)	89 (64.0)	15 (10.3)		85 (35.3)	71 (62.8)	14 (10.9)	
23–25 kg/m^2	72 (25.3)	28 (20.2)	44 (30.1)		63 (26.1)	23 (20.4)	40 (31.3)	
25.0 kg/m^2–	99 (34.7)	12 (8.6)	87 (59.6)		85 (35.3)	11 (9.7)	74 (57.8)	
CRP (mg/dl), (mean (± SD))	0.24 (± 0.99)	0.22 (± 0.89)	0.26 (± 1.09)	0.773	0.21 (± 0.85)	0.21 (± 0.88)	0.21 (± 0.83)	0.977
Histology, (no. (%))				0.033				1.000
Clear cell	241 (84.6)	113 (81.3)	128 (87.7)		241 (100.0)	113 (100.0)	128 (100.0)	
Papillary	24 (8.4)	10 (7.2)	14 (9.6)		0 (0.0)	0 (0.0)	0 (0.0)	
Chromophobe	14 (4.9)	11 (7.9)	3 (2.1)		0 (0)	0 (0.0)	0 (0.0)	
Unclassified	6 (2.1)	5 (3.6)	1 (0.6)		0 (0)	0 (0.0)	0 (0.0)	
Fuhrman nuclear grade, (no. (%))			0.146				0.439	
Grade 1	69 (24.2)	33 (23.8)	36 (24.7)		68 (28.2)	32 (28.3)	36 (28.1)	
Grade 2	189 (66.3)	88 (63.3)	101 (29.2)		155 (64.3)	70 (61.9)	85 (66.4)	
Grade 3/4	27 (9.5)	18 (12.9)	9 (6.1)		18 (7.5)	11 (9.8)	7 (5.5)	
Pathological T stage, (no. (%))				0.390				0.244
pT1a	198 (69.5)	101 (72.7)	97 (66.4)		171 (71.0)	85 (75.2)	86 (67.2)	
pT1b	48 (16.8)	19 (13.7)	29 (19.9)		37 (15.3)	13 (11.5)	24 (18.8)	
pT2a	10 (3.5)	6 (4.3)	4 (2.7)		9	5 (4.3)	4 (3.1)	
pT2b	4 (1.4)	1 (0.7)	3 (2.1)		2	0 (0)	2 (1.6)	
pT3a	22 (7.7)	10 (7.2)	12 (8.2)		19	8 (7.2)	11 (8.5)	
pT3b	2 (0.7)	2 (1.4)	0 (0)		2	2 (1.8)	0 (0)	
pT3c	0 (0)	0 (0)	0 (0)		0	0 (0)	0 (0)	
pT4	1 (0.4)	0 (0)	1 (0.7)		1	0 (0)	1 (0.8)	
Tumor size (cm), (mean (± SD))	3.5 (± 2.2)	3.3 (± 2.0)	3.6 (± 2.4)	0.213	3.4 (± 2.1)	3.1 (± 1.9)	3.6 (± 2.2)	0.111
Microvascular invasion, (no. (%))				0.837				0.526
No	229 (80.4)	111 (79.9)	118 (80.8)		192	92 (81.4)	100 (78.1)	
Yes	56 (19.6)	28 (20.1)	28 (19.2)		49	21 (18.6)	28 (21.9)	

VFA, visceral fat area; BMI, body mass index; CRP, C-reactive protein.

Table 2. Univariate and multivariate Cox regression analyses for prediction of recurrence-free survival following curative surgery for localized renal cell carcinoma (all histology and clear cell renal cell carcinoma)

Variable	All histology				Clear cell							
	Univariate	Multivariate			All cases				Organ confined cases (pT1 and 2)			
					Univariate	Multivariate			Univariate	Multivariate		
	P value	HR	HR (95% CI)	*P* value	*P* value	HR	HR (95% CI)	*P* value	*P* value	HR	HR (95% CI)	*P* value
Age (years), continuous	0.099			–	0.045	1.03	0.997–1.069	0.071	0.099			–
Sex (male vs. female)	0.227			–	0.182			–	0.495			–
BMI	0.077			–	0.179			–	0.272			–
–23.0 kg/m^2												
23.0–25.0 kg/m^2												
25.0 kg/m^2–												
VFA (<120 vs. ≥ 120 cm^2)	0.043	1.91	0.840–4.360	0.122	0.021	1.97	1.524–9.266	0.042	0.025	4.28	1.529–11.989	0.006
CRP (mg/dl), continuous	0.089			–	0.001	1.23	1.016–1.496	0.034	0.847			–
Histology (Clear cell vs. non-clear cell)	0.082			–	–			–	–			–
Fuhrman nuclear grade (Grade 3/4 vs. Grade 1/2)	<0.001	4.64	2.067–10.425	<0.001	<0.001	2.95	1.146–7.571	0.025	0.001	1.62	0.542–4.864	0.387
Pathological T stage (≥pT3a vs. <pT3a)	<0.001	2.91	1.144–7.374	0.025	<0.001	2.49	0.918–6.737	0.073	–			–
Tumor size (cm), continuous	<0.001	1.12	0.956–1.308	0.162	<0.001	1.24	1.026–1.503	0.026	<0.001	1.38	1.101–1.727	0.005
Microvascular invasion (yes vs. no)	<0.001	2.94	1.233–7.005	0.015	<0.001	2.85	1.090–7.442	0.033	<0.001	3.99	1.490–10.678	0.006

HR, hazard ratio; CI, confidence interval.

Figure 2. RFS estimates according to VFA in 241 patients who underwent curative surgery for localized clear cell RCC.

microvascular invasion (HR = 4.677, $P = 0.002$). Meanwhile, in the subgroup analysis using the data of female patients, disease recurrence in the high VFA group was not significantly different from that in the low VFA group ($P = 0.487$), although all two patients who had disease recurrence belonged to the high VFA group.

Discussion

The incidence of RCC has rapidly increased around the world, therefore, accurately predicting an individual patient's cancer recurrence based on clinicopathologic parameters is very helpful when designing appropriate post-operative surveillance programs tailored to the patient's risk of cancer recurrence. Several parameters, such as TNM classification, Fuhrman nuclear grade and CRP (23), are already established as predictors of recurrence. However, whether obesity is a useful predictor of recurrence is still controversial.

In the present study, we evaluated the association between visceral obesity and RFS after curative surgery for localized RCC. We revealed that RFS in the high VFA group is significantly longer than that in the low VFA group in all RCC histologies. Furthermore, we demonstrated that VFA is an independent predictor of RFS in clear cell RCC, while BMI is not a predictor. These results suggest that visceral obesity is significantly associated with RFS after surgery for localized RCC, especially clear cell RCC, and it is a more useful predictor than BMI.

Recently, Park et al. (24) reported about the relationship between visceral obesity and disease recurrence. In that study, visceral adipose tissue % (VAT%, visceral adipose tissue/total adipose tissue × 100) was used as an index of visceral obesity. They concluded that a U-shaped relationship between VAT% at the time of diagnosis. The risk of RCC recurrence, with the lowest risk observed among patients in VAT% quartile 2, and a significant increase in disease recurrence was observed in the lowest (HR 3.198, $P = 0.036$) and highest (HR 4.760, $P = 0.010$) VAT% quartiles. To the best of our knowledge, the present study was a second report to evaluate an association between visceral obesity and recurrence after curative surgery for localized RCC. However, VFA used as an index of visceral obesity in the present study is a quite different index from VAT% used in the previous study; therefore, it is not possible to simply compare the results of the two studies. Further study is needed to elucidate the association

between visceral obesity and survival, and an optimal index of visceral obesity should be evaluated.

In the present study, the VFA of male patients was significantly different from that of female patients as shown in the results. Thus, it is concerned whether there is an association between visceral obesity and RFS in both male and female. In male patients, disease recurrence in the high VFA group was significantly lower than that in the low VFA group, and a low VFA was an independent predictor of worse RFS. Therefore, we think there is a significant association between visceral obesity and RFS in male. Meanwhile, in female patients, disease recurrence in the high VFA group was not significantly different from that in the low VFA group. However, in the present cohort, the number of female was too small; therefore, we think further study with large cohorts is needed to clarify an association between visceral obesity and RFS in female.

Obesity is an established risk factor as a pathogenesis of RCC. Although no definitive mechanism has been established yet, several hypotheses have been proposed. They include chronic tissue hypoxia, insulin resistance, compensatory hyperinsulinemia, altered endocrine milieu and production of adipokines, obesity-induced inflammatory response lipid peroxidation and oxidative stress (25). Obesity in particular is more associated with the development of clear cell histology than other histologies (26). Furthermore, it was reported that overweight and obese patients were likely to present with less aggressive tumors compared with normal weight patients (7,9). In the present study, the distribution of clear cell histology in the high VFA group was significantly higher than that in the low VFA group, whereas there was no significant difference in Fuhrman nuclear grade, pT stage, tumor size or microvascular invasion between the high and low VFA groups.

Meanwhile, the association between obesity and prognosis including RFS in RCC is still controversial. Most previous studies evaluated it using BMI as an indicator of obesity. However, the true effect of obesity on cancer survival should be evaluated by the degree of visceral obesity instead of BMI, because visceral fat is the largest endocrine organ and secretes several humoral factors. The association between visceral obesity and survival in RCC was evaluated in only one study. Naya et al. (27) evaluated the data of 117 male patients undergoing radical or partial nephrectomy for clear cell RCC, and reported that patients with high VFA ($\geq$75 cm^2) had significantly higher cumulative cancer-specific survival (CSS) when compared with patients with low VFA (<75 cm^2) and VFA was an independent predictor of better cancer-specific survival. Although the reason why patients with substantial visceral adipose tissue had better survival is unclear, increased serum insulin-like growth factor-1 (IGF-1) and leptin in obese patients might be associated with the better survival. Rasmuson et al. (28) evaluated the association between serum IGF-1, leptin and prognosis in 256 RCC patients. In their study, both serum IGF-1 and leptin were positively related to BMI, and patients with high serum IGF-1 and leptin had a more favorable prognosis compared with those with lower levels in univariate analysis. Furthermore, lower serum IGF-1 was identified as an independent prognostic factor in multivariate analysis. However, the exact mechanism of the association between visceral obesity and a better prognosis has not yet been elucidated, therefore, further research is required to clarify it.

A strong association between obesity and better prognosis, especially in low stage RCC, has been previously reported. Waalkes et al. (29) evaluated the data of 1338 patients who underwent renal surgery for clear cell RCC, and reported BMI was an independent predictor of better CSS in organ confined RCC (pT1 and pT2) although it was not a predictor in advanced RCC (pT3–T4 and/or metastasis). In the present study, similar results were obtained. VFA was a useful and independent predictor of better RFS in organ confined clear cell RCC; however, there was no significant difference in RFS between the high and low VFA groups in locally advanced clear cell RCC.

It should be mentioned that this study has a limitation with respect to the definition of obesity using BMI. The BMI of Asian populations is significantly lower than that of Western populations (30), and it was reported that the percentage of the population with a BMI $\geq$ 30 kg/m^2 is not >2.0–3.0% in Japan (31). In the present study, only 14 patients (4.9%) had BMI $\geq$ 30.0 kg/m^2, therefore, we adopted the definition of the Western Pacific Regional Office of WHO (20). We believe the present study is very meaningful in terms of elucidating the association of visceral obesity with RFS after curative surgery for localized RCC in a Japanese population, although further study is required to validate whether the results of the present study apply to Western populations.

Also, we did not analyze CSS because the number of people who died from RCC was small. To clarify the association between visceral obesity and CSS after curative surgery for localized RCC, further study with larger cohorts and longer follow-up periods is required. Furthermore, the impact of visceral obesity on overall survival is also an important subject of future investigation. Visceral obesity is one of the diagnostic criteria of metabolic syndrome, and patients with rich visceral fat often have other comorbidity, such as hypertension, hyperglycemia and hyperlipidemia. As shown in the results, in the present cohort, the prevalence of hypertension and hyperlipidemia in the high VFA group was significantly higher than that in the low VFA group. These diseases are definite risk factors for cardiovascular disease, therefore, the impact of overall survival as well as CSS should also be carefully considered.

Conflict of interest statement

None declared.

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