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Morphomics Can Predict Oncological Features and Survival of Metastatic Renal Cell Carcinoma After Cytoreductive Nephrectomy

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Abstract. *Background/Aim: This study analyzed the ability of body composition to predict the outcome of patients with metastatic renal cell carcinoma (RCC) who received cytoreductive nephrectomy followed by systemic therapy. Patients and Methods: A retrospective study was conducted from December 2010 to November 2017 in a single tertiary medical center. The medical charts and computed tomography images were reviewed. Statistical analysis included oncological features, their correlation with body composition factors, and overall survival. Results: Skeletal muscle volume was significantly higher in patients with Fuhrman grade 2 RCC than those with grade≥3. Patients with intermediate International Metastatic RCC Database Consortium risk had significantly higher BMI and skeletal muscle compared to those with poor risk. Multivariate analysis showed that increased skeletal muscle and decreased visceral adipose tissue were significant predictors of a better overall survival. Conclusion: Body composition highly correlated with the oncological features of metastatic RCC and impacted survival.*

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Key Words: Metastatic renal cell carcinoma, body composition, visceral fat, subcutaneous fat, skeletal muscle, computed tomography scan, morphomics.

Renal cell carcinoma (RCC) is a malignancy that arises from the kidney parenchyma, accounts for approximately 3% of all adult malignancies, and represents the 6th most common cancer in men and the 10th most common cancer in women. For local or locally advanced RCC, surgical resection remains the only curative treatment option (1-4). Clear cell subtype is the predominant histologic type in RCC, represents 80% of RCC, and derives from the tubular epithelium. Papillary cell type and chromophobe account for 15% and 5% of cases, respectively (5, 6).

Previous studies have shown that body mass index (BMI) correlates with RCC and potentially predisposes to it (7). Type 2 diabetes mellitus among the female population and high BMI/blood pressure among the male population are also independent risk factors for RCC (8, 9). In addition, metabolic syndrome was also found to have significant impact on higher RCC nuclear grade and tumor size (10). Based on the above evidence, body metabolic status plays an important role in the oncogenesis of RCC.

Compared to BMI, body composition can better represent the metabolic status and is an important factor in the pathogenesis of many illnesses including several malignancies (11-13). The measurement of body composition

is evaluated by several imaging exams, including computed tomography (CT), magnetic resonance imaging (MRI), and dual-energy X-ray absorptiometry (DEXA) (14). In cancer patients, CT scan is easily available for analysis staging, follow up, and surveillance.

The impact of body composition, including lean tissue (skeletal muscle) and adipose tissue, on RCC has been previously studied (15-25). Sarcopenia is the decrease of skeletal muscle mass accompanied with impaired muscle strength and function, which is highly prevalent in cancer patients (13, 14). A systemic review and meta-analysis evaluated the influence of sarcopenia in RCC, and documented that sarcopenia is associated with the prognosis of patients with RCC. However, the results are controversial (16-19, 26).

In addition to skeletal muscle mass, adipose tissue is also an important component of body composition. Adipose tissue can be divided into two compartments: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT). In contrast to the skeletal muscle, relative less studies have focused on the impact of adipose tissue on RCC.

In our study, we focused on the impact of body composition on patients with *de novo* metastatic RCC who received cytoreductive nephrectomy followed by systemic therapy. We analyzed CT scan images acquired for cancer staging to measure the volume of body composition factors including skeletal muscle and adipose tissue. This study aimed to correlate aggressiveness of RCC to body composition factors, and also to discover the impact of body composition on overall survival in this specific group of patients.

Patients and Methods

Patients. We conducted a retrospective study including consecutive patients with *de novo* metastatic RCC who underwent cytoreductive nephrectomy (CN) followed by systemic therapy from December 2010 to November 2017 in a single tertiary medical center. In this study, we reviewed the medical charts and radiographic images of patients diagnosed with metastatic RCC and were eligible for CN after evaluation in urology-oncology multidisciplinary meetings. Patients who decided to undergo CN after discussion with the surgeons were enrolled in the study.

This study was approved by Chang Gung Medical Foundation Institutional Review Board. (IRB Number: 201902123B0) and conducted in accordance with the ethical principles mentioned in the Declaration of Helsinki (2013).

The patients' consent to review their medical records was waived by the IRB Chang-Gung Memorial Hospital due to the retrospective nature of the study. Patient data confidentiality fulfilled the Declaration of Helsinki.

Data collection. Preoperative general characteristics including sex, age, body height, body weight, body mass index (BMI), underlying disease, Eastern Cooperative Oncology Group (ECOG) Performance Status, and American Society of Anesthesiologists (ASA) score were recorded.

Data on tumor-related parameters such as tumor stage, tumor histology, pathological Fuhrman grade, renal vein invasion (RVI), lympho-vascular invasion (LVI), lymph node status, and distant metastasis status were also collected. Largest diameters of the primary tumor were recorded, and tumor volume was estimated using $\pi\times$(length$\times$width$\times$height)/6 based on computed tomography (CT).

Overall survival was recorded as the endpoint. Patients were followed for survival status (regardless of treatment duration) until the time of the final analysis. Overall survival (OS) was defined as the time period from the date of diagnosis to the date of death due to any cause. In the absence of confirmation of death, survival time was censored at the last date on which the patient was known to be alive.

Image analysis. The parameters of body composition were measured based on CT images for cancer staging. Abdominal CT scans were performed with and without intravenous contrast before surgery as a routine practice. The slice thickness and interval ranged from 3 to 10 mm with a median of 5 mm. Body composition analysis was performed using 3D slicer (27) and a semiautomatic segmentation method. Abdominal CT images were segmented into three components: skeletal muscle tissue (SMT), subcutaneous adipose tissue (SAT), and visceral adipose tissue (VAT). CT attenuation value of adipose tissue was defined by ranges of −190 to −30 Hounsfield unit (HU). Three-dimensional (3D) volumes from the level of the costophrenic angle to the iliac crest and two-dimensional (2D) cross-section areas at the level of the third lumbar spine level (L3) showing both transversal processes of these three body components were calculated. Figure 1 shows an example of a body composition analysis based on abdominal CT images.

Statistical analyses. We analyzed the correlation between body composition factors and tumor grade, size, and International Metastatic RCC Database Consortium (IMDC risk) group with Pearson correlation test and independent-*t* test. Survival was analyzed with the cox regression survival and Kaplan-Meier survival tests. We regarded *p*-values less than 0.05 as significant. All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. (Armonk, NY, USA: IBM Corp.).

Results

A total of 47 patients were included in this study, with a male to female ratio of 2.67. Mean age at diagnosis was 56.1 years. The detailed general characteristics such as body height, body weight, BMI, underlying disease, ECOG performance status, and ASA score are listed in Table I.

All the patients had metastatic diseases, and the primary tumor stage was T3 dominant. Fuhrman grade 3 or higher accounted for 73% of patients. Mean primary tumor diameter was 9.2±3.8 cm, with a mean tumor volume 292 ml. Clear cell histology accounted for 83% of all tumors. Other tumor related factors including renal vein invasion, lympho-vascular invasion, distant metastasis sites, IMDC risk group classification, and first line systemic treatments are listed in Table I.

Based on abdominal CT for staging, the body composition factors of the patients were calculated. Mean SMT volume was 1,735.3 cm^3, while the adipose tissue was divided into subcutaneous adipose tissue (SAT) and visceral adipose tissue

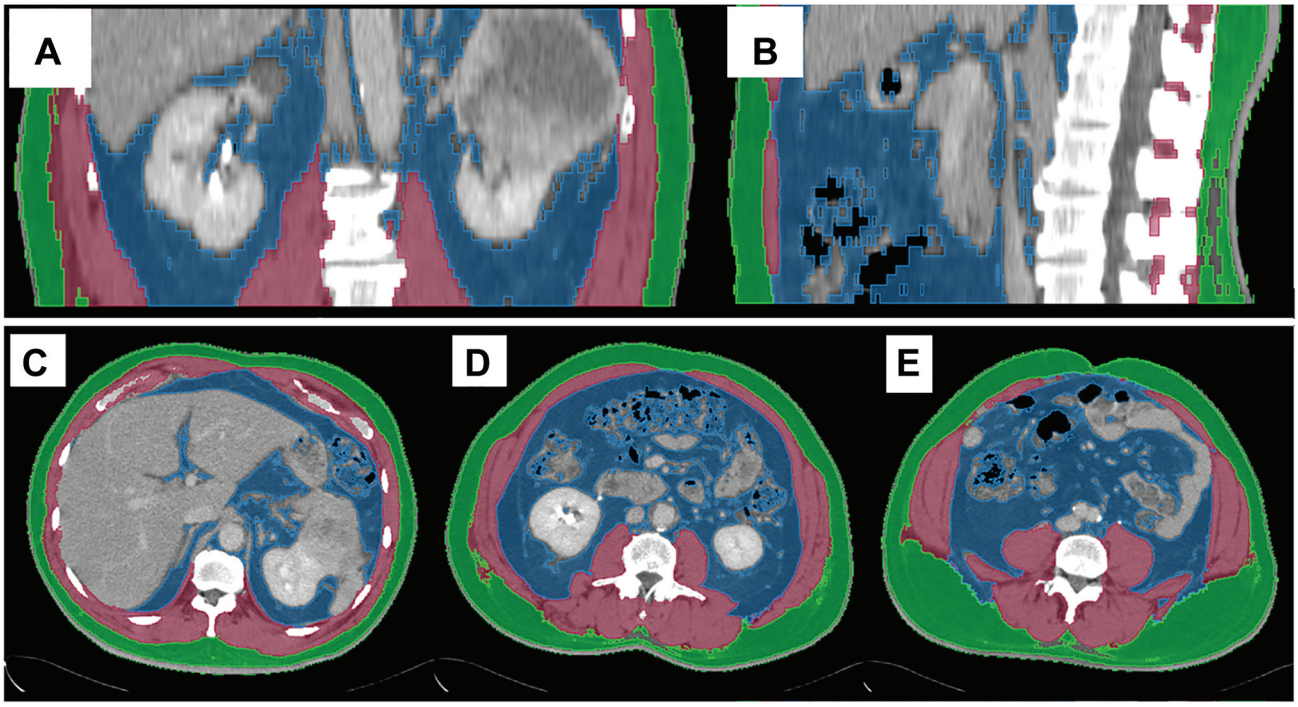

Figure 1. *Illustration of abdominal computed tomography by body composition analysis. Skeletal muscle tissue (red area), subcutaneous adipose tissue (green area), and visceral adipose tissue (blue area) are segmented. A: coronal plane, B: sagittal plane; C: axial plane at the level of costophrenic angle, D: axial plane at the level of L3, E: axial plane at the level of iliac crest. Three-dimensional (3D) volumes from the level of costophrenic angle to iliac crest and two-dimensional (2D) cross-section areas at the level of L3 were calculated.*

(VAT) with a mean volume of 1,559.8 and 1,523.2 cm^3, respectively.

We then correlated the body composition factors to tumors with different pathological grade, tumor size and IMDC risk group. The SMT volume was significantly higher in patients with Fuhrman grade 2 RCC than those with grade ≥3 (2,095.9 *vs*. 1,616.1 cm^3, *p*-value=0.005). Although patients with larger main tumor size trended to have less visceral adipose tissue volume than those with smaller main tumor size, the difference did not reach statistical significance. When we divided patients according to IMDC risk group classification, patients with intermediate risk had significantly higher BMI and SMT compared to those with poor risk (25.7 *vs*. 22.7 kg/cm^2 and 1,744.3 *vs*. 1,310.8 cm^3 respectively, *p*-value=0.020 and 0.044, respectively). The detailed comparisons and analysis are listed in Table II.

Finally, we used BMI, SMT volume, SAT volume, VAT volume, SMT L3 area, SAT L3 area, and VAT L3 area to predict overall survival. As shown in Table III, among the body composition factors, SMT L3 area and VAT volume were significant predictors in multi-variate analysis (*p*-value=0.001 and 0.042, respectively). The Kaplan-Meier survival curves divided by the mean value of IMDC risk and SMT L3 area are illustrated in Figure 2.

Discussion

To our knowledge, this is the first study to evaluate the impact of body composition on patients with *de novo* metastatic RCC who received cytoreductive nephrectomy followed by systemic treatment.

The impact of skeletal muscle volume on long term outcome of metastatic RCC remained unclear in previous studies. Ishihara *et al*. identified sarcopenia by skeletal muscle index (SMI) based on CT scans and did not find an association between OS and decreased skeletal muscle in patients with metastatic RCC (18). Auclin *et al*. also used SMI and observed that decreased skeletal muscle was not significantly associated with OS in patients with metastatic RCC, but the highest *versus* lowest SMI tercile was an independent prognostic factor (28). However, Fukushima *et al*. and Sharma *et al*. identified that sarcopenia was associated with poor OS in patients with metastatic RCC (17, 18). Hu *et al*., performed a meta-analysis on 771 patients with RCC and observed that sarcopenia was associated with poor overall survival in the advanced/metastatic RCC group (29).

In our study, we found that patients with Fuhrman Grade 2 had significantly higher SMT volume compared to those with Fuhrman Grade≥3, and both BMI and SMT volume were

Table I. *Patient general characteristics*.

Patient general characteristics				
Variables	Mean/ Number	SD	Range/ Percentage	
Total number	47			
Gender				
Male	35		73.3%	
Female	12		26.7%	
Age	56.09	15.11	11-75	Year-old
Height	162.8	8.69	139-182	cm
Weight	65.0	13.4	29-95	kg
BMI	24.4	4.27	15.01-36.04	kg/cm^2
Hypertension				
Yes	18		38.3%	
No	29		61.7%	
Diabetes mellitus				
Yes	7		14.9%	
No	40		85.1%	
ESRD				
Yes	3		6.4%	
No	44		93.6%	
ECOG				
0	31		66.0%	
1	12		25.5%	
2	3		6.3%	
3	1		2.1%	
ASA				
2	10		21.3	
3	35		0.744	
4	2		4.3	

Tumor related parameters				
Variables	Mean/ Number	SD	Range/ Percentage	
Xp11.2 Translocation	2		4.3%	
Renal vein invasion				
Yes	18		38.3%	
No	29		61.7%	
Lymphovascular Invasion				
Yes	21		44.7%	
No	26		55.3%	
Tumor diameter	9.32	3.83	3.8-21.0	cm
Tumor volume	293.9	396.6	17.7-2,520.0	cm^3
Distant metastasis				
Lung	29		0.617	
Liver	2		2.1%	
Bone	16		0.34	
Brain	3		6.4%	
IMDC risk group				
Intermediate	27		0.574	
Poor	20		0.426	
1st line target Agent				
Sunitinib	31		66.0%	
Pazopanib	7		0.149	
Everolimus	2		4.3%	
Sorafenib	3		6.4%	
Interferon+IL-2	4		8.5%	
Overall survival	719.3	508.3	36-2,369	days

Tumor related parameters				
Variables	Mean/ Number	SD	Range/ Percentage	
T stage				
1	5		0.106	
2	6		0.128	
3	34		0.723	
4	2		0.043	
Grade				
2	12		25.5%	
3	30		63.8%	
4	5		10.6%	
Histology				
Clear cell	39		83.0%	
Papillary	6		12.8%	

Body composition factors				
Variables	Mean/ Number	SD	Range/ Percentage	
Skeletal muscle tissue (SMT)	1,735.3	520.0	705-3,300	cm^3
Subcutaneous adipose tissue (SAT)	1,559.8	1,139.9	5-4,742	cm^3
Visceral adipose tissue (VAT)	1,523.2	1,209.1	24-5,726	cm^3
Cross section area of SMT at L3	133.7	31.4	58-216	cm^2
Cross section area of SAT at L3	125.2	80.8	1-429	cm^2
Cross section area of VAT at L3	118.5	88.8	2-344	cm^2

BMI: Body mass index; ESRD: end stage renal disease; ECOG: Eastern Cooperative Oncology Group performance status; ASA: American Society of Anesthesiologists Classification; IMDC: International Metastatic RCC Database Consortium.

higher in patients with IMDC intermediate risk compared to those with poor risk. In general, patients with more aggressive or more advanced RCC have less SMT volume. Besides, overall survival was also associated with SMT, and patients with less SMT had poor overall survival (p=0.001).

The relationship between skeletal muscle volume and survival in cancer patients is indistinct. The survival of advanced and metastatic cancer mainly depends on the response to systemic treatment, including chemotherapy, targeted therapy, or immunotherapy. In previous studies, decreased skeletal

Table II. *Body composition factors in oncological subgroups*.

Histological Fuhrman Grade						
			Mean	SD	95%CI for Exp(B)	*p*-Value
BMI	kg/cm^2	Fuhrman Grade 2	25.3	3.4	23.2~27.5	0.351
		≥3	23.9	4.5	22.3~25.8	
SMT	cm^3	Fuhrman Grade 2	2,095.9	465.3	1,800.2~2,391.6	0.005*
		≥3	1,616.1	490.5	1,416.1~1,782.9	
SAT	cm^3	Fuhrman Grade 2	1,848.1	1,088.0	1,156.8~2,539.4	0.172
		≥3	1,364.4	1,020.1	997.1~1,773.1	
VAT	cm^3	Fuhrman Grade 2	2,028.4	1,429.4	1,120.2~2,936.6	0.097
		≥3	1,346.3	1,109.8	951.8~1,794.3	
SMT L3	cm^3	Fuhrman Grade 2	153.8	30.5	134.4~173.2	0.010*
		≥3	126.9	29.4	116.0~137.4	
SAT L3	cm^3	Fuhrman Grade 2	139.7	67.6	87.8~197.4	0.213
		≥3	111.1	67.1	79.6~147.7	
VAT L3	cm^3	Fuhrman Grade 2	141.1	88.6	84.8~197.4	0.302
		≥3	109.7	89.9	79.6~147.7	
Tumor size						
			Mean	SD	95%CI for Exp(B)	*p*-Value
BMI	kg/cm^2	Larger primary tumor	23.7	4.7	-1.68~3.61	0.467
		Smaller primary tumor	24.7	4.0		
SMT	cm^3	Larger primary tumor	1,755.3	455.8	-348.6~-303.9	0.885
		Smaller primary tumor	1,733.0	567.9		
SAT	cm^3	Larger primary tumor	1,399.4	1,120.9	-506.3~-795.8	0.665
		Smaller primary tumor	1,544.1	1,019.5		
VAT	cm^3	Larger primary tumor	1,182.8	892.7	-201.4~1,284.7	0.110
		Smaller primary tumor	1,724.4	1,354.2		
SMT L3	cm^3	Larger primary tumor	129.9	30.7	-13.4~25.9	0.518
		Smaller primary tumor	136.2	32.6		
SAT L3	cm^3	Larger primary tumor	106.6	71.6	-22.7~60.7	0.377
		Smaller primary tumor	125.6	65.5		
VAT L3	cm^3	Larger primary tumor	89.3	64.9	-8.7~99.4	0.067
		Smaller primary tumor	134.7	98.6		
TIMDC risk group						
			Mean	SD	95% CI for Exp(B)	*p*-Value
BMI	kg/cm^2	Intermediate	25.7	3.8	0.49-5.44	0.020*
		Poor	22.7	4.4		
SMT	cm^3	Intermediate	1,865.4	513.5	9.0~602.6	0.044*
		Poor	1,559.6	487.2		
SAT	cm^3	Intermediate	1,744.3	1,249.8	-211.8~1,078.7	0.183
		Poor	1,310.8	946.2		
VAT	cm^3	Intermediate	1,652.5	1,082.8	-448-5~1,056.1	0.418
		Poor	1,348.7	1,370.8		
SMT L3	cm^3	Intermediate	141.7	283.6	-0.57~36.6	0.046*
		Poor	122.9	32.4		
SAT L3	cm^3	Intermediate	139.3	90.6	-11.9~78.2	0.145
		Poor	106.1	62.5		
VAT L3	cm^3	Intermediate	130.7	89.1	-24.0~81.3	0.278
		Poor	102.0	87.9		

BMI: Body mass index; SMT: skeletal muscle tissue; SAT: subcutaneous adipose tissue; IMDC: International Metastatic RCC Database Consortium; VAT: visceral adipose tissue; SMT/SAT/VAT L3: SMT/SAT/VAT cross section area at L3 level. **p*-Value<0.05; ***p*-Value<0.01.

Table III. *Body composition factors to predict overall survival.*

				Univariate analysis		Multivariate analysis	
		Mean	SD	95%CI	*p*-Value	95%CI	*p*-Value
BMI	kg/cm^2	24.4	4.27	0.871-1.050	0.350		
SMT volume	cm^3	1,735.3	520.0	0.999-1.000	0.217		
SAT volume	cm^3	1,559.8	1,140.0	1.000-1.000	0.723		
VAT volume	cm^3	1,523.2	1,209.7	1.000-1.000	0.578	1.000-1.001	0.042*
SMT L3	cm^3	133.3	31.7	0.970-0.995	0.006*	0.963-0.991	0.001**
SAT L3	cm^3	125.2	80.8	0.994-1.004	0,749		
VAT L3	cm^3	118.5	88.8	0.996-1.005	0,858		

BMI: Body mass index; SMT: skeletal muscle tissue; area at L3 level; SAT: subcutaneous adipose tissue; VAT: visceral adipose tissue; SMT/SAT/VAT L3: SMT/SAT/VAT cross section. *p-Value<0.05; **p-Value<0.01.

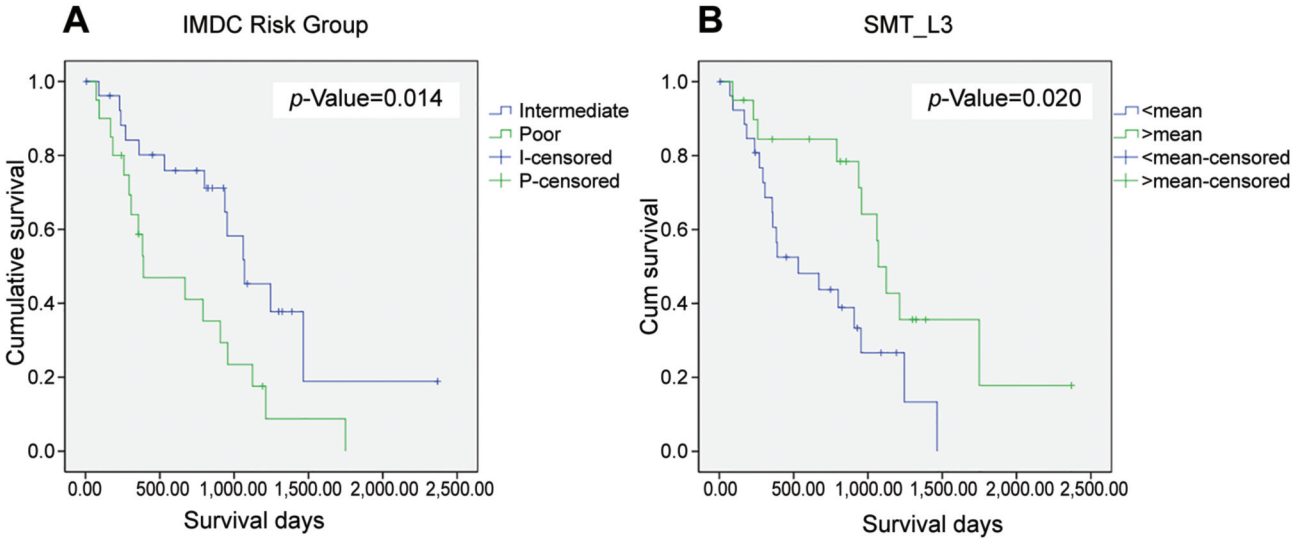

Figure 2. *Kaplan-Meier's survival curve. A: International Metastatic RCC Database Consortium (IMDC) risk group, B: skeletal muscle tissue (SMT) at L3 level group.*

muscle correlated to the higher toxicity and poor response to systemic treatment, and thus worse survival (30, 31). In addition to the toxicity and efficacy of anti-cancer drugs, skeletal muscle may also impact the prognosis of cancer patients through its secretory function. The skeletal muscle can secrete cytokines and many other peptides including interleukin-6 (IL-6), IL-8, and leukemia inhibitory factor, which play a vital role in the inflammatory mechanism (32). Decreased skeletal muscle might also indicate reduced anti-cancer inflammatory process. After all, decreased skeletal muscle also implies a relatively poor overall body condition, such as impaired immune function or nutritional conditions (33).

Besides skeletal muscle, adipose tissue is also an important component of body composition. However, most studies evaluating the body composition of patients with mRCC focused on skeletal muscle, and only few considered adipose tissue.

Several studies attempted to discover the role of VAT in RCC, but the results are inconclusive. In localized or advanced RCC, some studies suggested that patients with low VAT have poor prognosis (20-22), while another study reported that VAT was not associated with overall survival (23).

In regards to the impact of VAT on the survival of patients with mRCC receiving systemic therapy, there are only few studies, with contradictory results. For example, Mizuno *et al.* mentioned that high VAT might be a possible predictor of a better prognosis of mRCC patients treated with systemic therapy (24). In contrast, Ladoire *et al.* concluded that a high VAT could be a predictive biomarker for shorter survival in patients administered first-line antiangiogenic agents for mRCC (25).

In contrast to previous studies, we focused on patients with metastatic RCC that received cytoreductive nephrectomy followed by systemic therapy. In these patients, VAT or SAT were not correlated with histological tumor grade, tumor size, or IMDC risk. However, VAT volume was significantly associated with survival, and patients with less VAT trended to have better overall survival.

The possible reasons for the impact of VAT on metastatic RCC may be explained by the secretory function of the adipose tissue. Similarly to the skeletal muscle, adipose tissue has been shown to have endocrine and paracrine functions and could release adipokines, which may promote cancer growth and dysregulate angiogenesis (34-36). For instance, adipocytes produce insulin-like growth factor, which could promote carcinogenesis in renal cells (37, 38).

Based on existing evidence, body composition plays an important role in the carcinogenesis and prognosis of renal cell carcinoma. In addition to the prediction of survival or response to anti-cancer medication, improvement of body composition may be another goal of treatment. In a meta-analysis of 6 randomized trials, resistance exercise could increase skeletal muscle mass in patients with non-metastatic cancer (39). In another meta-analysis of five randomized trials, anamorelin (a ghrelin agonist) also significantly increased skeletal muscle mass, but not overall survival in patients with advanced or metastatic cancer (40, 41).

Early screening for the adverse features of body composition, such as decreased skeletal muscle mass in patients with metastatic RCC, may help to identify those with risk for poor overall survival. Multimodal interventions including life-style modifications, exercise, or medication may possibly reverse the adverse body composition features. Whether the correction of adverse body composition features could potentially improve survival outcome requires more detailed study.

Limitations of our study are the relatively small number of patients, the single-center patient recruitment, and the retrospective design. Dynamic changes of body composition factors based on CT scans during oncological follow-up may also provide useful information about the impact of body composition on RCC patients.

Conclusion

In this study, we focused on the impact of body composition on oncological features and prognosis of patients with metastatic RCC that received nephrectomy followed by systemic therapy. Patients with higher Fuhrman grade tumor had lower SMT, while those with poor IMDC risk group also had lower BMI and SMT. Decreased SMT and increased VAT was significantly associated with poor overall survival.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Conception and design: Chun-Te Wu, See-Tong Pan, I-Hung Shao; Provision of study materials or patients: Chun-Te Wu, See-Tong Pan, Ying-Hsu Chang, I-Hung Shao, Cheng-Keng Chuang; Collection and assembly of data: Chin-Chieh Tan, Ting-Wen Sheng, I-Hung Shao; CT image analysis: Ting-Wen Sheng, Li-Jen Wang; Data analysis and interpretation: I-Hung Shao, Chin-Chieh Tan; Manuscript writing: I-Hung Shao.

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