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Review

The Prognostic Relevance of Computed Tomography-assessed Skeletal Muscle Index and Skeletal Muscle Radiation Attenuation in Patients With Gynecological Cancer

ANGIOLO GADDUCCI and STEFANIA COSIO

Department of Clinical and Experimental Medicine,
Division of Gynecology and Obstetrics, University of Pisa, Pisa, Italy

Abstract. *The evaluation of the whole skeletal muscle area at the level of the third lumbar vertebra on computed tomography (CT) scans has often detected loss of skeletal muscle mass, defined as sarcopenia, and reduced skeletal muscle radiation attenuation (SMRA) in patients with different malignancies. Baseline sarcopenia has been detected in 33.3%-51.8% of patients with advanced cervical cancer, 33.6%-50% of those with endometrial cancer, and 11%-64% of those with advanced ovarian cancer. We reviewed the literature data on the clinical relevance of CT-assessed skeletal muscle status in gynecological malignancies. Overall, baseline skeletal muscle index and SMRA have an uncertain prognostic relevance, whereas their changes during treatment usually correlate with progression-free survival and overall survival. Multicenter clinical trials are strongly warranted to assess the effects of pharmacological agents and physical exercise in the management of skeletal muscle damage in patients with gynecological cancer.*

Cancer cachexia is a wasting syndrome characterized by loss of skeletal muscle mass and functional strength defined as sarcopenia with or without loss of fat mass, associated with anorexia, inflammation, insulin resistance, and decreased quality of life (1, 2). Mitochondria, which produce adenosine triphosphate (ATP) through oxidative phosphorylation and beta-oxidation, have a pivotal role in the pathogenesis of cachexia (3, 4). Elevated Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α and Transforming Growth Factor (TGF)-β levels affect mitochondrial homeostasis. Dysfunctional mitochondria release reactive oxygen species and decrease ATP production, thus leading to enhanced protein catabolism and decreased muscle mass.

In an experimental murine model of human ovarian cancer, cachexia was associated with high tumor-derived IL-6 levels in plasma and ascites as well as with elevated phospho- signal transducer and activator of transcription proteins $(STAT)_3$, decreased phospho-AKT and increased protein ubiquitination and expression of ubiquitin ligases in skeletal muscles of tumor hosts (5). Therefore IL-6-induced $STAT_3$ activation appears to be involved in muscle wasting.

With the introduction of methods of *in vivo* body composition evaluation such as magnetic resonance imaging (MRI) and computed tomography (CT), the measurement of skeletal muscle mass with cross-sectional imaging has become a very common tool of sarcopenia assessment, although there is a wide heterogeneity in both the parameters taken into consideration and the diagnostic criteria used by different authors (6-18). The assessment of psoas muscle area-only is easy and quick, but it is not representative of the total body skeletal muscle (19). Moreover, degenerative diseases of the lumbar spine can cause local atrophy of the trunk muscles and psoas muscle not specifically related to cancer-induced sarcopenia. Conversely, the evaluation of whole skeletal muscle area at the level of the third lumbar vertebra is a more reliable and widely validated method for the assessment of the total body skeletal muscle (20-22), especially in cancer patients (6, 23-28). The cross-sectional area of skeletal muscles normalized for the patient height to calculate the skeletal muscle index (SMI) (23). Sarcopenia is usually defined as an SMI lower than the selected cut-off value.

Correspondence to: Angiolo Gadducci, MD, Department of Clinical and Experimental Medicine, Division of Gynecology and Obstetrics, University of Pisa, Via Roma 56, Pisa, 56127, Italy. Tel: +39 50992609, e-mail: a.gadducci@med.unipi.it

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Table I. *Baseline skeletal muscle assessment by CT scan in locally advanced cervical carcinoma.*

Authors	Pts	FIGO stage	Landmark	SM assessment	Percentage
Lee *et al*. (23)	245[a]	Ib_2-IV or pelvic N+	L3	SMI ≤41 cm^2/m^2 SMRA <41 HU if BMI <25.0 kg/m^2 or <33 HU if BMI ≥25.0 kg/m^2	51.8% 62.9%
Matsuoka *et al*. (11)	236[b]	Ib1-IVa	L3	Median SMI 36.5 cm^2/mm^2 Median PMI 3.94 cm^2/mm^2	
Sanchez *et al*. (32)	55[a]	II-III	L3	SM <38.5 cm^2/m^2	33.3%
Kiyotoki *et al*. (28)	60[a]	Ib_2-IVa	L3	Median SM 90.29 cm^2 Median PM 10.07 cm^2	

[a]Concurrent chemoradiotherapy; [b]Concurrent chemoradiotherapy or radiotherapy. CT: Computed tomography; pts: patients; SM: skeletal muscle; N: lymph nodes; L3: third lumbar vertebra; SMI: skeletal muscle index; SMRA: skeletal muscle radiation attenuation; HU: Hounsfield Units; BMI: body mass index; PMI: psoas muscle index.

Radiation attenuation, which is tissue-specific, ranges from –190 to –30 Hounsfield Units (HU) for adipose tissue and from –29 to +150 HU for muscle, which allows to discriminate fat from muscle and to quantify fatty muscle infiltration (29). Skeletal muscle contains lipid droplets within the cytoplasm of myocytes as well as intermuscular adipocytes. Muscles of cancer patients often show an increase of intramyocellular lipid droplets, which are more abundant in patients with progressive cancer-related weight loss compared to weight-stable individuals (30). A low skeletal muscle radiation attenuation (SMRA) associated with lipid accumulation has been often observed in CT scans of cancer patients (29, 31).

Sarcopenia is an index of frailty associated with longer hospital stay, higher risk of surgical complications, increase chemotherapy toxicity and unfavorable prognosis in patients with different malignancies including breast cancer (6, 9), pancreatic cancer (10), colon cancer (13), cholangiocarcinoma (14) and oropharyngeal squamous cell carcinoma (15). For instance, Shachar *et al*. (9), who assessed 40 metastatic breast cancer women receiving first-line taxane-based chemotherapy, found grade 3-4 toxicity in 57% and 18%, respectively, of sarcopenic and non-sarcopenic patients (p=0.02). Among 55 women with metastatic breast cancer resistant to anthracycline and/or taxane, Prado *et al*. (6) reported capecitabine-related toxicity in 50% of sarcopenic *versus* 20% of non-sarcopenic patients (p=0.03). The impact of sarcopenia in patients with malignancies of the female genital tract has yet to be clearly elucidated (12, 16, 17, 19, 23, 26, 28).

Since CT is commonly used for staging, assessment of response to treatment and surveillance of gynecological cancers, this imaging technique can offer useful information on the prognostic relevance of baseline and post-treatment SMI and SMRA in patients with these malignancies. The aim of the present article is to review the literature data on the clinical relevance of CT-assessed skeletal muscle status in locally advanced cervical cancer, endometrial cancer and advanced ovarian cancer.

Cervical Cancer

Baseline sarcopenia has been detected in 33.3%-51.8% of patients with locally advanced cervical cancer (11, 23, 28, 32) (Table I). This variable has no impact on the clinical outcome, whereas SMI decrease during definitive radiotherapy or concurrent chemo-radiotherapy significantly correlated with poorer prognosis (Tables II and III).

In the study of Lee *et al*. (23) baseline sarcopenia was defined as an SMI of ≤41.0 cm^2/m^2 and a low SMRA was defined as a mean attenuation of <41 HU in patients with a body mass index [BMI] of <25.0 kg/m^2 or <33 HU in patients with a BMI of ≥25.0 kg/m^2 in agreement with Martin and coworkers (24). During concurrent chemo-radiotherapy the patients lost an average of 0.6% of SMI/150 days, and the incidence of SMI loss was higher in patients with adenocarcinoma than in those with squamous cell carcinoma (43.3% *versus* 17.2%, p=0.003). Most studies have reported that adenocarcinoma has a more aggressive biological behavior and a poorer clinical outcome compared with squamous cell carcinoma (33), and the higher skeletal loss may be a mechanism by which adenocarcinoma can detrimentally impact on patient prognosis (23). Baseline low SMI and low SMRA were not associated with the clinical outcome. An SMI loss during treatment >10.0%/150 days had a detrimental impact on both overall survival (OS) [hazard ratio (HR)=6.02; p<0.001] and cancer specific survival (CSS) (HR=3.49; p=0.006) at multivariate analysis, whereas SMRA change was not an independent predictor for either progression-free survival (PFS) or OS.

Table II. *Prognostic relevance of skeletal muscle assessment by CT scan in locally advanced cervical carcinoma: Baseline assessment.*

Author	Clinical outcome: PFS			Clinical outcome: OS			Clinical outcome: CSS	
				5-year survival		*p*-Value	5-year survival	*p*-Value
Lee *et al*. (23)								
Low *vs*. high SMI				82.6% *vs*. 83%		0.68	87.9% *vs*. 86.6%	0.84*
Low *vs*. high SMRA				89.9% *vs*. 86.1%		0.26	87.4% *vs*. 87.11	0.84*
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value		
Matsuoda *et al*. (11)								
Low *vs*. high SMI	1.143	0.738-1.773	0.549*	1.126	0.697-1.818	0.628*		
Low *vs*. high PMI	1.176	0.758-1.823	0.469*	1.118	0.692-1.805	0.648*		
Kiyotoki *et al*. (28)								
Low *vs*. high SM			0.738*			0.376*		
Low *vs*. high PM			0.958*			0.515*		

*Univariate analysis; **multivariate analysis. CT: Computed tomography; SMI: skeletal muscle index; OS: overall survival; CSS: cancer specific survival; PFS: progression-free survival; HR: hazard ratio; 95%CI: 95% confidence interval; PMI: psoas muscle index; SM: skeletal muscle.

Table III. *Prognostic relevance of skeletal muscle assessment by CT scan in locally advanced cervical carcinoma: Changes during treatment.*

Author	Clinical outcome PFS			Clinical outcome OS			Clinical outcome CSS		
				5-year survival		*p*-Value	5-year survival		*p*-Value
Lee *et al*. (23)									
SMI loss >10% *vs*. stable				45.2% *vs*. 91.2%		<0.001*	59.8% *vs*. 92.6%		<0.001*
SMI *vs*. SMI gain				*vs*. 95.6%			*vs*. 95.6%		
				HR	95%CI		HR	95%CI	
SMRA change				6.02	3.04-11.93	<0.001**	3.49	1.44-8.42	0.006**
(per 1HU increase)				0.80	0.74-0.88	<0.001*	0.85	0.76-0.94	0.001*
				0.95	0.87-1.03	0.19*	0.92	0.82-1.05	0.21**
	HR	95% CI	*p*-Value	HR	95%CI	*p*-Value			
Sanchez *et al*. (32)									
SMI loss >10%	2.957[a]	-	0.006	2.572[b]		0.06			
Kiyotoki *et al*. (28)									
SM loss >15%	4.714	1.860-11.947	<0.001*	6.035	2.182-16.69	0.001*			
	1.619	0.527-4.971	0.4**	2.892	0.744-11.240	0.125**			
PM loss >15%	6.638	2.651-16.620	0.001*	12.571	4.403-35.893	<0.001*			
	6.001	1.908 18.871	0.002**	8.515	2.159-33.585	0.002**			

*Univariate analysis; **multivariate analysis. CT: Computed tomography; SMI: skeletal muscle index; OS: overall survival; CSS: cancer specific survival; PFS: progression-free survival; HR: hazard ratio; 95%CI: 95% confidence interval; PMI: psoas muscle index; SM: skeletal muscle. [a]Higher tumor recurrence; [b]Trend to reduced OS.

A retrospective Japanese study found that pretreatment SMI and psoas muscle index [PMI] (*i.e*. psoas muscle normalized for the patient height) significantly correlated with parametrial status (p=0.034 and p=0.002) but not with PFS and OS (11). An observational prospective Mexican study revealed that at diagnosis no patients were malnourished although 33.3% presented sarcopenia, whereas at the end of treatment 69% were malnourished and 58% were sarcopenic (32). The patients who lost ≥10% of SMI experienced a significantly higher recurrence rate

Table IV. *Skeletal muscle assessment by CT scan and its prognostic relevance in endometrial carcinoma: Baseline assessment.*

Authors	Pts	FIGO stage	Landmark	SM assessment	Percentage
Kukori *et al*. (8)	122[a]	I-IV	L3	SMA ≤4.33 cm^2	50.0%
Rodriguez *et al*. (34)	208[b]	I-IV	L3	Median SMI 42.45 cm^2/m^2 Median SMRA 30 HU	
Lee *et al*. (35)	131[c]	III	L3	SMI <39.3 cm^2/m^2 SMRA <33 HU	33.6%
Ganju *et al*. (36)	64[d]	Ib-IVa	L3	SMI <41 cm^2/m^2: SMRA <41 HU if BMI <25 kg/m^2 and SMRA <33 HU if BMI >25 kg/m^2	44% 80%

[a]Surgery, 122; adjuvant treatment, radiotherapy, 18; chemotherapy, 27; chemotherapy/radiotherapy, 19; [b]Surgery, 111; surgery plus chemotherapy, 66; palliative treatment, 31; [c]Surgery plus chemotherapy and radiotherapy; [d]Surgery plus radiotherapy with (n. 25) or without chemotherapy.

Table V. *Skeletal muscle assessment by CT scan and its prognostic relevance in endometrial carcinoma: Prognostic relevance.*

Baseline assessment

Author	Clinical outcome PFS			Clinical outcome OS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Kukori *et al*. (8)						
Low *vs*. high SMA	Median 23.5 *vs*. 32.1 months		0.046*	median 29.4 *vs*. 33.9 months		0.587*
	3.99	1.42-11.3	NA**	1.98	0.81-4.86	NA**
Rodriguez *et al*. (34)						
High SMI + high SMRA				1 (reference)		0.004**
Low SMI + high SMRA				2.10	0.48-9.16	
High SMI + low SMRA				2.20	0.67-7.16	
Low SMI + low SMRA				5.31	1.71-16.51	
Lee *et al*. (35)						
Low *vs*. high SMRA	70.5% *vs*. 80.7%		0.24*	76.7% *vs*. 81.3%		0.47*
Ganju *et al*. (36)						
Low *vs*. high SMI				2.42	0.87-6.72	0.09*
Low *vs*. high SMRA				3.52	0.81-15.3	0.09*
Low SMI + low SMRA				4.25	1.53-11.79	<0.01*
				3.02	1.04-8.74	0.04**

Changes after treatment

Author	Clinical outcome PFS			Clinical outcome OS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Lee *et al*. (35)						
SMI loss *vs*. stable			0.16*			0.14*
SMI *vs*. SMI gain						
SMRA loss *vs*. stable	5-year survival 55.9% *vs*. 92.8% *vs*. 85.7%		<0.001*	5-year survival 59.7% *vs*. 94.0% *vs*. 90.5%		*p*<0.001*
SMRA *vs*. SMRA gain	8.24	2.32-29.23	0.001**	11.08	2.43-50.58	0.002**

CT: Computed tomography; pts: patients; FIGO: International Federation of Gynecology and Obstetrics; SM: skeletal muscle; L3: third lumbar vertebra; SMA: lumbar psoas muscle cross-sectional area; SMI; skeletal muscle index; SMRA: skeletal muscle radiation attenuation; HU: Hounsfield Units; BMI: body mass index; NA: not available.

Table VI. *Baseline skeletal muscle assessment by CT scan in advanced ovarian carcinoma.*

Authors	Pts	FIGO stage	Landmark	SM assessment	
Aust *et al*. (39)	140[a]	I-IV	L3	SM ≤41 cm^2/m^2	28.9%
				SMRA <39 HU	35.0%
Kumar *et al*. (40)	296[a]	IIIc-IV	L3	SMI <39 cm^2/m^2	44.6%
				Median SMRA	33.4 HU
Bronger *et al*. (41)	105[a]	III-IV	L3	SMI <38.5 cm^2/m^2	11%
Rutten *et al*. (42)	216[a]	IIb-IV	L3	SMI <38.73 cm^2/m^2	32.4%
				Median SMRA	36.64
Kim *et al*. (16)	179[b]	III-IV	L3	SMI <39 cm^2/m^2	42.5%
Staley *et al*. (43)	201[b]	I-V	L3	SMI <41 cm^2/m^2	64.0%
Atavesen *et al*. (44)	323[a]	IIIb-IV	L3	SMI <38.5 cm^2/m^2	29.4%
				SMI <39 cm^2/m^2	33.7%
				SMI <41 cm^2/m^2	47.1%
				SMRA <32 HU	21.1%
Huang *et al*. (45)	139[a]	III	L3	SMI <39.2 cm^2/m^2	33.8%
				SMRA <35.5 HU	33.1%
Rutten *et al*. (26)	123[c]	IIB-IV	L3	SMI <41.5 cm^2/m^2	50.4%
Yoshino *et al*. (46)	60[c]	III-IV	L3	SMI <39 cm^2/m^2	60%
				SMRA <0.96	43%
Conrad *et al*. (47)	102[a]	III-IV	L4	Mean CMI 2.8 cm^2/m^2	

[a]Primary debulking surgery; [b]either primary debulking surgery or interval debulking surgery; [c]interval surgery. CT: Computed tomography; pts: patients; FIGO: International Federation of Gynecology and Obstetrics; SM: skeletal muscle; L3: third lumbar vertebra; SMI: skeletal muscle index; SMRA: skeletal muscle radiation attenuation; HU: Hounsfield Units; SMRA: pre- and post-neoadjuvant chemotherapy; SM area ratio; CMI: core muscle index.

(HR=2.957, p=0.006) and a trend to a lower OS (HR=2.572, p=0.06).

In another retrospective Japanese investigation, baseline skeletal muscle and psoas muscle were not associated with the clinical outcome (28). Conversely, the loss of skeletal muscle ≥15% after concurrent chemo-radiotherapy correlated with poorer PFS (HR=4.714, p=0.001) and poorer OS (HR=6.035, p=0.001) at univariate analysis, and the loss of psoas muscle >15% was an independent poor prognostic factor for both PFS (HR=6.001, p=0.002) and OS (HR=8.515, p=0.002).

Endometrial Cancer

Pretreatment sarcopenia has been reported in 33.6%-50% of patients with endometrial cancer (8,34-36) (Table IV). Conflicting data are currently available as for the prognostic relevance of SMI and SMRA (Table V).

Kuroki *et al*. (8) noted that 50% of surgically–treated patients had sarcopenia, defined as a CT-measured lumbar psoas muscle cross-sectional area <4.33 cm^2, and that 22% had sarcopenic obesity defined as sarcopenia plus BMI >30 kg/m^2. There were no significant differences between sarcopenic and non-sarcopenic patients as for hospital stay, early and late complications and tumor features such as histological type, tumor grade, stage or microsatellite instability. Sarcopenia was an independent poor prognostic variable for PFS (HR=3.99) but not for OS.

A retrospective cohort study subdivided endometrial cancer patients according to whether SMI and SMRA were below or above the median values of 42.45 cm^2/m^2 and 30 HU, respectively (34). Longer median OS was observed among patients with high SMI and high SMRA as well as with low SMI and high SMRA, whereas shorter median OS was found among those with low SMI and low SMRA. At Cox regression analysis only the low SMI and low SMRA phenotype correlated with 1-year mortality (HR=5.31, p=0.004).

Lee *et al*. (35) assessed patients with stage III endometrial cancer who underwent total hysterectomy, bilateral salpingo-oophorectomy and lymphadenectomy followed by 3 cycles of paclitaxel 175 mg/m^2 + carboplatin area under curve (AUC)5 every 3 weeks, external beam radiotherapy plus brachytherapy, and 3 additional cycles of paclitaxel + carboplatin. In the entire cohort 5-year PFS was 76.1% and 5-year OS was 79.7%. Baseline SMI and SMRA did not correlate with PFS and OS. During treatment, patients lost an average of 2.1% of SMRA/210 days [95% confidence interval (CI): −4.0 to −0.2] and of 0.2% of SMI /210 days, but changes in SMRA and SMI did not correlate with changes in BMI (p=0.13 and p=0.20, respectively). SMRA loss had a detrimental impact on both PFS (HR=8.24, p=0.001) and OS (HR=11.08, p=0.002) at multivariate analysis, whereas SMI changes had no prognostic relevance.

Ganju *et al*. (36), who retrospectively assessed 64 patients treated with surgery and radiotherapy and with or

Table VII. *Prognostic relevance of skeletal muscle assessment by CT scan in advanced ovarian carcinoma. Baseline assessment.*

Author	Clinical outcome PFS			Clinical outcome OS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Aust *et al.* (39)						
Low *vs.* high SMI	1.13	0.75-1.81	0.605*	0.92	0.50-1.98	0.786*
	1.31	0.76-2.26	0.366**	1.23	0.61-2.48	0.565**
Low *vs.* high SMRA	1.54	1.01-2.34	0.046*	2.41	0.24-0.70	0.001*
	1.22	0.69-2.17	0.500**	2.25	1.09-4.65	0.028**
Kumar *et al.* (40)						
Low *vs.* high SMI				0.98	0.78-1.23	0.85*
				1.26	1.08-1.46	0.002*
Low *vs.* high SMRA				1.23	1.05-1.43	0.009**
Broger *et al.* (41)	15 *vs.* 22 months			23 *vs.* 48 months		
Low *vs.* high SMI	2.64	1.24-5.64	0.012*	3.17	1.29-7.80	0.012*
	2.52	1.10-5.81	0.030**	2.89	1.11-7.54	0.031**
Rutten *et al.* (42)						
Low *vs.* high SMI				1.536	1.105-2.134	0.011*
				1.362	0.968-1.916	0.076**
Low *vs.* high SMRA				1.417	1.011-1.984	0.043*
						ns**
Kim *et al.* (16)	Median: 18.3 *vs.* 18.7 months			5-year survival 64.1 *vs.* 59.3%		
Low *vs.* high SMI	0.879	0.629-1.228	0.451*	0.747	0.436-1.280	0.289*
	1.292	0.906-1.843	0.157**	0.870	0.488-1.550	0.636**
Among sarcopenic pts	Median: 18.3 *vs.* 18.2 months			5-year survival: 4.7 *vs.* 80.0%		
FMR ≥2.1 *vs.* <2.1	1.262	0.762-2.092	0.366*	2.476	0.989-6.199	0.053*
	1.073	0.576-1.999	0.825**	3.377	1.170-9.752	0.024**
Staley *et al.* (43)	Median: 14.9 *vs.* 13.1 months,		0.37*	Median: 28.5 *vs.* 26.7 months		0.8*
Low *vs.* high SMI						
Atavensen *et al.* (44)				Median:		
SMI <38.5 *vs.* ≥38.5 cm^2/m^2				47 *vs.* 48 months		0.838*
<39 *vs.* ≥39 cm^2/m^2				47 *vs.* 48 months		0.613*
<41 *vs.* ≥41 cm^2/m^2				50 *vs.* 48 months		0.730*
SMRA low *vs.* high				28 *vs.* 56 months		0.001*
				1.79.	1.22-3.63	0.003**
Huang *et al.* (45)						
Low *vs.* high SMI	5-year PFS: 22.3% *vs.* 38.5%		0.03*	5-year OS: 54.7% *vs.* 63.2%		0.08*
	1.03°	1.01-1.06	0.04**	1.08°	1.03-1.11	0.002**
Low *vs.* high SMRA	5-year PFS: 21.8% *vs.* 37.7%		0.24*	5-year OS: 48.4% *vs.* 65.7%		0.02*
	1.04°°	1.01-1.09	0.03**	1.04°°	0.99-1.10	0.13**
Loss *vs.* no SMI loss	5-year PFS: 10.4% *vs.* 43.4%		<0.001*	5-year OS: 44.4% *vs.* 68.8%		0.001*
	1.04°°°	1.01-1.06	0.003**	1.04°°°	1.01-1.08	0.002**
SMRA loss *vs.* no loss	5-year PFS: 21.8% *vs.* 38.5%		0.02*	5-year OS: 49.8% *vs.* 67.2%		0.10*
	1.02°°°	0.99-1.04	0.11**			
Rutten *et al.* (26)						
Low *vs.* high SMI				0.887	0.556-1.414	0.613*
SM loss during CT				2.218	1.280-3.844	0.005*
				1.773	1.018-3.088	0.043**
Joshino *et al.* (46)						
Low *vs.* high SMI				Not associated with OS		0.12*
Low *vs.* high SMAR				Poorer OS		0.025*
				3.17	1.18-9.06	0.022**

Table VII. *Continued*

Table VII. *Continued*

Author	Clinical outcome PFS			Clinical outcome OS		
	HR	95%CI	*p*-Value	HR	95%CI	*p*-Value
Conrad *et al*. (47)						
Low *vs*. high CMI				Similar OS		
Low CMI+hypoalbunemia				Poorer OS		
vs. Low CMI+normal albumin				3.75	1.15-9.38	0.02*

°1 cm^2/m^2 decrease; °°1HU decrease; °°°per 1%/180 days decrease; *univariate analysis; **multivariate analysis. CT: Computed tomography; PFS: progression-free survival; SMI: skeletal muscle index; HR: hazard ratio; 95%CI:95% confidence interval: NA: not available; FMR, fat-to-muscle ratio: SM: skeletal muscle; SMRA: pre- and post-neoadjuvant chemotherapy SM area ratio; CMI: core muscle index.

without chemotherapy, reported that patients with low SMI and low SMRA were less likely to complete the planned chemotherapy ($p<0.01$) whereas radiotherapy was well tolerated regardless of SMI or SRMA. Three-year OS was 29% for the patients with both low SMI and low SMRA, 75% for those with low SMI and 75% for those with low SMRA. The patients with low SMI and low SMRA experienced the worst OS (HR=3.02, $p=0.04$) at multivariate analysis. In the study of Lee *et al*. (35) skeletal muscle gauge (SMG), *i.e*. the product of SMI per SMRA, was significantly associated with treatment delays, dose reductions, and discontinuation of chemotherapy, whereas the association of either SMI or SMRA with such changes was of borderline significance. Similarly, SMG was a better predictor of severe chemotherapy toxicity compared with either SMI or SMRA alone both in breast cancer women treated with an anthracycline/taxane-based regimen (37) and in colorectal cancer patients treated with 5-fluorouracil (38).

Ovarian Cancer

Baseline low SMI and low SMRA have been detected in 11%-64% and 21.1%-35% of patients with advanced ovarian cancer, respectively (Table VI) (16, 26, 39-47). The prognostic relevance of SMI and SMRA is reported in Table VII.

In an Austrian study, baseline SMI correlated with neither PFS nor OS (39). Conversely an elevated pretreatment SMRA was associated with a higher complete cytoreduction rate (60.4% *versus* 42.9%, $p=0.046$), a longer PFS at univariate analysis (HR=1.54, $p=0.046$) and a longer OS at multivariate analysis (HR=2.25, $p=0.028$). The patients with low SMRA had poor nutritional status, decreased albumin levels, and systemic inflammatory status.

In a series of patients with advanced ovarian cancer who underwent primary debulking surgery at Mayo Clinic, median OS was 33.2 months with no difference between sarcopenic and non-sarcopenic patients (40). Conversely, the risk of death increased linearly with decreasing values of SMRA, and at multivariate analysis the HR per 10 HU decrease in SMRA was 1.23 ($p=0.009$). Among patients without residual disease, median OS was significantly better for patients with SMRA ≥27.66 HU compared with those with SMRA<27.66 HU. Similarly, among patients with residual disease median, OS was significantly longer for patients with SMRA ≥36.40 HU compared with those with SMRA<36.40 HU. Therefore, SMRA related to lipid content and quality of skeletal muscle, seemed to have a greater prognostic relevance than skeletal muscle mass itself.

A German study found that baseline sarcopenia was an independent poor prognostic variable for PFS (HR=2.52, $p=0.030$) and OS (HR=2.89, $p=0.031$), whereas skeletal muscle mass changes over time did not correlate with OS (41).

A Dutch study (42) reported that complete cytoreduction rates (25.7% *versus* 35.6% $p=0.346$) and major surgical complication rates were not significantly different between sarcopenic and non-sarcopenic patients who underwent primary debulking surgery. Both baseline sarcopenia and low SMRA were predictors of poorer OS at univariate (HR=1.536, $p=0.011$ and HR=1.417, $p=0.043$, respectively) but not at multivariate analysis.

A Korean study assessed patients who underwent primary debulking surgery or interval debulking surgery and platinum/taxane-based chemotherapy (16). Baseline SMI itself did not correlate with the clinical outcome. However, among sarcopenic patients, a high fat-to-muscle ratio (FMR) was an independent poor prognostic variable for OS (HR=3.377, $p=0.024$) but not for PFS. Adipose stem cells from visceral and subcutaneous fat could enhance the proliferation and migration of ovarian cancer cells through the IL-6/STAT3 signaling pathway (48). Both sarcopenia and visceral obesity have been correlated with a chronic inflammatory state (49, 50). However, in the present Korean study SMI and SMRA were significantly associated with BMI ($p<0.001$ for both), but not with neutrophil-to-lymphocyte ratio, monocyte-to-

lymphocyte ratio, and platelet-to-lymphocyte ratio, which represent systemic inflammatory indices (16).

In the study of Staley *et al*. (43), median PFS and median OS were similar in sarcopenic and non-sarcopenic women at diagnosis. Moreover, no significant differences in chemotherapy toxicity, dose reduction and treatment delay according to SMI were detected among the 134 patients of whom chemotherapy records were available. Only a trend toward a more frequent neutropenia was noted in the sarcopenic group (82.2% *versus* 65.6%, p=0.07).

Ataseven *et al*. (44) found that preoperative SMI with any cut off value was not associated with OS in a series of patients undergoing primary debulking surgery. Conversely, preoperative SMRA<32 HU correlated with a lower complete surgical cytoreduction rate (38.2% *versus* 68.2%) and independently predicted a poorer OS (HR=1.79, p=0.003). It is noteworthy that SMRA correlated with OS in the subset of patients with residual disease after surgery (HR=1.87, 95%CI=1.13-3.10, p=0.015) but not in those who underwent a complete cytoreduction (HR=1.66, 95%CI=0.82-3.38, p=0.161).

A Chinese study reported a mean SMI loss of 1.8%/180 days and a mean SMRA loss of 1.7%/180 days in patients who underwent primary debulking surgery followed by platinum-based chemotherapy (45). Baseline SMI (1 cm^2/m^2 decrease; HR=1.03, p=0.04), SMI changes (1%/180 days decrease; HR=1.04, p=0.003) and baseline SMRA (1 HU decrease, HR=1.04, p=0.03) were independently associated with poorer PFS, and baseline SMI (HR=1.08, p=0.002) and SMI changes (HR=1.04, p=0.002) were also independent prognostic variables for OS.

Baseline sarcopenia was not related to OS in patients treated with neoadjuvant chemotherapy and interval debulking surgery (26). Conversely, median OS was significantly lower in patients with reduced skeletal muscle compared with those with stable or increased skeletal muscle during chemotherapy (916±99 *versus* 1431±470days, HR=2.218, 95%CI=1.280-3.844, p=0.005). Skeletal muscle loss during chemotherapy independently predicted OS (HR=1.773, p=0.043). Similarly, in another study, the skeletal muscle area measured at the third lumbar vertebra level decreased significantly after neoadjuvant chemotherapy (p=0.019) and a low post-to pre-neoadjuvant chemotherapy skeletal muscle area ratio (SMAR) was found to be an independent poor predictor of OS (HR=3.17; p=0.022) (46). Conversely, baseline sarcopenia was not associated with OS.

The areas of bilateral psoas muscles at the fifth lumbar vertebra level were measured by CT scan in 76 patients with ovarian cancer who received carboplatin/paclitaxel-based chemotherapy (51). The patients with psoas muscle cross-sectional area normalized to height [core muscle index (CMI)] <583 mm^2/m^2 had a 3.93-fold higher risk of developing grade ≥2 peripheral neuropathy compared with those with CMI>583 mm^2/m^2. Conversely, this variable did not correlate with neutropenia and thrombocytopenia.

Preoperative sarcopenia, defined as a CMI below the mean value of 2.8 cm^2/m^2, correlated with low serum albumin levels (p=0.0002) but not with short-term morbidity and OS in patients undergoing primary debulking surgery (47). Whereas in patients without sarcopenia albumin status did not impact OS (HR=1.11, 95%CI=0.37-3.29 p=0.85). Patients who had both sarcopenia and hypoalbuminemia had a 3.75-fold higher risk of death compared to sarcopenic patients with normal albuminemia (p=0.02).

A meta-analysis of 8 studies revealed that both baseline SMI and SMRA significantly correlated with OS (HR=1.11, 95%CI=1.03-1.20, p=0.007 and, respectively, HR=1.14, 95%CI=1.08-1.20, p<0.001) (26, 39-42, 44, 47, 52, 53). A more recent meta-analysis of 6 studies showed that normal SMRA was associated with a better 5-year OS compared with low SMRA (odds ratio=2.3, 95%CI=1.6-3.4, p<0.001), whereas sarcopenia did not significantly impact the clinical outcome (26, 39-42, 44, 54). However, all the individual studies had an overall high risk of bias and, moreover, the lack of standardized cut-offs for these variables made the interpretation of the results very difficult.

Conclusion

A consensus has not yet been reached as for the optimal cut-off values for skeletal muscle assessment in cancer patients (8). Some authors (23, 24, 36, 39, 43) defined sarcopenia as an SMI of <41.0 cm^2/m^2 and low SMRA as an attenuation of <41 HU in patients with BMI of <25.0 kg/m^2 or <33 HU in patients with a BMI of ≥25.0 kg/m2, whereas others used the lower cut-off of 38.5 cm^2/m^2 (25, 32, 41, 44) and 39 cm^2/m^2 (16, 40, 44, 46) for SMI. The wide range in the prevalence of baseline sarcopenia in patients with gynecological cancer depends on both the different cut-off values and the heterogeneity of the patient populations in the different studies.

The available data showed that baseline sarcopenia is not associated with the clinical outcome of patients with locally advanced cervical cancer, whereas a relevant skeletal muscle loss during chemo-radiotherapy is a poor prognostic variable for PFS and OS (23, 28, 32).

As for patients with surgically treated endometrial cancer, baseline sarcopenia and/or low SMRA correlates with unfavorable prognosis in some studies (8, 34), but not in others (35, 36). Decreased SMRA after surgery, chemotherapy and radiotherapy was independently associated with shorter PFS and OS in patients with stage III disease (35).

Among patients with advanced ovarian cancer treated with surgery and chemotherapy, baseline SMRA is usually related to a poorer clinical outcome (39, 40, 42, 44, 45). However, baseline sarcopenia has an unfavorable prognostic impact in

some studies (41, 42, 45), but not in others (16, 26, 39, 40, 43, 44, 46, 47). Two studies reported that skeletal muscle loss during neoadjuvant chemotherapy is detrimental for OS (26, 46).

In conclusion, the scanty literature data seem to suggest that baseline SMI and SMRA have an uncertain prognostic relevance in gynecological cancers, whereas their changes during treatment usually correlate with PFS and OS. Although there is no commonly accepted therapeutic strategy to prevent cancer-related skeletal muscle damage, pharmacotherapy, physical activity and nutritional supplements have been used in attempting to preserve skeletal muscle mass and quality in cancer patients (55-60). Several agents, including cytokine inhibitors, steroids such as medroxyprogesterone acetate and testosterone, nonsteroidal anti-inflammatory drugs such as celecoxib, branched-chain amino acids, eicosapentaenoic acid, vitamin/minerals, carnitine, and antiserotoninergic drugs, have been tested with uncertain results (55, 58, 60). Progressive resistance training could reduce the sarcopenic body changes through downregulation of different pro-inflammatory cytokines involved in skeletal muscle loss (56). The ongoing NCT0233092 randomized trial is evaluating the impact of nutrition intervention, home-based exercise, and anti-inflammatory drugs in preventing or attenuating cachexia in advanced cancer patients [Multimodal Exercise/Nutrition/Anti-inflammatory Treatment for Cachexia Trial (MENAC)]. Well-designed multicenter clinical trials are strongly warranted to assess the effects of pharmacological agents and physical exercise in the management of skeletal muscle damage in patients with gynecological cancer and especially in those with locally advanced cervical cancer and with advanced ovarian cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Conceptualization, Writing - original draft: AG; Data curation, Formal analysis, Methodology, Writing-review & editing: AG, SC.

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