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Prognostic Importance of Sarcopenia in Patients with Clear Cell Carcinoma

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ABSTRACT

Background: *Sarcopenia has recently been identified as a prognostic factor for various types of cancers. Our aim in this study was to investigate the relationship between sarcopenia and the clinical course and overall survival of patients with renal cell carcinoma (RCC) after surgical treatment.* ***Methods:*** *A retrospective analysis of the patients who underwent surgical treatment for RCC at our hospital, between 2008 and 2011, was conducted. Muscle mass was estimated by the cross-sectional area of the psoas major muscles at the level of L3, measured from computed tomography images. The area was normalized to height for between-comparison of the total psoas area (TPA, cm^2/m^2). The median pre- and postoperative TPA was used as a cut-off to classify patients into high and low TPA groups. Overall survival, clinical and pathological factors were compared between high and low TPA groups.* ***Results:*** *The study group included 108 patients (83 males and 25 females). The median pre- and postoperative TPAs were 4.85 cm^2/m^2 and 5.03 cm^2/m^2, respectively. Overall survival was longer among patients in the high than low TPA group (P=0.03), with sarcopenia being predictive of survival in males (P=0.004), but not in females. The pre- to postoperative change in TPA was predictive of postoperative adverse events, but not of surgical factors.* ***Conclusions:*** *A higher TPA is associated with longer overall survival after RCC surgery, particularly in males. The change in TPA after surgery was also predictive of postoperative adverse events, but did not influence operative factors.*

Keywords: Renal cell carcinoma, Sarcopenia, Prognosis

INTRODUCTION

Sarcopenia is defined as a general decrease in skeletal muscle mass and overall body strength [1]. The loss of muscle mass is initiated by a decrease in the synthesis of amino acids, which can result from aging, a poor nutritional status and various health conditions. More recently, sarcopenia has been identified as a prognostic factor in various types of cancer [2]. Our focus in this study was to evaluate the prognostic value of sarcopenia among patients with renal cell carcinoma (RCC).

Traditionally, the prognosis of RCC is based on the clinical stages of the tumour, pathological factors (including metastatic status), the individual's performance status, and other laboratory data [3,4]. More recently, sarcopenia has been associated with the clinical course of localized RCC [5]. However, the effects of surgical treatment on the association between RCC and sarcopenia have not been evaluated.

We hypothesize that surgical stress might be associated with a rapid deterioration in muscle mass status and, consequently, a worse prognosis for RCC. Therefore, our first aim in this study was to evaluate the pre- to postoperative change in skeletal muscle mass among patients with RCC. Our second aim was to evaluate the association between a low skeletal muscle mass and the incidence of adverse events postoperatively, as well as with overall survival among patients with RCC. Lastly, we evaluated if identified associations between sarcopenia and the postoperative clinical course of RCC were influenced by advanced (clinical stage III, IV) cancer status (localized versus advanced RCC).

METHODS

Study group

The study group for our retrospective analysis was formed of 108 patients (83 males, 25 females) who underwent surgical treatment of RCC at our hospital, between 2008 and 2011.

Image analysis

Muscle mass was quantified by the cross-sectional area (cm^2) of the psoas major muscle measured on computed tomography (CT) images at the level of the third lumbar vertebra (L3; Figure 1). The pre- to postoperative change in muscle area was calculated from the last CT obtained before surgery and the first CT obtained at 1-month post-surgery. Areas were calculated using ImageJ software [6]. The cross-sectional area of the psoas major muscle was outlined manually, and the area (cm^2) was normalized to body height (m^2) to obtain the total psoas area (TPA, cm^2/m^2) for between-subject analysis.

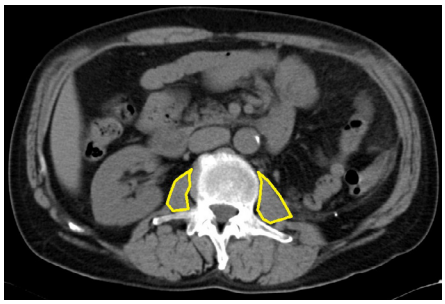

Figure 1 The area of the psoas measured on computed tomography images at the level of L3 is indicated in yellow

Operative data included in the analysis

The following variables were also extracted from the medical records for analysis: operative time, volume of intraoperative bleeding, duration of hospital stay post-surgery, adverse events (AE) post-operatively, and blood analyses.

Statistical analysis

The median pre- and postoperative TPA among all patients was used as a cut-off to classify patients into high and low TPA groups, with an independent classification for males and females. The Kaplan-Meier method was used to evaluate overall survival. Cox proportional hazard regression was used as a multivariate analysis, with Spearman's rank correlation coefficient used to evaluate the correlation among factors. Patient, clinical, and operative characteristics and overall survival were compared between the two groups. All analyses were performed using EZR [7].

RESULTS

Clinical characteristics

Patients' characteristics are summarized in Table 1. The median age among the 108 patients forming our study group was 61 (range, 32-84) years, with a mean postoperative follow-up period of 59.5 months. The median tumour size was 5.0 cm, with the distribution of clinical tumour stages as follows: stage I, 71 cases; stage II, 11 cases; stage III, 10 cases; and stage IV, 16 cases. The median preoperative TPA was 4.8 cm^2/m^2, with a significant difference between males and females (5.2 cm^2/m^2 and 4.0 cm^2/m^2, respectively; $P \leq 0.001$). The median preoperative TPA value of 4.8 cm^2/m^2 was used as the cut-off for classification of patients into the high and low preoperative TPA groups.

Table 1 Clinical characteristics

Patient Characteristics	Group	Female	Male	p value
n	-	25	83	-
Age (years) (median (range)	-	60.00 (32.00, 81.00)	63.00 (40.00, 84.00)	0.062
BMI (kg/m^2) (median (range)	-	24.20 (4.26)	24.39 (3.48)	0.823
Clinical tumour size (cm) (median (range)	-	5.00 (2.00, 14.00)	5.00 (1.70, 12.00)	0.933
Ope time (min) (median (range)	-	146.00 (57.00, 353.00)	148 (70.00, 635.00)	0.667
Bleeding (ml) (median (range)	-	187.00 (10.00, 3371.00)	293 (10.00, 6501.00)	0.192
Clinical Stage (%)	I	15 (60)	56 (67.5)	0.525
	II	3 (12)	8 (9.6)	-
	III	4 (16)	6 (7.2)	1
	IV	3 (12)	13 (15.7)	-

Clavien Dindo (%)	I	2 (28.6)	6 (26.1)	1
	II	5 (71.4)	15 (65.2)	-
	IIIa	0	1 (4.3)	-
	IVa	0	1 (4.3)	-
Cellular Classification (%)	Clear	20 (80)	64 (77.1)	1
	Not Clear	5 (20)	(19 (22.9)	
Pre TPA (cm^2/m^2) (median (range)	-	4.03 (2.18, 5.72)	5.23 (1.76, 11.28)	<0.001
Post TPA (cm^2/m^2) (median (range)	-	3.64 (2.14, 6.33)	5.30 (2.41, 10.10)	<0.001

Table 2 Univariate and multivariate analysis of overall survivals

Variables	n	Univariate Analysis					Multivariate Analysis		
		36M survival rate	95% CI	Median	95% CI	p	Hazard ratio	95% CI	p
C stage I, II	82	0.971	0.899-0.993	NA	NA	0.011	2.264	0.320-16.03	0.413
C stage III, IV	26	0.818	0.585-0.928	NA	65.9-NA	-	-	-	-
symptom+	35	0.906	0.7737-0.969	NA	NA	0.972	-	-	-
symptom-	70	0.949	0.851-0.983	NA	NA	-	-	-	-
Bleeding>median	54	0.908	0.773-0.964	NA	NA	0.728	-	-	-
Bleeding ≤ median	54	0.962	0.855-0.990	NA	NA	-	-	-	-
Ope time>median	54	0.938	0.819-0.979	NA	NA	0.328	-	-	-
Ope time ≤ median	48	0.927	0.791-0.976	NA	NA	-	-	-	-
AE	30	0.924	0.73-0.981	NA	NA	0.846	-	-	-
AE	78	0.941	0.851-0.978	NA	NA	-	-	-	-
Clear cell ca	84	0.948	0.867-0.980	NA	NA	0.477	-	-	-
Non-clear cell ca	24	0.885	0.614-0.970	NA	NA	-	-	-	-
ALP>ULN	19	0.733	0.436-0.891	NA	13.9-NA	0.003	1.722	0.353-8.413	0.502
ALP ≤ ULN	83	0.987	0.909-0.998	NA	NA	-	-	-	-
BMI>25	49	1	1.00-1.00	NA	NA	0.137	-	-	-
BMI ≤ 25	58	0.898	0.772-0.956	NA	NA	-	-	-	-
Ca>ULN	6	0.5	0.058-0.845	38.92	7.47-NA	<0.001	9.816	0.998-96.58	0.05
Ca ≤ ULN	95	0.952	0.876-0.982	NA	NA	-	-	-	-
CRP>median	50	1	1.00-1.00	NA	NA	<0.001	1.02×10^{-9}	0.00-inf	0.998
CRP ≤ median	51	0.884	0.743-0.950	NA	NA	-	-	-	-
eGFR<median	50	0.957	0.837-0.989	NA	NA	0.859	-	-	-
eGFR ≥ median	50	0.952	0.823-0.988	NA	NA	-	-	-	-
Hb<LLN	24	0.835	0.57-0.944	NA	52.7-NA	0.002	0.767	0.11-5.353	0.789
Hb ≥ LLN	84	0.961	0.883-0.987	NA	NA	-	--	-	-
LDH>LLN	14	1	1.00-1.00	NA	51.3-NA	0.14	-	--	-
LDH ≤ LLN	91	0.949	0.869-0.980	NA	NA	-	-	-	-
Lymphocyte ratio<LLN	16	0.667	0.337-0.860	NA	10.1-NA	<0.001	10.43	2.574-42.29	0.001
Lymphocyte ratio ≥ LLN	85	0.986	0.907-0.998	NA	NA	-	-	--	-
NLR<median	50	0.978	0.856-0.997	NA	NA	0.025	0.22	0.0226-2.135	0.192
NLR ≥ median	51	0.903	0.762-0.963	NA	NA	-	-	-	-
platelet>ULN	9	0.833	0.273-0.975	65.9	11.9-NA	0.008	6.55×10^{-9}	0.0-inf	0.998
Platelet ≤ ULN	99	0.943	0.869-0.976	NA	NA	-	-	-	
PreTPA ≥ median	51	0.976	0.843-0.997	NA	NA	0.018	1.222	0.837-17-84	0.883
PreTPA<median	50	0.909	0.776-0.965	NA	NA	-	-	-	-
postTPA median	52	0.979	0.858-0.997	NA	NA	0.043	0.3926	0.633-2.433	0.315
postTPA median	51	0.908	0.773-0.964	NA	NA				

Association between the total psoas area and overall survival

Overall, survival was significantly longer among patients in the high than low preoperative TPA group (P=0.018;

Figure 2). With regard to sex-specific effects, the significant association between a higher preoperative TPA and longer survival was maintained among males (P=0.022; Figure 3a) but not females (P=0.273; Figure 3b).

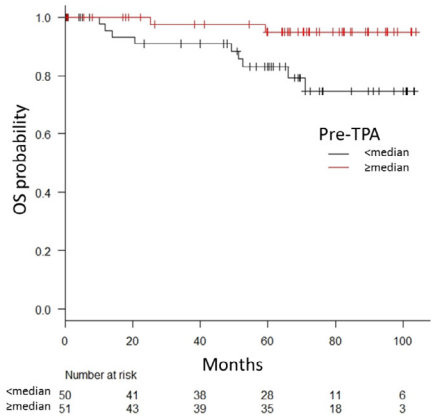

Figure 2 The Kaplan-Meier curves of overall survival for patients classified on the preoperative TPA cut-off into high and low TPA groups

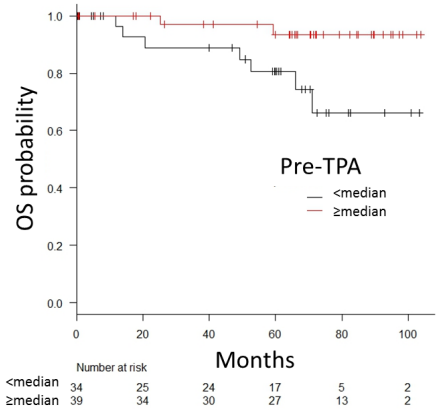

Figure 3a The Kaplan-Meier curves of overall survival for males with participants classified into high and low TPA groups based on the preoperative TPA cut-off

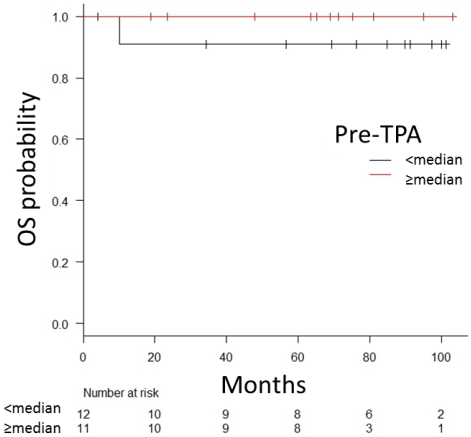

Figure 3b The Kaplan-Meier curves of overall survival for females with participants classified into high and low TPA groups based on the preoperative TPA cut-off

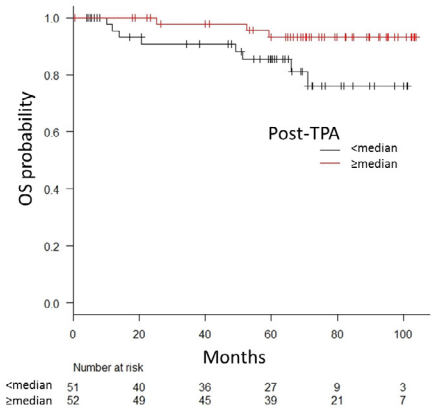

Figure 4 The Kaplan-Meier curves of overall survival for patients classified on the postoperative TPA cut-off into high and low TPA groups

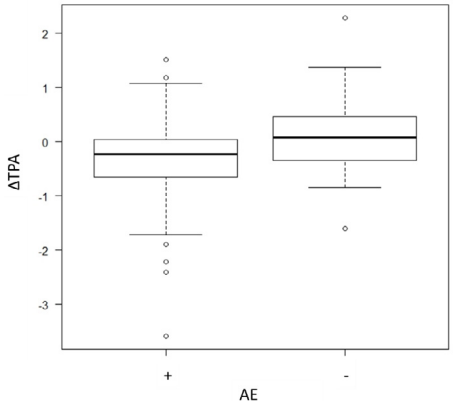

Figure 5 Spearman's rank correlation coefficient showing the association between the ΔTPA and adverse events (AE)

With regard to the postoperative TPA, the median group value of 5.03 cm^2/m^2 was used as the cut-off for classification of participants into the high and low TPA groups. Overall survival was longer among patients in the high than low post-TPA group (P=0.043; Figure 4). The pre- to postoperative change in TPA (ΔTPA) was not associated with overall survival (P=0.629).

Association between the total psoas area and postoperative clinical course

Postoperative AEs were identified in 30 cases, with these complications being minor (Clavien-Dindo grade ≤ 2) in 93.3% of cases. The preoperative TPA was not associated to the rate of postoperative AEs (P=0.667). The median postoperative hospital stay was 12 days. The rate of postoperative AE was higher among patients with a greater ΔTPA (P=0.01; Figure 5).

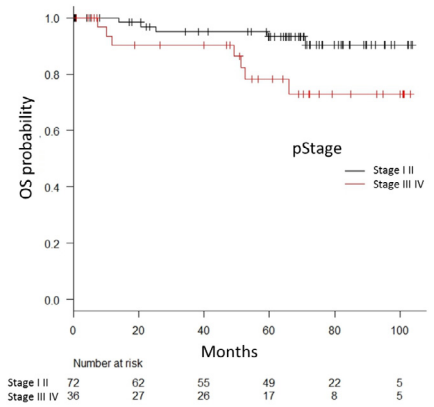

Figure 6 The Kaplan-Meier curves of overall survival by pathological tumour stage

The pathological tumour stage was naturally related to overall survival (P=0.027; Figure 6). Moreover, the preoperative TPA was significantly lower among patients with a high tumour stage (III and IV) than a low stage (I and II) (P=0.002; Figure 7). On multivariate analysis, lower lymphocyte ratio was identified as an independent prognostic factor of overall survival (P=0.001; Table 2).

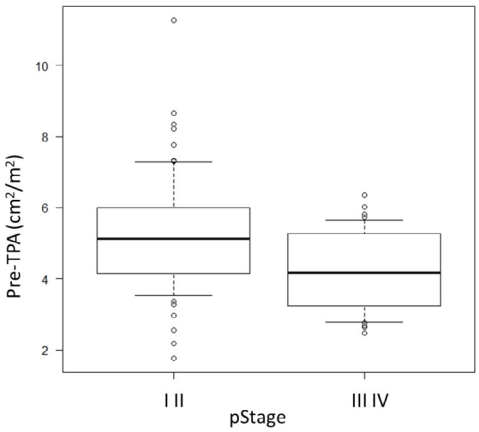

Figure 7 Spearman's rank correlation coefficient showing the association between preoperative TPA and the pathological tumour stage

DISCUSSION

The treatment of RCC has improved due to advances in assessment and diagnosis, surgical technique and the use of molecular targeted therapy. Surgery remains an important component of the treatment of RCC. However, there is a need to better evaluate the prognosis of patients after surgery. The Memorial Sloan Kettering Cancer Centre (MSKCC) risk classification for metastatic RCC [8-10], as well as other pathological classifications based on tumour specific factors [11], provide useful tools for predicting prognosis. However, in addition to tumour specific factors, patient-specific factors can also influence prognosis. Sarcopenia is one such patient-specific factor that has been associated with prognosis for various malignancies [12-14].

Sarcopenia is an indicator of a general decrease in an individual's physical strength and activities. Generally, sarcopenia is evaluated by self-report questionnaire and assessment of physical status. The skeletal muscle index (SMI) has been proposed as a more robust assessment of sarcopenia than self-report questionnaires and physical status measures [15]. However, the measurement of SMI does require sophisticated equipment and dedicated software. In contrast, the TPA is an easy-to-obtain measure that provides a reproducible objective index of sarcopenia [2]. Therefore, we selected the TPA over the SMI as it can be obtained from routine CT images, which are generally included in the assessment of patients with RCC, eliminating the need of exposing patients to additional testing.

On univariate analysis, preoperative TPA was significantly associated with overall survival for the study group as a whole, with this association remaining significant for males but not for females on sub analysis. On multivariate analysis, pre- and postoperative TPA was not a prognostic factor of overall survival, with the lymphocyte ratio being the only independent prognostic factor of overall survival. The absolute (P=0.010) and relative (P=0.017) ΔTPA were significantly associated with the incidence rate of postoperative AEs. Operative time and volume of intraoperative bleeding were not correlated to the absolute (operative time; r=0.135, bleeding; r=0.175) or relative (operative time; r=0.134, bleeding; r=0.178) ΔTPA.

Overall survival was significantly longer among patient clinical stage I and II tumours than for those with stage III and IV tumours (P=0.031). Preoperative TPA was significantly associated with overall survival, clinical factors, and pathological tumour staging.

Muscle volume plays an important role in the immune response of the body [16], secreting glutamine in time of stress to upregulate the response of the immune system [17]. Glutamine is also related to the tumorigenesis of RCC [18], with an upregulation of lymphocytes to fight cancer cells. Therefore, our identification of the lymphocyte ratio as an independent prognostic factor was not unexpected. Residual muscle volume after surgery may, therefore, be an

important indicator of an individual's stamina to fight against the cancer, providing sufficient glutamine to stimulate the lymphocyte response needed. Therefore, the stimulation of lymphocytes by glutamine may be important for cancer immunization.

The ΔTPA was not related to overall survival. Therefore, the absolute TPA (preoperative TPA) would be a more important predictor of overall survival than the stress of the surgery on muscle mass. However, the ΔTPA was associated to rate of postoperative AEs (P=0.010), with AEs, which were largely minor in our study group, not being an influence on overall survival. As well, a lower preoperative TPA (sarcopenia) indicated a more advanced disease status, but was not associated with higher rate of AEs (P=0.667) or increased operative time and volume of intraoperative bleeding. These results agree with those of previous studies that have reported sarcopenia as being associated with worse outcomes in various cancers, including pancreatic, breast and prostate cancer [19-22].

The interpretation of our results for practice is limited by the small number of patients in our study group. When we consider the multiple factors that influence skeletal muscle mass (age, sex, habitual physical activity, clinical tumour stage), then a larger study sample would be needed to control for these factors. Confirmation of the effects of sarcopenia on the clinical course of patients with RCC will require a prospective study design, controlling for factors influencing muscle mass and factors at the level of the disease status and treatment.

CONCLUSION

To our knowledge, this is the first study to have reported on the pre- to postoperative changes in TPA in patients with RCC. We identified a significant association between sarcopenia and overall survival after surgery in male patients with RCC.

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