Master of Medicine

Influence of Body Composition Parameters on the Treatment Response and Long-term Oncologic Outcomes in Patients with Primary Rectal Cancer

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Hyo Seon Ryu

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Hyo Seon, Ryu

Department of Medicine

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This certifies that the master of medicine
of Hyo Seon Ryu is approved.

Committee Chair Dr. In Ja Park

Committee Member Dr. Kyung Won Kim

Committee Member Dr. Jong Lyul Lee

Department of Medicine

Ulsan, Korea

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Abstracts

Purpose : Body compositions can be obtained readily from CT images and are modifiable. Body composition parameters such as obesity and sarcopenia have been reported to be associated with morbidity and mortality in patients with cardiovascular disease, chronic obstructive pulmonary disease, and metabolic syndrome. Recently, sarcopenia has been demonstrated as a prognostic factor in cancer patients. We evaluated the association of body composition with the preoperative chemoradiotherapy (PCRT) response and long-term oncologic outcomes in non-metastatic rectal cancer patients.

Methods : We enrolled 1,384 patients with stage(y)0-III rectal cancer who had been treated at Asan Medical Center between January 2005 and December 2012. The body composition at diagnosis was measured by abdomino-pelvic computed tomography (CT) using Asan-J software. Two consecutive axial CT images at the level of the L3 lumbar vertebra were processed and then averaged for each patient. Sarcopenia, visceral obesity (VO), and sarcopenic obesity (SO) were defined using CT-measured parameters such as the skeletal muscle index (total abdominal muscle area, TAMA), visceral fat area (VFA), and

VFA/TAMA. SMI was calculated as TAMA/height^2. We evaluated three types of criteria according to the SMI for sarcopenia. VO was defined as ≥ VFA of 100 cm^2. A VFA/TAMA ratio of over 3.2 was defined as SO. An inflammatory status was defined as a neutrophil-lymphocyte ratio of ≥3. Obesity was categorized by a body mass index (≥ 25 kg/m^2). Pathologic responses to PCRT were evaluated using the tumor regression grade (TRG) system according to the proportion of tumor cells as well as fibrosis.

Results : Among the 1,384 study patients, 894 (64.6%) were at the localized stage, and 490 (35.4%) had regional lymph node metastasis. A total of 536 (38.7%) patients in this series had received preoperative chemoradiotherapy. According to Western, Japanese and Korean criteria, 943 (68.2%), 834 (60.3%) and 215 (25.4%) patients were categorized as having sarcopenia, respectively. The records indicated that 307 (22.2%) patients had SO and 670 (48.4%) had visceral obesity. We further found that 458 (33.1%) cases had a BMI of 25 or higher and 278(20.2%) were in an inflammatory state with an NLR≥3. The total regression rate after PCRT was significant low in patients with VO (20.1%, p=0.029) and SO (11.5%,

p=0.038). The 5-year overall survival (OS) rate was significantly lower in SO patients (no SO vs. SO; 79.1% vs. 75.5%, p=0.02) but the 5-year recurrence-free survival (RFS) rate was not different (77.3% vs. 77.9% p=0.858). Sarcopenia, SO, VO, and obesity were not associated with RFS. However, obesity, SO, age, sex, inflammatory status, and tumor stage were confirmed as independent factors associated with poorer OS by multivariate analysis. In subgroup analysis based on the tumor stage or inflammatory markers, an association between SO and the OS rate was more prominent in patients with (y)p stage 0-2 and no inflammatory status.

Conclusion : The presence of SO and a low body mass index at diagnosis are individually associated with poorer OS in non-metastatic rectal cancer patients.

Key words: Rectal cancer, sarcopenia, obesity, overall survival, recurrence free survival

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Introduction

An assessment of body composition includes the quantitation of fat and muscle mass. To describe changes in the body composition, terminologies such as obesity, visceral obesity (VO), sarcopenia, sarcopenic obesity (SO) etc. are used. Obesity is defined as abnormal or excessive fat accumulation that presents a risk to health. Body mass index (BMI) is the most commonly used parameter to define obesity. Obesity is a major risk factor for metabolic disorders, cardiovascular disease and cancer. [1)]

VO refers to an excessive accumulation of visceral fat in the abdominal cavity but there is no definitive normal range due to variations associated with age, gender, race and comorbidities.[2)] VO is calculated as the ratio of the visceral fat area to the subcutaneous fat area. Visceral fat secrets more bioactive molecules and is associated with lower insulin sensitivity compared to subcutaneous fat.[2)] Increased insulin resistance and its influence on levels of endocrine hormonal secretion associated with VO is thought to be linked to adverse outcomes in cancer patients.

The term ‘sarcopenia’ has been used to describe an age-related decrease of muscle mass and is also used to refer to a decrease in skeletal muscle mass, strength and function with age. From a pathophysiological point of view, it is thought to be a muscle insufficiency caused by chronic disease or an increased length of hospital stay and bed rest.[3)] SO is a condition in which severe obesity and low muscle mass occur simultaneously. There are variations in the definition of SO in various studies, depending on the method of assessment.[2)]

The importance of body composition as a prognostic factor has been emphasized in different medical contexts including chronic diseases,[4)] critical care,[5)] in the elderly,[6)] and in cancer.[7)] Both obesity and sarcopenia are separate risk factors for poor health outcomes and can act synergistically to increase this risk.[8, 9)] Recently, many studies have demonstrated that

SO has adverse impacts on surviva.[8-11] In a recent meta-analysis study, Tien et al. concluded that SO was associated with a 24% increase in risk of all-cause mortality among hospitalized older patients.[9]

In various types of malignancies, the body composition is an important independent prognostic factor affecting surgical and oncologic outcomes. Recent research has provided increased evidence of the negative impacts of sarcopenia in cancer patients. However, no unified definition or cutoff values have been established. A high prevalence of sarcopenia in patients with malignant disease has been described: 57% in gastric cancer, 27.5% in hepatocellular carcinoma, and 29% in metastatic renal cell carcinoma.[12-14] The presence of sarcopenia in patients with malignant disease has also been associated with increased chemotherapy toxicity, post-operative complications, and poorer overall survival.[15] A recent systematic review and meta-analysis has evaluated the current literature on body composition assessments in patients with esophageal cancer and found that the sarcopenic cases had a higher incidence of postoperative pulmonary complications after an esophagectomy and poorer long-term survival outcomes.[16] Shlomit et al. reported that sarcopenia is associated with poorer overall survival and is an unfavorable prognostic factor for cancer-specific survival in patients with solid tumors including hepatocellular carcinoma, pancreaticobiliary cancer, gastroesophageal cancer, urothelial cancer, renal cell carcinoma and colorectal malignancies.[7] A synthesis of the literature by Aleixo et al. further revealed that sarcopenic patients have a higher chemotherapy toxicity and that overall survival (OS) is reduced in sarcopenic women with metastatic breast cancer.[17] Okumura et al. reported that VO and SO are associated with a poorer prognosis after resection in pancreatic cancer patients.[11]

In colorectal cancer (CRC) patients, sarcopenia has been associated with a higher incidence of postoperative complications,[18-20] and many other studies have also suggested that sarcopenia is a negative prognostic indicator in terms of OS.[20-22] Systemic inflammation

may be explainable cause of the mechanism in which how body composition works negatively. Also, it is meaningful prognostic factor itself.[19, 23] The results of a recent meta-analysis indicate that pretreatment NLR can predict disease-free survival in patients undergoing a primary resection for CRC and in patients undergoing a liver metastasectomy or ablation.[24]

Many studies to date have assessed the impacts of body composition and BMI on oncologic outcomes but these can only be calculated by body measurements and image work-ups, including CT scans, at the time of diagnosis. Information on body composition can therefore be obtained readily in almost all patients and this is both a modifiable and valuable prognostic indicator. However, no unified definition or cut off values have yet been established. Also large-scale studies which can reflect the demographic characteristics of each cohorts are needed. In addition, studies on the effect of body composition on the preoperative chemoradiation therapy (PCRT) response, which has become a standard treatment in locally advanced rectal cancer, are lacking.

We aimed in our current study to demonstrate the effect of body composition on oncologic outcomes, and determine whether it is associated with the PCRT response, in patients with primary rectal cancer.

Materials and methods

Study population

We enrolled 1,384 stage (y)0-III rectal cancer patients who received a curative resection at Asan Medical Center between January 2005 and December 2012. All of the included patients underwent an abdominopelvic CT and a blood test at the time of their first diagnosis. Any cases without such test records were not analyzed further. Cancer staging was based on the

most updated American Joint Committee on Cancer (AJCC) manual at the time of surgery. Patient stages were categorized in accordance with lymph node metastasis i.e. (y)p stage 0-2 vs. (y)p stage 3. Pathologic responses to PCRT were evaluated in the resected specimens using the tumor regression grade (TRG) system according to the proportion of tumor cells as well as fibroses suggested by the Gastrointestinal Pathology Study Group of the Korean Society of Pathologists. TRG was categorized according to the composition of residual tumor and fibrosis i.e. complete (no residual tumor cells and only a fibrotic mass), near-complete (difficult to microscopically find residual tumor cells in the fibrotic tissue), moderate (easily identifiable dominant irradiation-related changes with residual tumor), minimal (a dominant tumor mass with obvious irradiation-related changes), and no regression (no evidence of irradiation-related fibrosis, necrosis, or vascular changes).[25] Based on the TRG assessments, we assigned the patients into a good response group (patients with complete or near-complete regression) or poor response group (patients with moderate or minimal or no regression). The PCRT patients were also classified as total regression (patients with complete regression) and residual disease (all other patients).

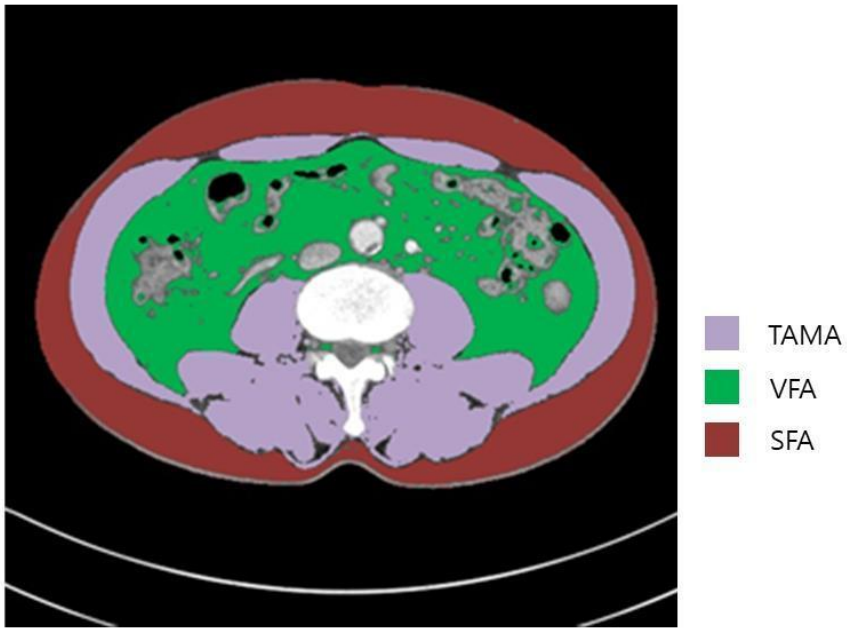
Measurements and definitions of body composition parameters

All CT images were retrieved from the Picture Archiving and Communication System (PACS) at our institution. The presence of sarcopenia was evaluated by abdominal CT scanning using Asan-J software, which was developed based on Image J (NIH, Bethesda, MD). Two consecutive axial CT images at the level of the inferior endplate of the L3 lumbar vertebra were processed and then averaged for each patient. Using the Asan-J software, the total abdominal muscle area (TAMA, cm2), including all muscles on the selected axial images i.e., psoas, paraspinal, transversus abdominis, rectus abdominis, quadratus lumborum, and internal and external obliques, were demarcated using predetermined thresholds for the HU on CT or the signal intensity (SI) on precontrast.[26] The visceral fat area (VFA, cm2) and

the subcutaneous fat area (SFA, cm2) were also demarcated using the adipose tissue thresholds on CT (Figure 1).

Figure 1. Body morphometric evaluation of the abdominal fat and muscle area

At the level of the inferior endplate of the L3 vertebra, an axial CT image was segmented into the total abdominal muscle area (TAMA), visceral fat area (VFA), and superficial fat area (SFA).



Sarcopenia was defined based on the skeletal muscle index (SMI), which is calculated as TAMA/height2. In our current study, we evaluated three types of sarcopenia criteria to determine which would be the most effective for our cohort. These included Western criteria which were previously used in a large population-based study of Prado et al.[8] The cut-off values for sarcopenia in this case were an SMI < 38.5 cm2/m2 in women, and <52.4 cm2/m2

in men. The second set of criteria were from a Japanese study by Miyamoto et al which classified the patient cohorts into quartiles according to sex.[21] SMI values of 32.6-49.5 cm2/m2 for men and 15.6-42.1 cm2/m2 for women were thereby used to defined sarcopenia. Finally, in the third Korean criteria, patients were also divided into sex-specific quartiles groups in accordance with their SMI: Q1 (male: 53.1-73.7, female: 40.6-55.9), Q2 (male: 48.3-52.9, female: 37.3-40.5), Q3 (male: 43.3-48.2, female: 33.7-37.2), and Q4 (male: 22.3-43.2, female: 16.4-33.6). When cox regression analysis was performed using these sex-specific quartiles, recurrence or mortality was found to be significantly increased in Q4 compared to Q1 (p=0.009; HR 1.434; 95% CI 1.094-1.879, Table 5). Based on this, Q4 (male: 22.3-43.2, female: 16.4-33) was defined as the sarcopenia group.

We define visceral obesity (VO) as ≥ VFA of 100 cm2 in accordance with the Japanese Society for the Study of Obesity.[27] Sarcopenic obesity was defined as VFA/TAMA ratio exceeding 3.2.[28] Body mass index (BMI) was calculated as weight (kg)/height (m) 2. A BMI ≥25 kg/m2 was considered high.

Markers of systemic inflammation

We used neutrophil-lymphocyte ratios (NLR) as indicators of systemic inflammation. We categorized high and low NLR groups based on the cutoff value of 3, which was verified as an independent prognostic factor.[29] A high NLR (3 or greater) was defined as an inflammatory state and low NLR (less than 3) as a non-inflammatory state.

Statistical analysis

All continuous variables are given as means with standard deviation (SD). Survival duration was determined from the time of first diagnosis to the period of death of any cause or last follow up date. Recurrence-free survival (RFS) was defined as the time from the first

diagnosis until the time of recurrence or death from any cause. SMI measurements are presented as median values and were categorized into sex-specific quartiles. Survival curves were estimated using the Kaplan-Meier method and analyzed using the log-rank test. Univariate and multivariate survival analyses were conducted using the Cox proportional hazards model to analyze hazards ratios (HRs) from which 95% confidence intervals (CIs) were obtained. The OS and RFS of each subgroup was analyzed using Kaplan-Meier curves and the HR was calculated by Cox regression. Backward stepwise elimination with a threshold of p=0.10 was used to select variables in the final model. Multicollinearity among correlated variables were checked using variance inflation factor and condition index.

Statistical significance was established with 2-sided test at $p < 0.05$. All statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL).

Results

Clinicopathological characteristics

The clinicopathological characteristics of the study patients are summarized in Table 1. A total of 1384 patients with non-metastatic rectal cancer who received a curative resection were included in our cohort. There were 888 men (64.2%) and 496 (35.8%) women. We found that 894 (64.6%) of these subjects were at the localized stage, and 490 (35.4%) had regional lymph node metastasis A total of 536 patients had preoperative chemoradiotherapy (38.7%). Among the 1384 rectal cancer patients in our total cohort, 943 (68.2%) and 834 (60.3%) were categorized as sarcopenic according to Western and Japanese criteria, respectively. When Korean criteria were applied however, only 215 (25.4%) of our study cases were classified as sarcopenic. Also in our series, 307 patients (22.2%) had SO and 670 (48.4%) had VO. The mean BMI was 23.9 +4.4; 458 cases (33.1%) had a BMI of 25 or

higher and 42 (3%) had a BMI of 30 or more. The mean NLR was 2.33+1.67, and 278 (20.2%) patients were in an inflammatory state with an NLR≥3.

Table 1. Clinicopathologic characteristics of the study patients

Variables	**Mean ± SD, or No (%)**
Age, years, mean ± SD	59.0±10.9
Sex	
Male	888 (64.2%)
Female	496 (35.8%)
Pathologic stage	
Stage 0-Ⅱ	894 (64.6%)
Stage Ⅲ	490 (35.4%)
Preoperative chemoradiation therapy	
Yes	536 (38.7%)
No	848 (61.3%)
Operation	
Abdominoperineal resection	157 (11.3%)
Hartmann procedure	7 (0.5%)
Sphincter preserving resection	1220 (88.2%)
Adjuvant chemotherapy	
Yes	731 (52.8%)
No	653 (47.1%)
Sarcopenia (Western)	
Yes	944 (68.2%)
No	440 (31.8%)
Sarcopenia (Japanese)	
Yes	834(60.3%)
No	548(39.7%)

Sarcopenia (Korean)	
Yes	215(25.4%)
No	633(74.6%)
Sarcopenic obesity	
Yes	307 (22.2%)
No	1077 (77.8%)
Visceral obesity	
Yes	670 (48.4%)
No	714(51.6%)
Body mass index, kg/m^2 , mean ± SD	23.9±4.4
<18.5	57 (4.1%)
18.5-23	494 (35.7%)
23-25	375 (27.1%)
25-30	416 (30.1%)
30<	42 (3%)
Neutrophil lymphocyte ratio (NLR), mean ± SD	2.33± 1.68
< 3	1099 (79.8%)
≥3	278 (20.2%)

SD, standard deviation

Distribution and correlation of sarcopenia, body mass index, and visceral obesity

The distribution of sarcopenia, BMI, and visceral obesity according to sex, stage and receipt of PCRT in our present patient series is shown in Table 2. In accordance with the Western criteria, men had a higher incidence of sarcopenia (72.2% vs 61.6%, p<0.001) and VO (56.0% vs 34.9%, p<0.01). By the Japanese criteria however, sarcopenia was more prevalent in the women (27.7% vs 61.6%, p<0.001). In contrast, when applying the Korean criteria there were no differences in the frequency of sarcopenia by sex, stage, or PCRT

distribution, which was found to be at a constant rate of about 25% for all categories. Patients T stage 0- had a higher incidence of VO ($p=0.02$).

For both the men and women in our present patient series, the SMI showed significant differences according to age (Table 3). In the men, the SMI was significantly different between all age groups. Among the women, only the patients over 70 years showed a significantly lower SMI than other age groups. In simple correlation analysis, the SMI and BMI values had a positive correlation ($r=0.637$, $p<0.001$), the SMI and visceral fat levels showed a weak positive correlation ($r=0.247$, $p<0.001$), and the BMI and visceral fat values had a slightly weaker positive correlation ($r=0.444$, $p<0.001$) (Figure 2).

Table 2. Distribution of sarcopenia, body mass index and visceral fat area according to sex, stage, and receipt of preoperative chemoradiation therapy (%)

		Sarcopenia(Western)			Sarcopenia(Japanese)			Sarcopenia(Korean)			BMI >25			VFA >100		
		No	Yes	P	No	Yes	P	No	Yes	p	No	Yes	P	No	Yes	P
Sex	Male	247 (27.8)	639 (72.2)		641 (72.3)	245 (27.7)		664 (75.0)	222 (25.0)		589 (66.3)	299 (33.7)		391 (44.0)	497 (56.0)	
	Female	193 (38.9)	303 (61.6)	<.001	193 (38.9)	303 (61.6)	<0.001	372 (75.0)	124 (25.0)	0.981	337 (67.9)	159 (32.1)	0.540	323 (65.1)	173 (34.9)	<.001
Stage	Stage 0-	291 (32.6)	603 (67.4)		550 (60.4)	361 (39.6)		674 (74.0)	237 (26.0)		585 (65.4)	309 (34.6)		433 (48.4)	461 (51.6)	
	Stage	149 (30.4)	341 (69.6)	0.413	284 (60.3)	187 (39.7)	0.978	362 (76.9)	109 (23.1)	0.243	341 (69.6)	149 (30.4)	0.116	281 (57.3)	209 (42.7)	0.002
PCRT	No	269 (31.6)	579 (68.4)		499 (58.8)	349 (41.2)		633 (74.6)	215 (25.4)		576 (67.9)	272 (32.1)		435 (51.3)	413 (48.7)	
	Yes	171 (32.1)	362 (67.9)	0.850	335 (66.6)	198 (33.4)	0.138	403 (75.6)	130(24.4)	0.687	350 (65.3)	186 (34.7)	0.312	279 (52.1)	257 (47.9)	0.784

BMI, body mass index; VFA,visceral fat area; PCRT, preoperative chemoradiation therapy

Figure 2. Correlation of the skeletal muscle index (SMI), body mass index (BMI) and visceral fat area (VFA). The SMI and BMI showed a significant positive correlation.

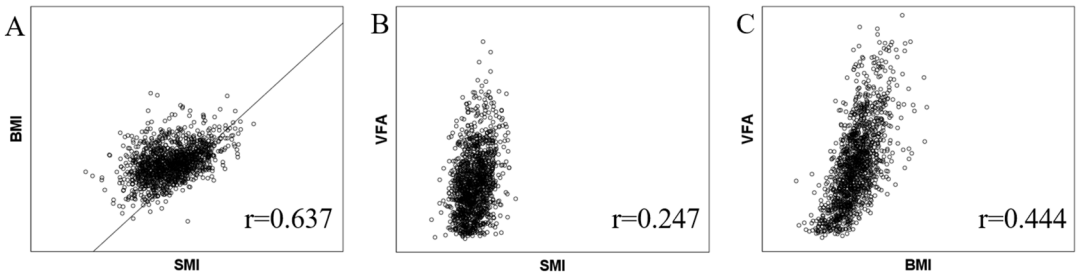


Table 3. Skeletal muscle index according to age and sex

Age group	Number	Skeletal muscle index, mean ± SD	P value
Male, yrs	888	18.45±10.76	
≤40s	168	52.81±19.1	
50s	290	49.84±7.33	0.018
60s	274	46.88±6.40	<.001
≥70s	156	43.89±6.86	<.001
Female, yrs	496	37.2±5.71	
≤40s	96	39±6	
50s	164	37.93±5.39	0.139
60s	140	37.29±5.12	0.299
≥70s	96	34.03±5.64	<.001

Association of body composition and inflammatory markers with the PCRT response

Sarcopenia (Western), sarcopenia (Japanese), obesity, VO, and SO were not found to be associated with the PCRT response (i.e. good vs. poor response). However, total regression was significantly less achieved in patients with VO and SO (22% vs. 14.2%, p=0.029; 20.1% vs 11.5%, p=0.038) (Table 4).

Table 4. Association between body composition parameters and the tumor response to preoperative chemoradiation therapy

Variable	Response classification 1			Response classification 2		
	Good response	Poor response	P	Total regression	Residual disease	P
Sarcopenia (Western)			0.213			0.465
No (n=165)	76 (46.1%)	89 (53.9%)		33 (20%)	132 (80%)	
Yes (n=346)	138 (39.9%)	208 (60.1%)		60 (17.3%)	286 (82.7%)	
Sarcopenia (Japanese)			0.193			0.628
No (n=324)	143 (44.1%)	181 (55.9%)		61 (18.8%)	263 (81.2%)	
Yes (n=187)	71 (38%)	116 (62%)		32 (17.1%)	155 (82.9%)	
Sarcopenia (Korean)			0.660			0.389
No (n=389)	165(42.4%)	224(57.6%)		74(19.0%)	315(81.0%)	
Yes (n=122)	49(40.2%)	73(59.8%)		19(15.6%)	103(84.4%)	
Obesity			0.258			0.439
No (n=335)	134 (40%)	201 (60%)		64 (19.1%)	271 (80.9%)	
Yes (n=176)	50 (45.5%)	96 (54.5%)		29(16.5%)	147 (83.5%)	
Visceral obesity			0.858			0.029
No (n=264)	112 (42.4%)	152 (57.6%)		58 (22%)	206 (78%)	

Yes (n=247)	102 (41.3%)	145 (58.7%)		35 (14.2%)	212 (85.8%)	
Sarcopenic obesity			1.000			0.038
No (n=398)	167 (42%)	231 (58%)		80 (20.1%)	318 (79.9%)	
Yes (n=113)	47 (41.8%)	66 (58.4%)		13 (11.5%)	100 (88.5%)	

Associations between VO, SO and total regression were evaluated in the inflammatory status subgroups (NLR groups). In the non-inflammatory state (NLR <3), neither VO nor SO showed any correlation with the PCRT response. In the inflammatory status patients however (NLR ≥ 3), total regression was significantly less achieved in patients with VO (p=0.044). SO was also showed less total regression although statistical significance was not achieved (Table 5).

Table 5. Association between visceral obesity, sarcopenic obesity and total regression according to the inflammatory status (NLR)

	Variable	**Total regression**	**Residual disease**	**P**
NLR <3	**Visceral obesity**			0.145
	No (n=183)	41 (22.4%)	142 (77.6%)	
	Yes (n=179)	29 (16.2%)	150 (83.6%)	
	Sarcopenic obesity			0.162
	No (n=276)	58 (21%)	218 (79%)	
	Yes (n=86)	12 (14%)	74 (86%)	

	Visceral obesity			0.044
	No (n=81)	17 (21%)	64 (79%)	
	Yes (n=68)	6 (8.8%)	62 (91.2%)	
NLR≥3	**Sarcopenic obesity**			0.078
	No (n=122)	22 (18%)	100 (82%)	
	Yes (n=27)	1 (3.7%)	26 (96.3%)	

*NLR, neutrophil—lymphocyte ratio

Association of body composition with oncologic outcomes.

Of the 1,384 patients in the total cohort, 292 (21.1%) developed disease recurrence. The median time to recurrence was 60.0 months (interquartile range, 26.1-70). In univariate and multivariate analysis, a high NLR resulted in a significantly poorer RFS (HR, 1.718; 95% CI, 1.343-2.165). Sarcopenia determinations using the Western, Japanese and Korean criteria were independently analyzed to check for an association with RFS outcomes. Body composition was not found to be associated with a poorer RFS (Table 6, Table 7).

Table 6. Risk factors associated with recurrence free survival (n=1384, recurrence=292)

Variables	**Univariate analysis**		**Multivariate analysis**	
	Hazard Ratio (95%CI)	***p***	**Hazard Ratio (95%CI)**	***p***
Sarcopenic obesity				
No	1			
Yes	1.026 (0.778-1.351)	0.858		
Sarcopenia *				
Sarcopenia (Korean)	0.967 (0.739-1.267)	0.809		

Sarcopenia (Western)	1.001 (0.784-1.278)	0.992		
Sarcopenia (Japanese)	0.942 (0.743-1.193)	0.619		
Visceral obesity				
No	1			
Yes	0.934 (0.742-1.174)	0.557		
Obesity				
No (BMI <25)	1			
Yes (BMI ≥25)	0.851 (0.664-1.092)	0.205		
Age, yrs				
<65	1			
≥65	0.967 (0.752-1.242)	0.790		
Stage				
Stage 0-Ⅱ	1		1	
Stage Ⅲ	3.334 (2.64-4.21)	0.000	3.547 (2.803-4.488)	0.000
Gender				
Male	1			
Female	0.932 (0.732-1.186)	0.566		
PCRT				
No	1		1	
Yes	1.573 (1.25-1.978)	0.000	1.671 (1.318-2.118)	0.000
NLR				
Low	1		1	
High	1.961 (1.527-2.518)	0.000	1.753 (1.357-2.266)	0.000

BMI, body mass index; PCRT, preoperative chemoradiotherapy; NLR, neutrophil-lymphocyte ratio *Control groups under each set of criteria comprised non-sarcopenic cases

Table 7. Risk factors associated with recurrence-free survival: independent analysis using various criteria for sarcopenia (n=1384; deaths=292)

Variables	Crude		Adjusted*	
	Hazard Ratio (95%CI)	***p***	**Hazard Ratio (95%CI)**	***p***
Sarcopenic obesity				
No	1		1	
Yes	1.026 (0.778-1.351)	0.858	1.101 (0.835-1.451)	0.494
Sarcopenia				
Sarcopenia(Korean)	0.967 (0.739-1.267)	0.809	0.923 (0.703-1.21)	0.561
Sarcopenia(Western)	1.001 (0.784-1.278)	0.992	0.913 (0.714-1.167)	0.469
Sarcopenia(Japanese	0.942 (0.743-1.193)	0.619	0.921 (0.727-1.168)	0.499

*adjusted for BMI, age, stage, sex, and NLR

In univariate analysis, sarcopenia (all criteria), SO, and obesity (BMI ≥25), showed an association with overall survival. Determinations of sarcopenia under each set of criteria were independently checked for any association with overall survival, adjusted for BMI, age, stage, sex, and NLR. Among these body composition parameters, SO and obesity were confirmed as associated factors with overall survival with age, stage, sex, and NLR in multivariate analysis (Tables 8 and 9). Obesity was included in the model and we checked for multicollinearity using variance inflation factor and condition index and found it to be acceptable.

Table 8. Risk factors associated with overall survival (n=1384;deaths =339)

Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95%CI)	***p***	**Hazard Ratio (95%CI)**	***p***
Sarcopenic obesity				
No	1		1	
Yes	1.332 (1.043-1.702)	0.022	1.396 (1.068-1.824)	0.015
Sarcopenia *				
Sarcopenia (Korean)	1.496 (1.187-1.886)	0.001		
Sarcopenia (Western)	1.415 (1.115-1.796)	0.004		
Sarcopenia (Japanese)	1.286 (1.036-1.595)	0.022		
Visceral obesity				
No	1			
Yes	0.942 (0.761-1.166)	0.582		
Obesity				
No (BMI <25)	1		1	
Yes (BMI ≥25)	0.682 (0.536-0.868)	0.002	0.639 (0.494-0.828)	0.001
Age, yrs				
<65	1		1	
≥65	2.113 (1.702-2.622)	0.000	2.205 (1.762-2.76)	0.000
Stage				
Stage 0-Ⅱ	1		1	
Stage Ⅲ	2.664 (2.151-3.301)	0.000	3.066 (2.468-3.809)	0.000
Gender				
Male	1		1	
Female	0.788 (0.625-0.993)	0.043	0.787 (0.624-0.992)	0.043
PCRT				
No	1			
Yes	1.091 (0.879-1.355)	0.430		

NLR				
Low	1		1	
High	2.222 (1.769-2.79)	0.000	2.187 (1.739-2.75)	0.000

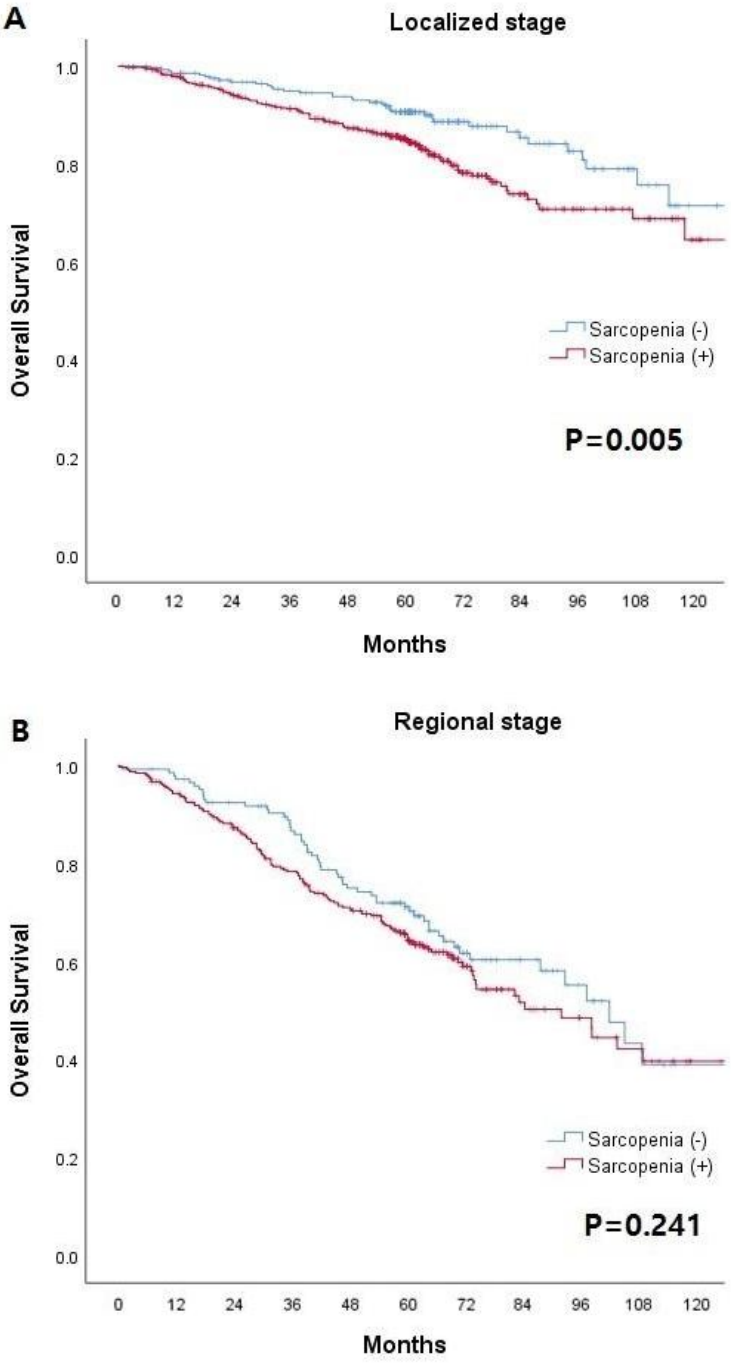
BMI, body mass index PCRT, preoperative chemoradiation therapy NLR, neutrophil-lymphocyte ratio

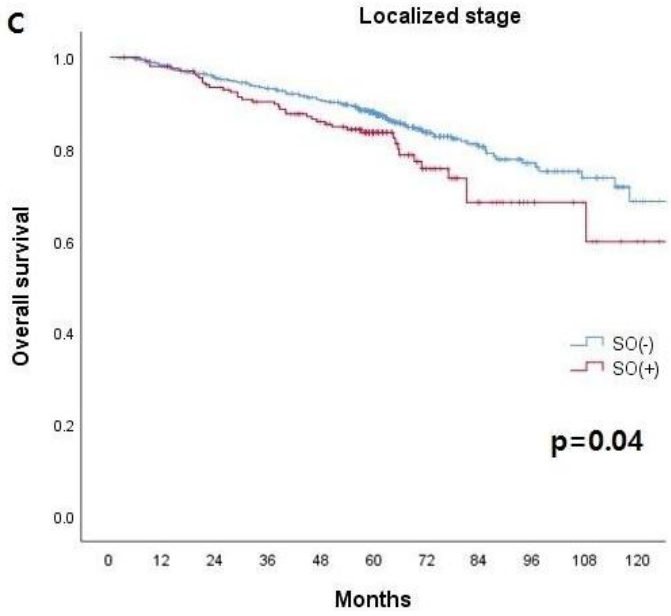
*Control groups under each set of criteria comprised non-sarcopenic cases

Subgroup analysis I: Influence of sarcopenia and sarcopenic obesity on overall survival according to stage and inflammatory status

Oncologic outcomes according to sarcopenia and SO were analyzed in accordance with the staging or inflammatory status. For patients at the localized stage (Stage 0-), the OS was significantly decreased in the cases with sarcopenia (p=0.005), whereas no such difference was observed in the OS outcomes among the patients with a regional stage cancer (Stage) (p=0.241) (Figure 3). Similarly, the patients with SO had a significantly poorer survival rate if they had a localized stage but there was no statistical difference in this regard for regional stage cases (p=0.04; p=0.07 respectively). In patients with a non-inflammatory state (NLR<3), both sarcopenia and SO were associated with a decreased OS (p=0.014; p=0.006) whereas in cases showing an inflammatory state neither sarcopenia nor SO affected the OS (Figure 4).

Figure 3. Association between overall survival (OS) and sarcopenia, sarcopenic obesity (SO) according to pathologic stage. Influence of sarcopenia in (A) localized stage and (B) regional stage patients. Association between SO and OS in (C) localized stage and (D) regional stage patients.




C
Localized stage
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Months
SO(-)
SO(+)
p=0.04

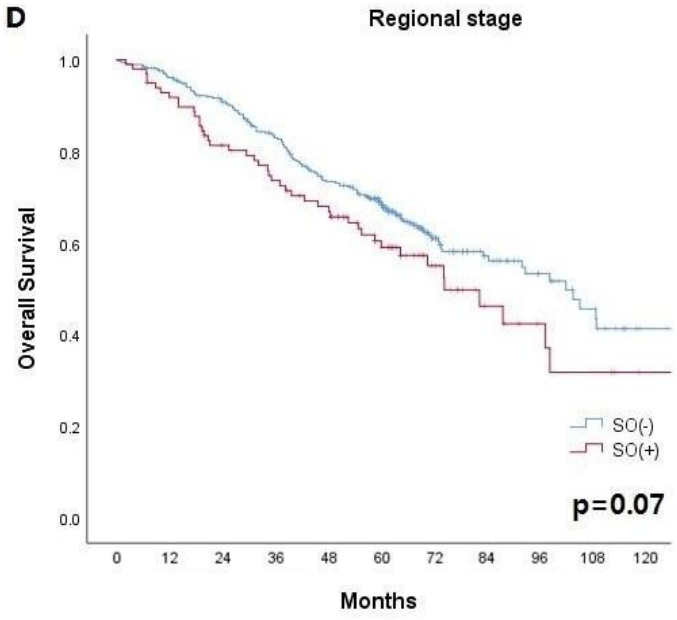
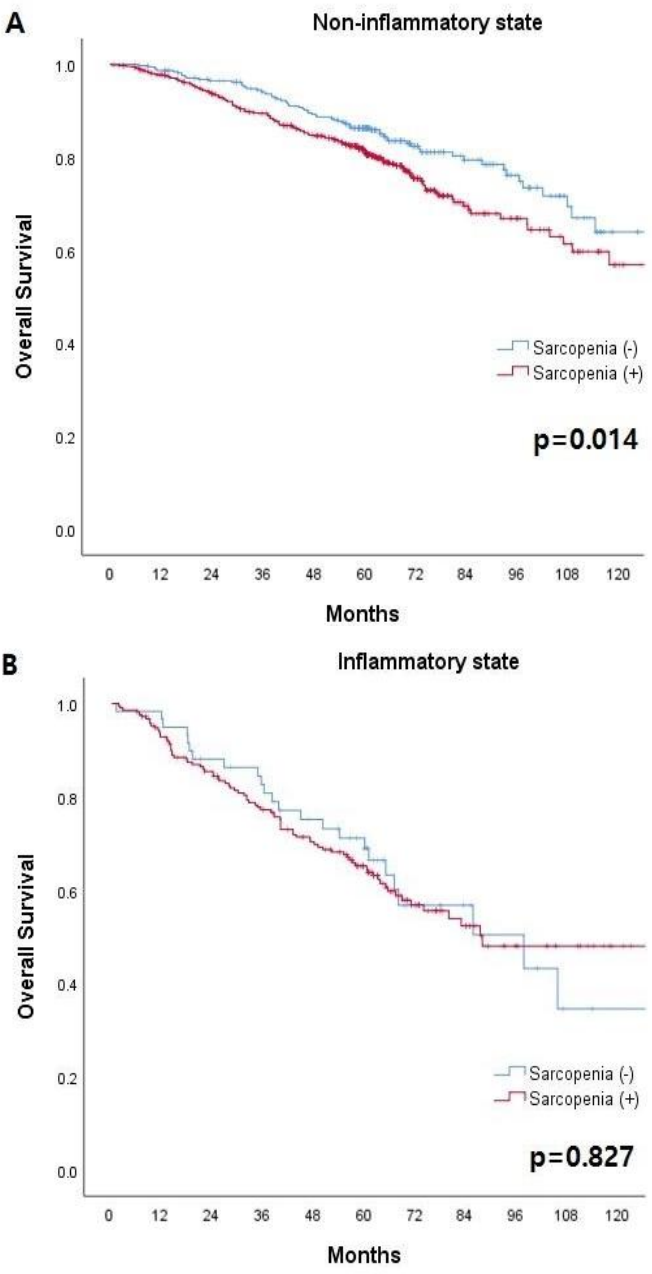
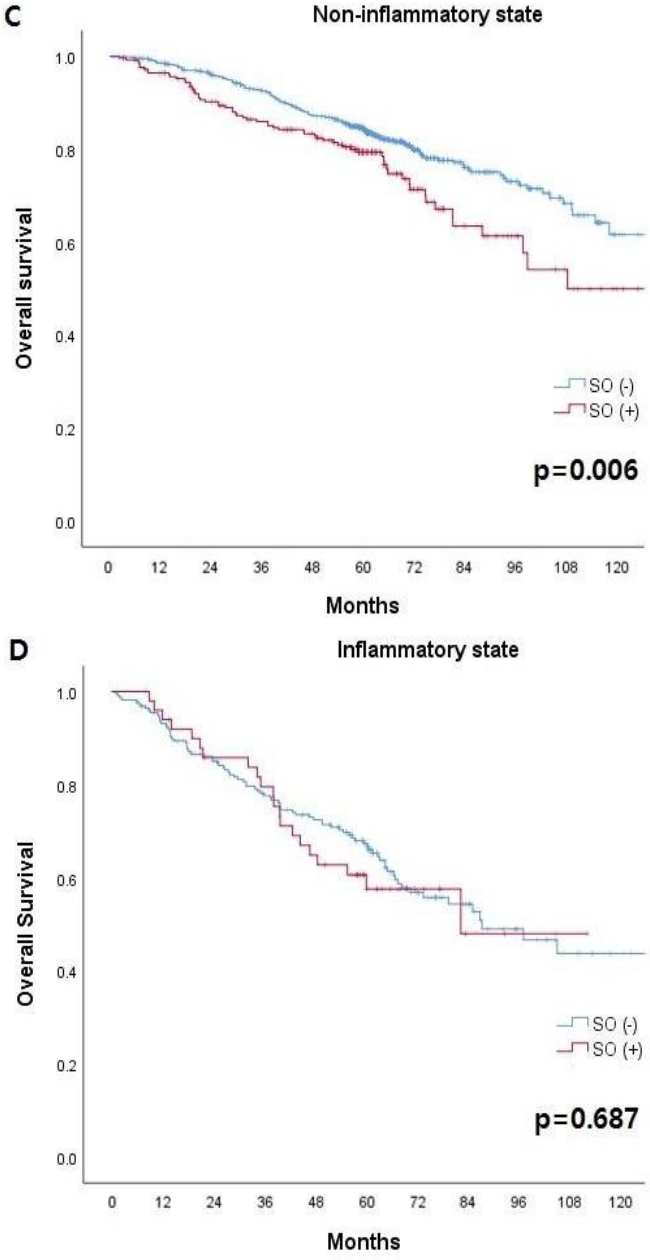

D
Regional stage
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Months
SO(-)
SO(+)
p=0.07

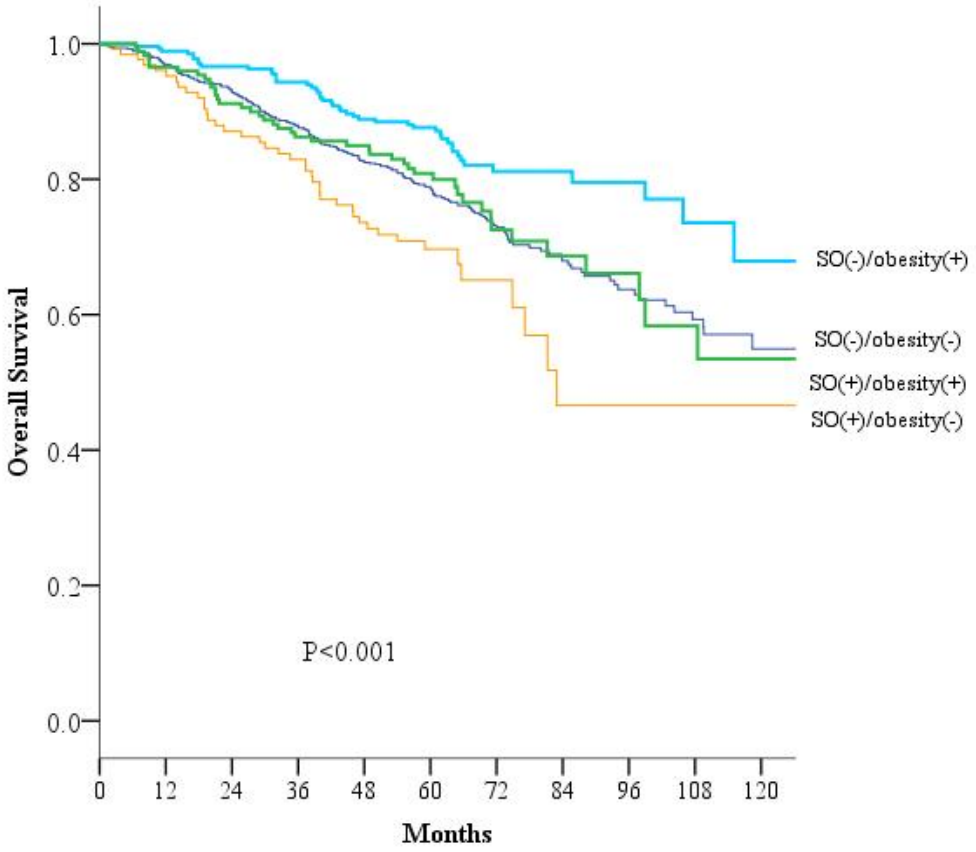
Figure 4. Association between overall survival (OS) and sarcopenia, sarcopenic obesity (SO) according to the inflammatory status of the patient. Influence of sarcopenia in cases with a (A) non-inflammatory and (B) inflammatory status. Association between SO and OS in patients with a (C) non-inflammatory and (D) inflammatory status.




C
Non-inflammatory state
Overall survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Months
SO (-)
SO (+)
p=0.006
D
Inflammatory state
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
12
24
36
48
60
72
84
96
108
120
Months
SO (-)
SO (+)
p=0.687

SO and no obesity were confirmed as independent risk factors for OS in Cox regression analysis. Hence, the combined influence of SO and obesity on OS outcomes was evaluated. We categorized patients into four groups in accordance with SO and/or obesity i.e. SO(+)/obesity (+), SO(+)/obesity (-), SO(-)/obesity (+), and SO(-)/obesity (-) (Fig 5). The SO(+)/obesity(-) patients showed the poorest OS among these four groups (P<0.001). Patients with either the SO or obesity (-) risk factor did not show differences in OS.

Figure 5. Combined influence of SO and obesity on overall survival (OS). The OS rate was significantly lower in SO(+)/obesity(-) cases.



Discussion

Our current study findings have indicated that SO, low BMI, and an inflammatory status are independent negative prognostic factors for OS. Furthermore, our subgroup analysis demonstrated that the association between OS and SO was more prominent in patients without lymph node metastasis or with no inflammatory status. We analyzed the long-term outcomes of SO in our current rectal cancer patient series and were able to observe the effects of current practical treatment settings on survival outcomes by including the patients who had undergone PCRT, which has recently become a standard therapy for rectal cancer, and by considering combined treatment effects.

SO has been reported as an associated factor for OS outcomes in some solid tumors. In a prior retrospective study of patients with pancreatic cancer, the OS and RFS rates in patients with SO were significantly lower than those in patients with a low visceral to subcutaneous fat ratio.[11] A cross-sectional study has further found that SO in patients with solid tumors of the respiratory tract, colon or rectum was associated with a significantly poorer survival outcome and these authors described SO as an independent predictor of survival.[8] In a study of pancreatic cancer, SO showed a close association with mortality and recurrence after resection.[11]

Studies on the association between body composition and long-term outcomes in colorectal cancer have shown inconsistent results. Sarcopenia has been reported as a risk factor for worse OS in some reports,[21-23] but, its influence on RFS has varied in different studies,[21, 22] Some studies in colorectal cancer that evaluated the influence of both body fat and skeletal muscle mass on oncologic outcomes have indicated that SO is an independent predictor of poorer outcomes.[8, 22, 30, 31] Another recent study analyzed sarcopenia and systemic inflammation together and reported that these are independent factors for a decreased OS and RFS and are predictors of a higher risk of poor survival if found in combination.[23] That

study further discussed the effects of sarcopenia in concert with systemic inflammation on survival.

The exact mechanism of how body composition (such as sarcopenia and SO) affects the survival of cancer patients remains unknown. Systemic inflammation might be a possible explanation.[23] A systemic inflammatory condition is known to increase the risk of cancer[32] and reduce a patient's response to treatment.[33] Sarcopenia and systemic inflammation are further known to be correlated and this relationship would be substantial in obese patients who were defined as having SO.[24] Other possible explanations of how SO is independently related to mortality and morbidity might be the associations between immunity, inflammation, and myokines and adipocytokines.[24, 34, 35] Myokines play a pivotal role in cancer prevention as mediators of the beneficial effects of physical activity, counteracting the harmful effects of pro-inflammatory adipokines.[36, 37] SO may be a condition that causes a worsening of the cytokine imbalance.

Our present subgroup analysis indicated an OS difference in SO patients, which was more pronounced in patients without lymph node metastasis or with no inflammatory status. This supports the possibility that systemic inflammation is a mechanism in which SO affects cancer survival. It may be possible that a severe inflammatory state itself has the principal negative effect on survival and that SO worsens this risk but relatively weakly. Although a non-inflammatory state accompanies SO, it might still progress into the aforementioned vicious cycle, exacerbate systemic inflammation, and thus have a relatively larger negative impact on survival. Since the advanced stage of CRC is also associated with a high inflammatory state,[38, 39] the effects of stage without lymph node metastasis can possibly be explained in a manner similar to the no inflammatory state. Further studies will be needed to elucidate these possibilities.

In our current analyses, SO was associated with OS but not RFS. Obese patients are more likely to be affected by hypertension, diabetes, cardiac disease, and metabolic syndrome, and

these conditions are usually associated with increased morbidity and mortality. Therefore, it was suspected that the adverse effects of SO on OS might be associated with medical co-morbidities rather than an effect of SO itself. In our analyses, however, we used CT-measured parameters for the definition of SO and not the combination of obesity and sarcopenia. Indeed, obesity itself was found to be associated with a better OS in our present findings. Hence, the negative effect of SO on OS was not considered to be principally due to medical co-morbidities. An inflammatory status was the most potent associated factor in terms of both RFS and OS outcomes in our cohort. The impact of SO on OS differed in degree in accordance with the inflammatory status in our current patient series. Therefore, SO might be associated with OS through inflammation-related processes. The mechanism of how SO is associated with OS in colorectal cancer needs to be studied further.

Whilst many studies support the negative impacts of sarcopenia and SO, it is of interest that Lodewick et al. found that neither condition affected postoperative complications or long-term outcomes. These authors pointed out that because of differences in the proportion of sarcopenia or SO patients, depending on the cut off value setting, prior studies that reported increased morbidity and worse long term outcomes were likely to have underestimated sarcopenia and may have selected patients with severe muscle wasting.[40] Depending on the cut off setting, the definition of sarcopenia or sarcopenic obesity may change, which may affect the survival analysis results. In our current study series, various cut-offs were applied in consideration of the above possibilities. The reason why the sarcopenia group in accordance with the Japanese criteria was relatively high in proportion to female patients was because the SMI cut off value for women is higher in this system, and that for men is lower, in comparison to Western criteria. Our application of the Korean criteria resulted in a much lower proportion of sarcopenic cases (25.4%) compared with the use of Western (68.2%) and Japanese (60.3%) systems. This suggests that due to ethnically dependent differences in muscle mass and fat distribution, appropriate reference points are needed for cohorts of different nationalities rather than applying standardized cut off values. Treatment

strategies should also therefore be customized to the characteristics of the patient group.

Previous studies have focused primarily on the effects of body composition and systemic inflammation on postoperative complications and survival in cancer patients. Our present study is the first to show an association between body composition and the PCRT response in rectal cancer. We found that the PCRT response was significantly poorer in patients with VO or SO. In particular, the PCRT response was significantly worse when both inflammation and visceral obesity were present. The presence of SO in an inflammatory state was not statistically significant, but it might have affected the PCRT response clinically. The number of patients with an NLR $\geq$ 3 and SO was 27, which was too small to test for statistical significance. Ota et al. have reported that the presence of sarcopenia prior to neoadjuvant chemotherapy in esophageal cancer is an independent predictor of a poor pathologic response.[41] Anandavadivelan et al. also reported in sarcopenic and SO patient populations with esophageal cancer had a five-fold higher risk of developing dose limiting toxicity during cycle 1 chemotherapy.[42] In breast cancer and renal cell carcinoma, studies have shown that sarcopenia can increase chemotoxicity by two- to six-fold.[7, 43] Sarcopenia may reflect the increased metabolic activity of a biologically more aggressive tumor.[44] Inflammation, cytokines, myokines, and other process have all been found to play a role in the development and progression of sarcopenia. As skeletal muscle mass decreases and adipose tissue increases, a shift from anti-inflammatory cytokine production towards pro-inflammatory cytokine production occurs.[41] This pro-inflammatory state is thought to contribute to the potential for increased chemoradiation toxicities.[45] Poor pathologic responses may have been related to reduced dose or a delayed treatment schedule due to higher dose limiting toxicity.[46]

To our knowledge, our present investigation is the largest study to date to focus on the clinical effects of body composition on the treatment response and long-term prognosis of patients with rectal cancer. Most previous studies on the effects of sarcopenia in cancer

patients have adopted the cut-off value defined by Prado et al. (sarcopenia in women, SMI < 38.5 cm2/m2, sarcopenia in men, SMI <52.4 cm2/m2).[19, 22, 23, 30, 47] In our current report, we not only applied the previously proposed western criteria but also considered the characteristics of our cohort with a relatively large number of cases So, this study can support the prognostic value of SO in an Asian population.

There were some limitations to our study of note. In the first instance, it was a retrospective cohort study and the possibility of unknown confounders existed. In addition to cancer, sarcopenia can also be affected by age, comorbidities, and physical activity. We could not assess these effects using only electronic medical records. In addition, we analyzed the effects of body mass composition parameters and inflammation based on single measurements prior to treatment and were unable to examine postoperative changes over time. Furthermore, since our analyses were retrospective in nature and we had to use medical records to determine the inflammatory state, our analysis of the effects of inflammatory markers was limited. Notwithstanding these limitations however, we enhanced the reliability of our data through the use of a larger-scale cohort that ensured greater statistical power. We thus believe that we have provided valid early study findings on the possibility of using SO as a prognostic factor in rectal cancer patients.

Conclusion

In conclusion, SO, low BMI, and an inflammatory status are independent negative prognostic factors for OS in rectal cancer patients. Patients with VO or SO also have a poor PCRT response. These findings suggest the potential utility of body composition assessments when conducting PCRT patient selection strategies. Pre-evaluations and a correction of SO and VO may be valid strategies to improve PCRT responses and OS. Future studies are

needed to verify whether nutritional intervention can improve survival or the efficacy of PCRT.

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국문요약

연구목적

신체 구성비는 컴퓨터 단층촬영 영상을 통해 쉽게 얻을 수 있고 교정이 가능하다. 비만, 근육감소증과 같은 신체 구성비 변수들이 심혈관계질환, 만성 폐쇄성 호흡기질환 및 대사질환에서 이환율 또는 사망률과 관계가 있다는 내용들이 다수 보고되고 있고 최근 암 환자에서도 근육감소증이 중요한 예후 예측 인자임이 발표 되고 있다. 본 연구에서는 원격 전이를 동반하지 않은 직장암 환자에서 신체 구성비가 수술 전 항암화학요법 치료 반응에 영향을 미치는 지 여부와 장기적인 생존율에 미치는 영향에 대해 평가하였다.

연구 방법

서울아산병원에서 2005년 1월부터 2012년 12월까지 근치적 절제술을 받았던 0-III기 직장암 환자 1,384을 연구 대상으로 하였다. 진단 당시 시행한 컴퓨터 단층촬영 (CT) 영상에서 Asan-J software를 통해 신체 구성비를 측정하였다. L3 요추 위치에서 선택된 축상 이미지상의 모든 근육을 포함한 총 복부 근육 면적을 CT상의 HU에 대한 미리 결정된 임계 값 또는 신호 강도를 사용하여 경계를 정했다. CT 영상에서 측정된 변수 - 골격근 지수, 내장 지방 면적, 내장 지방 면적/총 복부 근육 면적 값에 따라 근육 감소증, 내장 비만 (VO), 근육 감소를 동반한 비만 (SO)을 정의하였다. 골격근지수는 총 복부 근육 면적/신장^2 으로 계산하였다. 근육감소증은 골격근 지수 수치에 따라 3가지 기준을 각각 적용하여 분석하였다. 내장 비만은 내장 지방 면적이 100 cm^2 이상인 경우로 정의하였고, 근육 감소를 동반한 비만은 내장 지방 면적/총 복부 근육 면적비가 3.2 이상인 경우로 정의하였다. 호중구-림프구 비가 3 이상인 경우는 전신적인 염증을 동반한 상태로 정의하였다. 체질량 지수가 25 kg/m^2 이상인 환자는 비만으로 분류하였다. 수술 전 항암화학요법에 대한 병리조직학적 반응성은 암 세포와 섬유화의 비율에 따라 평가하였다.

연구 결과

1,384 명의 직장암 환자들 중 894 (64.6%) 명은 림프절 전이가 없었고 943 (68.2%) 명은 림프절 전이가 있다. 수술 전 항암화학요법을 받은 환자들은 536 (38.7%) 였다. 적용 기준에 따라 943 (68.2%), 834(60.3%), 215(25.4%) 명이 근육감소증으로 분류되었다. 307 (22.2%) 는 근육감소증을 동반한 비만이었고 670 (48.4%)는 내장 비만이 있었다. 458 (33.1%) 체질량 지수가 25 이상인 비만 이었다. 278 (20.2%) 는 호중구-림프구비가 3 이상인 염증이 있는 상태로 평가 되었다. VO가 있는 환자와 (20.1%, p=0.029) SO가 있는 환자에서 (11.5%, p=0.038) 수술 전 항암화학요법 치료 후 완치율이 통계적으로 유의하게 낮았다. 근육감소증을 동반한 비만 환자에서 5년 생존율이 유의하게 낮았으나 (84% vs. 78%, p=0.02) 5년 재발 없는 생존기간에는 차이가 없었다 (77.3% vs. 77.9% p=0.957). 근육감소증, 근육감소증이 동반된 비만, 내장 비만, 그리고 비만 모두 RFS과는 연관성이 없었다. 다변량 분석에서 비만, SO, 나이, 성별, 염증 상태, 그리고 병기는 전체 생존율에 영향을 미치는 독립적인 예후 예측인자로 나타났다. 병기 또는 염증상태에 따른 하위 그룹 분석에서 근육감소증을 동반한 비만과 전체 생존율의 연관성은 병기가 0-2기이고 염증이 없는 상태의 환자에서 더욱 뚜렷하게 나타났다.

결론 및 제언

원격 전이를 동반하지 않은 직장암 환자에서 SO와 낮은 체질량지수는 전체 생존율에 부정적인 영향을 미친다.

Key words: 직장암, 신체 구성비, 근육감소증, 비만, 전체 생존율