Impact of Body Composition in Overweight and Obese Patients With Localised Renal Cell Carcinoma

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Abstract. *Background/Aim:* To investigate the impact of body composition on morbidity and mortality at the initial diagnosis of localised renal cell carcinoma (RCC) in patients with overweight or obesity. *Patients and Methods:* Sarcopenia was defined using sex-specific cut-off points and other body composition parameters by median values with computed tomography imaging. *Results:* Among the 96 patients, 40 had sarcopenia (43.0%) at diagnosis. Body composition had no effect on morbidity and 5-year disease-free survival contrary to the classic factors ($p < 0.05$). In the subgroup of obese patients, those with sarcopenia had a poor prognosis ($p = 0.04$) but not in the population with overweight ($p = 0.9$). *Conclusion:* Sarcopenia was frequently associated with localised RCC at the initial diagnosis. Body composition did not affect morbidity or outcomes. BMI was involved in morbidity and there was paradoxically longer survival in the obesity group.

Most diagnoses of renal cell cancer (RCC) are performed when the disease is at a localised stage with a potentially curative treatment (1). Malnutrition is a poor prognostic factor for RCC regardless of the stage (2). While body mass index (BMI) distinguishes the nutritional status of patients, it does not differentiate between lean mass and fat mass. Thus, some studies have demonstrated that body composition parameters could produce interesting results (3). Among

body composition factors, decreased skeletal muscle mass, commonly known as sarcopenia, is associated with decreased efficacy of treatment, increased toxicity of cancer therapy (4), increased frequency of postoperative complications (5), and poor patient outcomes (6) in different cancers.

Most kidney cancer studies have been performed in a metastatic setting and have demonstrated that sarcopenia has a negative impact on treatment tolerance (7, 8) as well as overall survival (OS) (9-12). By contrast, there is discordance regarding the impact of sarcopenia on localised RCC, length of hospital stay and survival after curative treatment (13, 14).

In parallel, obesity is significantly associated with RCC [body mass index 35 vs. < 25 kg/m²: hazard ratio (HR)=1.71, 95%CI=1.06-2.79] in Europe (15). Despite a high frequency of overweight/obese patients with localised RCC, the impact of sarcopenia has not been studied in this specific overweight or obese population, even if sarcopenic obesity has a negative impact on the management of other cancers (16-18). Less is known about myosteatosis, which is a pathological infiltrate by muscle fat that can be assessed by computed tomography (CT) imaging using muscle radiodensity or skeletal muscular density (SMD) (14). One study showed that low muscle density, which reflects low muscle quality, seems to have higher impact on survival of patients with metastatic RCC than with sarcopenia (19). Furthermore, it is related to the prognosis in other cancers (20, 21).

In this study, we assessed the impact of body composition (studied by CT scans) on morbidity and outcomes in an overweight or obese population with localised RCC.

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Patients and Methods

Study design and patients. We performed a retrospective study that included patients with localised RCC who were treated at Limoges University Hospital from January 2006 to December 2017. The patients were selected according to the following criteria: adults aged > 18 years who were overweight or obese, as assessed via BMI (kg/m²) at diagnosis; a CT scan performed before surgery in our

institution to assess body composition; patients who received a nephrectomy (partial or radical) without adjuvant treatment.

Patients with metastatic disease, lymph node involvement at diagnosis, or with other neoplasia (being treated or treated <5 years ago) were excluded.

Clinical data were collected in accordance with French bioethics laws regarding patient information and consent. Data collection and use were approved by Limoges Hospital Ethics Committee (approval number: 2165046 v 0).

Assessments and procedures. Clinical and biological characteristics. The following data were collected at the initial diagnosis: comorbidities (the presence of smoking, high blood pressure and diabetes), age and performance status (PS); pathological characteristics, such as TNM staging, histology, number of metastatic sites; stage, size, grade and necrosis (SSIGN) (22) and USLA integrated staging system (UISS) scores (23); and surgical characteristics, including partial or radical nephrectomy, adrenalectomy, and thrombectomy.

Selected data were collected using CROSSWAY software (patient data management software, licensed to the hospital) and from handwritten patient records.

Anthropometric measures. Weight and height were documented from the patient's anaesthesia records or the surgeon's consultation report at the diagnosis. BMI was calculated, and categories were defined according to the World Health Organization as follows: overweight, 25-29.9 kg/m² and obese, ≥30 kg/m².

CT scan imaging. CT scans with intravenous contrast agent were performed at Limoges University Hospital. Images were retrieved from digital storage in the Picture Archiving and Communication System (TELEMIS society). The image analyses were performed by a radiologist blinded to the patients' survival status, using AW software (GE Healthcare, 2018 General Electric Co, Buc, Yvelines, France) and performed as described previously (24).

Skeletal muscle mass (SMM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and infiltration inter-muscular adipose tissue (IMAT) (cm²) were evaluated on a single image at the third lumbar vertebrae (L3) using Hounsfield unit thresholds (HU): muscle (-29 to 150), visceral adipose tissue (-150 to -50), subcutaneous adipose tissue, and inter-muscular adipose tissue (-190 to -30).

The skeletal muscle index (SMI), VAT index, SAT index, and IMAT index in cm²/m² were defined by tissue cross-sectional area (cm²) normalised to square meters (m²). To evaluate myosteatosis or SMD, mean attenuation in HU was used as described previously (16). SMD was quantified as the muscle cross-sectional area across the L3 vertebral body level and was assessed between -29 and +150 HU. Muscle density assessed by this method reflects fatty muscle infiltration.

Study end-points. The primary objective was to assess the impact of BMI and body composition on morbidity and outcomes among a population of overweight or obese individuals with localised RCC. We also evaluated the correlation between body composition and BMI.

Sarcopenia was defined using sex-specific SMI cut-off points: <41 cm²/m² (females) and <53 cm²/m² (males) (9). Similar to previous studies, a threshold of median was the choice for SMD to define myosteatosis (9, 16). Cut-off points for VAT, SAT, and the IMAT indices were based on median values (25).

Morbidity was defined by infections requiring post-surgical treatment or increased length of hospital stay.

Infection was diagnosed if a patient had fever or needed antibiotics for up to 1 month after the surgical treatment. Length of hospital stay was calculated from the day of treatment to the day of discharge from the urology ward (to home or to a convalescent ward). An extended length of stay was considered >7 days after a partial nephrectomy and 10 days after a radical nephrectomy (26).

Disease-free survival (DFS) and OS. DFS was measured as the interval between surgery and the date of first recurrence. OS was calculated from the date of diagnosis to death or the last follow-up. Patients were followed until death or April 31, 2019, at which time they were censored on the last date they were documented to be alive.

Statistical analyses. All data were collected and analysed using STATVIEW software (SAS Institute, Cary, NC, USA) and R software (V.3.5.1; R Foundation for Statistical Computing, Vienna, Austria). Quantitative results are expressed as mean±standard deviation or median (range), and qualitative results are expressed as numbers and percentages. Nominal variables were compared between the groups using the chi-square or Fisher's exact tests, as appropriate. Means were compared using the non-parametric Mann-Whitney *U*-test for continuous variables and the Wilcoxon signed-rank test for paired tests. The correlation between BMI and body composition was assessed using Pearson's correlation coefficient analyses.

Survival curves were obtained using the Kaplan-Meier technique. Median survival was compared using the parametric log-rank test. The Cox proportional hazards model was used to evaluate the relationships between variables and survival. Variables with *p*<0.10 in univariate analyses were included in multivariate analyses. *p*-values <0.05 were considered significant.

Results

Characteristics of the patients. Among the 620 patients screened, 96 were included in the final analyses (Figure 1). Most patients were excluded because of an unavailable preoperative CT scan or tomographic artefact. The baseline CT scan used to assess the radiological features with a median delay of 1.7 months (range=-0.2-10.3 months) before treatment. The initial characteristics of the patients according to BMI are presented in Table I.

The median BMI of the 96 patients was 29.8 kg/m² (range=25.1-44.1 kg/m²). Fifty-one patients (53%) were overweight, and 45 (47%) obese. Mainly adult men (*p*=0.02) were included in the overweight group. No significant differences in PS, RCC risk factors (such as smoking and high blood pressure), TNM classification, histology, type of surgery (partial or radical nephrectomy), or associated procedures (*e.g.*, thrombectomy) were observed between the two groups.

Correlation between body composition and BMI status. Among the patients in the population, 43% patients (*n*=40) were sarcopenic (Table II). Some patients with sarcopenia had a

Figure 1. Flow diagram showing patient selection. BMI: Body mass index; CT: computed tomography; N: number of patients; RCC: renal cell carcinoma.

lower BMI than those without sarcopenia (29 vs. 11 patients, $p=0.0009$) independently of gender (Table II).

A total of 50.5% patients had a low SMD ($n=47$), and there were no differences according to weight. As expected, patients with obesity had a higher VAT and SAT ($p=0.0006$ and $p<0.0001$) (Table II).

The SMI was related to BMI ($r=0.58$, $p=0.019$) (Figure 2). SMI was also more related to BMI in women ($r=0.55$) than in men ($r=0.51$) as shown by the SAT index ($r=0.74$ and $r=0.53$, respectively).

A moderate correlation was detected between BMI and the VAT and SAT indices ($r=0.578$, $p<0.0001$ and $r=0.506$, $p<0.0001$) (Figure 2). No differences in IMAT or SMD were observed between the overweight and obese groups ($r=-0.116$, $p=0.352$ and $r=-0.014$, $p=0.91$).

Moreover, only VAT and SAT were slightly related ($r=0.38$, $p=0.018$). The other parameters were not associated.

Impact of body composition on postoperative morbidity. Data on infections were available for 92 patients. Infections

Table I. Characteristics of the patients.

	Total	Overweight	Obese	p-Value
Number of patients	96	51 (43)	45 (47)	
Gender				0.02
Men	68 (70)	41 (80)	27 (60)	
Women	28 (30)	10 (20)	18 (40)	
PS				0.4
0	63 (66)	35 (69)	28 (62)	
1	29 (30)	15 (29)	14 (31)	
2	4 (4)	1 (2)	3 (7)	
Age Median (Range)	66 (43-89)	67 (43-84)	65 (43-89)	0.6
BMI, median (kg/m ²)	29.8 (25.1-44.1)	28.3 (25.1-29.9)	33.9 (30.0-44.1)	
pTNM				0.3
pT1a	29 (30)	13 (25)	16 (36)	
pT1b	28 (29)	17 (33)	11 (24)	
pT2a/b	18 (19)	9 (18)	9 (20)	
pT3 a/b	19 (20)	10 (20)	9 (20)	
pT4	2 (2)	2 (4)	0 (0)	
Histology				0.2
Clear cell RCC	81 (85)	42 (82)	39 (87)	
Papillary RCC	9 (9)	4 (8)	5 (11)	
Chromo phobe RCC	6 (6)	5 (10)	1 (2)	
Type of surgery				0.6
Partial nephrectomy	30 (31)	15 (30)	15 (33)	
Radical nephrectomy	66 (69)	36 (70)	30 (67)	
Associated procedure: surrenalectomy, thrombectomy	22 (23)	15 (29)	7 (15)	0.1
Complications*				
Length of stay, days (min-max)	8.0 (3-30)	3.5 (3-22)	8.0 (3-30)	0.2
>cut-off	28 (30)	11 (22)	17 (40)	0.06
Infections	17 (18)	4 (8)	13 (29)	0.007
>cut-off	2 (12)	1 (8)	1 (25)	0.3
SSGIN score	N=90			0.2
Low risk	38 (42)	18 (37.5)	20 (48)	
Intermediate risk	17 (19)	12 (25)	5 (12)	
High risk	35 (39)	18 (37.5)	17 (40)	
UISS score	N=92			0.5
Low risk	22 (24)	10 (21)	12 (28)	
Intermediate risk	14 (15)	9 (18)	5 (12)	
High risk	56 (61)	30 (61)	26 (60)	

*Missing data; BMI: body mass index; PS: performance status.

Table II. Characteristics of body composition according to the body mass index

	Total	Overweight	Obese	p-Value
Number	93	44	49	
SMI (cm ² /m ²): median (range)	50.8 (12.6-96.0)	54.4 (38.5-96.0)	49.7(13.6-67.4)	0.02
Sarcopenia: yes vs. no	40 (43)/53 (57)	29 (60)/20 (40)	11 (25)/33 (75)	0.0009
Men: yes vs. no	33(36)/32 (34)	25 (64)/14 (36)	8(30)/18 (70)	0.008
Women: yes vs. no	7 (8)/21 (22)	4 (40)/6 (60)	3 (17)/15 (83)	0.1
VAT Index (cm ² /m ²), median (range)	87.7 (16.5-175.0)	78.4 (16.5-134.7)	107.4 (34.1-175.0)	0.0006
SAT Index (cm ² /m ²), median (range)	84.4 (30.5-229.6)	66.2 (30.5-137.7)	107.1 (44.3-229.6)	<0.0001
IMAT Index (cm ² /m ²), median (range)	0.0 (0.0-1.1)	0.0 (0.0-1.1)	0.0 (0.0-0.7)	0.7
SMD (HU), median (range)	46.6 (13.7-71.2)	45.6 (13.7-67.7)	46.6 (15.9-71.2)	0.6
Low SMD vs. High SMD	47 (50.5)/46 (49.5)	22(50)/22(50)	25 (51)/24 (49)	0.9

IMAT: Infiltration inter-muscular adipose tissue; SAT: subcutaneous adipose tissue, SMD: skeletal muscle (radio)density; SMI: Skeletal Muscle Index; VAT: visceral adipose tissue.

Figure 2. Scatterplot of the relationship between body mass index, body composition and skeletal mass density. Blue dot and dotted line for male patients, pink dot and solid line for female patients, (A) skeletal muscle index; (B) visceral adipose index; (C) subcutaneous adipose index and (D) skeletal mass density.

Table III. Univariate and multivariate analyses of body composition parameters for disease-free survival (DFS) and overall survival (OS).

	Disease free survival				Overall survival			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value	HR (95%CI)	p-Value	HR (95%CI)	p-Value
PS: 0-1 vs. 2	0.2 (0.06-1.1)	0.08			0.3 (0.08-1.5)	0.1		
Type of surgery: NP vs. NT	0.3 (0.1-1.0)	0.05	0.6 (0.1-1.8)	0.02	0.3 (0.1-1.1)	0.09		
Tumor grade	2.5 (1.4-4.5)	0.001	2.3 (1.3-4.2)	0.004	2.1 (1.1-3.9)	0.01	1.9 (0.9-3.9)	0.05
Stage: pT1-pT2 vs. pT3-pT4	0.3 (0.12-0.73)	0.004	0.4 (0.1-0.9)	0.02	0.3 (0.12-0.73)	0.007	0.37 (0.1-0.9)	0.04
BMI: obese vs. overweight	1.5 (0.7-3.3)	0.2			0.8 (0.3-1.9)	0.7		
Sarcopenia: yes vs. no	1.0 (0.4-2. »)	0.9			0.4 (0.1-0.9)	0.04	0.5 (0.2-1.4)	0.1
SMD: low vs. high	1.7(0.8-3.9)	0.1			0.8 (0.3-2.1)	0.7		

BMI: Body mass index; NP: partial nephrectomy; NT: total nephrectomy; PS: performance status; SMD: skeletal muscle (radio)density.

occurred significantly more often in obese than overweight patients (29% vs. 8%; $p=0.007$). No differences in occurrence of infections were observed according to body composition.

Data on the length of hospital stay after surgery were known for 91 patients. The length of hospital stay was longer in obese than overweight patients (22% vs. 40%, $p=0.06$). Body composition did not affect the length of hospital stay.

Figure 3. Overall survival curves according to sarcopenia and body mass index. Results were obtained depending on the presence or absence of sarcopenia (A), the body mass index (B), the presence or absence of sarcopenia in obese patients (C), and presence or absence of sarcopenia in overweight patients (D).

Impact of body composition on outcomes. The median follow-up time was 36.5 months (range=0.5-137 months), and 25 patients (26%) relapsed. The 5-year DFS rate for the cohort was 61%. Twenty-three patients (24%) died. The 5-year OS rates for the cohort was 65%.

In univariate and multivariate analyses, BMI and body composition did not affect 5-year DFS in any of the groups contrary to the classic factors, such as stage, type of surgery, and tumour grade ($p < 0.05$) (Table III).

In univariate analyses, stage, type of surgery, tumour grade and sarcopenia were significantly associated with OS (Figure 3A) but sarcopenia was not an independent prognostic factor in multivariate analyses (Table III). Obese patients tended to have longer survival than overweight patients (Figure 3B).

We further investigated the prognostic value of sarcopenia in the subgroups of BMI. The effect was highlighted in the

obese population ($p = 0.04$) but not in the overweight population ($p = 0.9$) (Figure 3C, D).

Discussion

In our study, we showed that body composition did not affect morbidity or outcomes but BMI was involved in morbidity and there was paradoxically longer survival in the obesity group.

The impact of sarcopenia at diagnosis was assessed in overweight or obese patients for the first time in a localised RCC population, and 40% patients suffered from sarcopenia.

Martin *et al.* demonstrated in a large cohort ($n = 1,473$) that the cut-offs should be adapted in patients affected by overweight/obesity compared to other patients (16). We investigated the prevalence of sarcopenia in patients with a BMI ≥ 25 kg/m² using cut-offs specific for overweight and

obese patients with localised RCC. The prevalence of sarcopenia observed in our population was slightly higher in patients with obesity (25%) than that reported (19%) in subgroups of obese patients with localised RCC (13). However, Psutka *et al.* used a sarcopenia BMI cut-off $>30 \text{ kg/m}^2$ ($55 \text{ cm}^2/\text{m}^2$ for men and $39 \text{ cm}^2/\text{m}^2$ for women) and did not include overweight patients. We also noticed that the incidence of sarcopenia was close to that in patients with urological cancers (22%) (27, 28).

As we showed that sarcopenia was correlated with BMI, we hypothesize that specific cut-offs should be applied to overweight and obese patients. Similar variability has been observed in patients with metastatic RCC (11, 19).

In our study, sarcopenia had no effect on survival in the population. It has been emphasised that the prognostic significance of sarcopenia is evident in patients with locally advanced disease (pT3/4 or pN+) but not in those with organ-confined disease (28). Psutka *et al.* showed that sarcopenia has a negative effect on 5-year OS of patients with localised RCC compared to those without sarcopenia (65% vs. 74%, $p=0.005$) when they had a worse prognosis (13). In that study, the median disease progression at a median of 0.9 years after surgery contrasts with our study showing a longer DFS. Moreover, sarcopenia is usually a prognostic factor in metastatic RCC (29).

We showed that obese RCC patients had longer survival than non-obese patients. These results support the “obesity paradox” in RCC and the idea that a high BMI is associated with significantly longer cancer-specific survival (30, 31). A recent meta-analysis highlighted the opposite association between BMI and mortality in patients with RCC (32). In this subgroup of obese patients, sarcopenia seemed to be a poor prognosis factor, as shown previously (33).

Sarcopenia has been linked with more frequent postoperative complications in patients with other cancers than in those with RCC (10), but it remains unclear in urologic cancer. Unlike Sharma *et al.* who reported on metastatic RCC (34), we did not observe any effects of sarcopenia on postoperative complications in an adjuvant setting. In others studies, sarcopenia was not associated with postoperative complications in patients with upper-tract urothelial carcinoma and obesity who underwent radical nephroureterectomy (27). We suggest that BMI plays a more important role in postoperative complications than body composition (35, 36). In conclusion, weight control might be necessary before surgery for patients with RCC, and more preventive measures for complications should be taken for the obese population compared to overweight patients.

To the best of our knowledge, SMD has only been explored in patients with metastatic RCC (9, 12, 19) and only one study has reported that an SMD above the median (38 HU for males and 36 HU for females) is associated with a longer OS (29 vs. 14 months, $p=0.001$) and longer

progression-free survival (8 vs. 4 months, $p<0.001$) (11). In our study, we did not detect a relation between SMD (median: 46 HU) and OS.

There are no widely accepted cut-off points to categorise patients as sarcopenic or myosteatotic based on CT measurements. Most studies have used a global cut-off independent of patient characteristics, and skeletal muscle mass and density have differed greatly between studies. One solution could be to develop nomograms based on age, BMI, and/or sex to predict normal skeletal muscle mass and density measures to evaluate the optimal cut-off for skeletal muscle mass and density (37).

In conclusion, body composition did not affect morbidity or progression of localised RCC with a good prognosis. BMI was associated with morbidity and there was paradoxically longer survival in the obese group. A prospective study is needed to confirm the cut-off points and to categorise patients.

Conflicts of Interest

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

Authors' Contributions

DT, FG, DL participated in the data acquisition. LS did the statistical analysis. DT, DE, and LS analysed the data. DE and TMN supervised the work. DT and DE were the major contributor in writing the manuscript. All Authors contributed to the manuscript, critically revised the manuscript, and approved the final version.

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