QUALITY OF SKELETAL MUSCLE AS PREDICTOR OF EARLY MORTALITY IN WOMEN WITH OVARIAN ADENOCARCINOMA

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INTRODUCTION

Malnutrition and weight loss at diagnosis are common in ovarian cancer and frequently are aggravated during cancer treatment, determining unfavorable outcomes.[1,2] Retrospective studies that assessed the prognostic value of the changes in body composition in cancer patients concluded that reduced skeletal muscle mass (sarcopenia), low skeletal muscle attenuation and increased fat mass are independent risk factors for shorter survival[3-7]. Recently, our group have shown that the amount of high-radiodensity skeletal muscle seems to be a better prognostic factor than the average muscle attenuation or the total amount of skeletal muscle in endometrial cancer patients. Moreover, combined phenotypes for quantitative and qualitative skeletal muscle parameters have worsen the patient´s outcomes. [8]

OBJECTIVE

This study aimed to determine the prognostic value of the quantitative and qualitative parameters of the skeletal muscle in patients with ovarian adenocarcinoma.

METHODS

Elegible patients: all patients with histopathological confirmation of epithelial adenocarcinoma ovarian cancer and who performed the first cancer treatment (surgery with curative proposal or chemotherapy) in a leading cancer treatment institute in Brazil from October 2008 to December 2015, with available lumbar CT images taken up to 45 days prior to or up to 15 days after the first treatment were included in this retrospective cohort study.

Data collection: clinical data were collected from medical records and the following variables were obtained: sociodemographic data, information related to cancer treatment, presence of comorbidities and date of death.

Skeletal muscle assessment: Slices taken at the 3rd lumbar vertebra (L3) of the CT scans of the patients' abdomen and pelvis were analyzed with the aid of the SliceOmatic software program 5.0 (Tomovision, Canada). We divided the overall skeletal muscle range into two sub-ranges: the area of skeletal muscle in the range -29 to +29 HU was denominated as low-radiodensity skeletal muscle index (LRSMI, cm^2/m^2) and the area in the range +30 to +150 HU was denominated as high-radiodensity skeletal muscle index (HRSMI), representing the cross-sectional muscle area with low and high attenuation, respectively (Figure 1). They were categorized according to the population distribution quartiles (see table 2). In addition, four different skeletal muscle phenotypes were purposed: 1) *High SMI + High HRSMI*; 2) *Low SMI + High HRSMI*; 3) *High SMI + Low HRSMI*; 4) *Low SMI + Low HRSMI*. High or low HRSMI was classified as HRSMI above or below median (22.638 cm^2/m^2) of our own population, respectively; and high or low SMI was determined considering the cut-off point established for the overall skeletal muscle tissue to classify sarcopenia (38.9 cm^2/m^2).[9]

Data analysis: statistical analysis was performed using the SPSS statistical package for Windows (Chicago, IL, USA) version 22.0. One-year survival was estimated by Kaplan-Meier method and statistical significance among groups was assessed by the log-rank test. Those who remained alive within 365 days based on the date of the first cancer treatment were censored. For all statistical analysis, two-sided p values <0.05 were accepted as statistically significant.

Ethical criteria: the study was approved by the Ethics and Research Committee of the Brazilian National Cancer Institute (466.070/2013).

RESULTS

We enrolled 139 eligible patients, with a median age of 55 (22-83) years. Regarding the one-year survival analysis, 37 (27%) deaths were recorded within the study period.

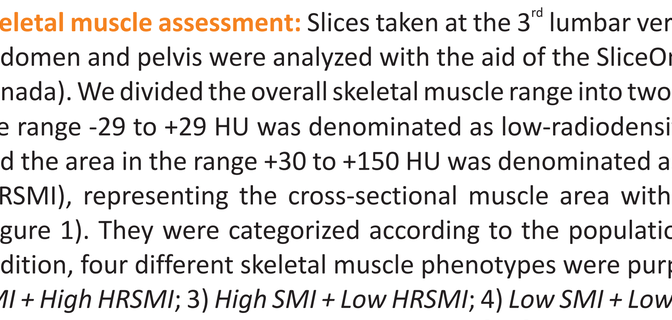

Figure 1. Skeletal muscle classification purpose according to sub-ranges of radiodensity.

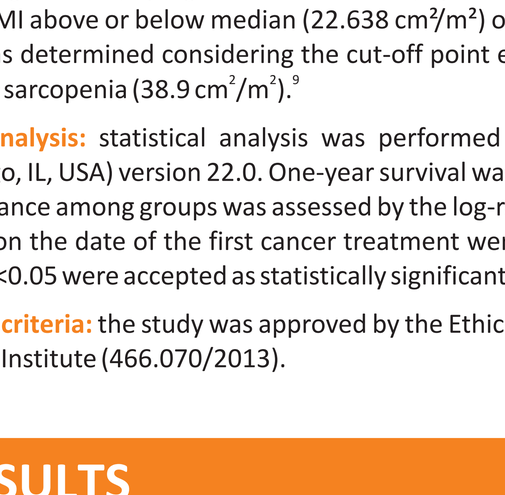

Figure 2. Kaplan Meier curve for one-year survival according to skeletal muscle phenotypes (SMI + HRSMI classification).

Legend: HRSMI: high-radiodensity skeletal muscle index – skeletal muscle area in range +30 to +150 HU; SMI: skeletal muscle index in range -29 to +150 HU; High SMI: >38.9 cm2/m2; Low SMI: <38.9 cm2/m2; High HRSMI: HRSMI above median of the study population (>22.638 cm^2/m^2); Low HRSMI: HRSMI below median of the study population (<22.638 cm^2/m^2). *There was a significant difference between: Low SMI + Low HRSMI vs. High SMI + High HRSMI (p=0.005) and High SMI + Low HRSMI vs. High SMI + High HRSMI (p=0.021).

Table 1. Patient sociodemographic, clinical and nutritional characteristics (n=139).

Variables	N (%)
Age category	
<65 years	112 (80.6)
≥ 65 years	27 (19.4)
Ethnic group	
Caucasian	79 (57.2)
Mixed races	46 (33.3)
Black	13 (9.4)
Educational level	
Illiterate	5 (3.6)
Elementary School	87 (62.6)
High school	36 (25.9)
Higher education	11 (7.9)
Marital status	
Single	46 (33.1)
Married	55 (39.6)
Divorced	15 (10.8)
Widowed	23 (16.5)
Occupation	
Housewife	71 (54.2)
Employee	45 (34.3)
Retired	15 (11.5)
Histopathological characteristics	
Histologic subtype	
Serous	70 (64.8)
Mucinous	14 (13)
Endometrioid	10 (9.3)
Others	14 (13)
Degree of cell differentiation	
I	12 (13.6)
II	16 (18.2)
III	60 (68.2)
Cancer Stage (FIGO, 2009)[10]	
I	11 (9.2)
II	10 (8.4)
III	62 (52.1)
IV	36 (30.3)
Comorbidities	
Hypertension	56 (40.3)
Diabetes	18 (12.9)
Hypertension + Diabetes	12 (8.6)
Others*	21 (29.6)
Type of cancer treatment – 1st line	
Exclusive surgery	10 (7.2)
Chemotherapy plus surgery	80 (57.55)
Exclusive chemotherapy	49 (35.25)
LRSMI (cm^2/m^2)	
Quartile 1	15.0431
Quartile 2	18.7146
Quartile 3	23.1719
HRSMI (cm^2/m^2)	
Quartile 1	18.568
Quartile 2	22.638
Quartile 3	28.770
SMI (cm^2/m^2)	
Low SMI	48 (34.5)
High SMI	91 (65.5)
Skeletal muscle phenotypes	
High SMI + High HRSMI	66 (47.48)
Low SMI + High HRSMI	12 (8.63)
High SMI + Low HRSMI	36 (25.90)
Low SMI + Low HRSMI	25 (17.99)

Legend: FIGO: International Federation of Gynecology and Obstetrics; HRSMI: high-radiodensity skeletal muscle index; LRSMI: Low-radiodensity skeletal muscle index; SMI: skeletal muscle index. *Others comorbidities: dyslipidemia, renal insufficiency, heart failure, and chronic obstructive pulmonary disease.

Table 2. One-year survival analysis by Kaplan-Meier method according to the sociodemographic, clinical and nutritional characteristics of women with ovarian adenocarcinoma (n=139).

			Survival (days)		
Variables	**Women**	**Events**	**Average**	**CI 95%**	**p-value***
Age category					
<65 years	112	28	321.4	303.7 – 339.2	0.348
≥ 65 years	27	9	291.3	239.8 – 342.8	
Ethnic group					
Caucasian	79	20	320.9	298.7 – 343.0	0.429
Mixed races	46	12	317.5	287.5 – 347.5	
Black	13	5	270.8	200.5 – 341.2	
Histologic subtype					
Serous	10	1	350.4	323.3 – 377.6	0.255
Mucinous	70	11	341.2	322.0 – 360.4	
Endometrioid	14	2	316.1	253.3 – 378.9	
Others	14	5	296.0	238.8 – 353.2	
Degree of differentiation					
I	12	1	364.9	364.8 – 365.1	0.618
II + III	76	10	349.4	335.2 – 363.7	
Stage category					
I + II	21	1	347.9	315.1 – 380.6	0.450
III + IV	98	25	328.0	311.1 – 344.9	
SMI (cm^2/m^2)					
Low SMI	91	20	325.8	307.1 – 344.5	0.079
High SMI	48	17	296.2	260.5 – 331.8	
LRSMI (cm^2/m^2)					
LRSMI <Q1	33	8	317.8	282.2 – 353.4	0.244
≥Q1 LRSMI <Q2	35	6	333.2	304.6 – 361.8	
≥Q2 LRSMI <Q3	36	14	298.9	264.5 – 333.2	
LRSMI ≥Q3	35	9	313.9	274.1 – 353.8	
HRSMI (cm^2/m^2)					
HRSMI <Q1	36	13	285.8[a]	239.1 – 332.5	**0.014**
≥Q1 HRSMI <Q2	37	12	304.2[a]	269.5 – 338,9	
≥Q2 HRSMI <Q3	35	10	324.5[a]	296.3 – 352.7	
HRSMI ≥Q3	34	2	347.1[b]	323.0 – 371.2	
Skeletal muscle phenotypes					
High SMI + High HRSMI	66	10	333.5 [a]	313.5 – 353.6	**0.033**
Low SMI + High HRSMI	12	3	305.2 [a,b]	245.8 – 364.6	
High SMI + Low HRSMI	36	14	286.1 [b]	243.3 – 328.8	
Low SMI + Low HRSMI	25	10	285.1[b]	238.9 – 331.3	
Type of cancer treatment					
Chemotherapy plus surgery	80	6	355.2[a]	345.1 – 365.3	**0.000**
Exclusive chemotherapy	49	26	268.2[b]	233.3 – 303.0	
Exclusive surgery	10	4	227.0[b]	122.0 – 332.0	

Legend: CI: confidence interval; HRSMI: high-radiodensity skeletal muscle index; LRSMI: low-radiodensity skeletal muscle index; Q: quartile; SMI: skeletal muscle index *log-rank test.
High SMI: ≥38.9 cm ^{2}/m^2; Low SMI: <38.9 cm ^{2}/m^2; High HRSMI: HRSMI above median of the study population (≥22.638 cm^2/m^2); Low HRSMI: HRSMI below median of the study population (<22.638 cm^2/m^2). Groups with different overlapping letters have significant differences in the pairwise comparison by log -rank test.

Table 3. Multiple logistic regression for one-year survival according to the different skeletal muscle parameters evaluated.

Variables	p-value	HR	CI 95%
Model 1			
HRSMI	0.021	2.85	1.17 – 6.95
Model 2: Skeletal muscle phenotypes			
High SMI + High HRSMI			
Low SMI + High HRSMI	0.319	2.13	0.482 – 9.363
High SMI + Low HRSMI	0.268	1.89	0.613 – 5.822
Low SMI + Low HRSMI	0.021	3.32	1.202 – 9,150

Legend: CI: confidence interval; HR: hazard ratio; HRSMI: high -radiodensity skeletal muscle index; LRSMI: low -radiodensity skeletal muscle index. *Adjusted models for the following confounding variables: age, presence of comorbidities (systemic arterial hypertension plus diabetes mellitus), staging and type of treatme nt performed.

FINAL CONSIDERATIONS

We conclude that the quality of skeletal muscle, specifically the amount of HRSMI, directly implies a better prognosis in adenocarcinoma ovarian cancer, despite an inadequate amount of skeletal muscle. More studies are needed to understand the role that different body composition phenotypes exert in cancer prognosis.

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