ASTR

ORIGINAL ARTICLE
pISSN 2288-6575 • eISSN 2288-6796
https://doi.org/10.4174/astr.2020.99.3.153
Annals of Surgical Treatment and Research

Clinical impact of sarcopenia in patients with colon cancer undergoing laparoscopic surgery

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Purpose: Previous studies have reported that progressive muscle loss, known as sarcopenia, has a negative impact on colon cancer treatment. However, the majority of studies have analyzed on patients undergoing open resection, and the association of sarcopenia with clinical outcomes is not clear for patients with colon cancer undergoing laparoscopic surgery. Thus, the aim of this study was to evaluate the impact of sarcopenia on clinical outcomes after laparoscopic surgery for colon cancer.
Methods: A total of 423 patients who underwent laparoscopic surgery for colon cancer between November 2010 and October 2014 were included. Body composition was assessed by measuring muscle and fat areas at the third lumbar vertebra (L3) on preoperative computed tomography. The L3 skeletal muscle area was used to calculate the skeletal muscle index and to assess for sarcopenia.
Results: Sarcopenia was identified in 54 patients (12.8%). The median time to first flatus (3 days), median time to tolerable soft diet (4 days), and median length of hospital stay (7 days) were not significantly different between patients with and without sarcopenia. However, sarcopenia was an independent risk factor for postoperative complications in the logistic regression multivariate analysis (P = 0.015). Sarcopenia was not associated with overall or disease-free survival.
Conclusion: Sarcopenia was not negatively associated with functional recovery, hospital stay, and oncologic outcomes in patients with colon cancer who underwent laparoscopic surgery. However, sarcopenia was associated with postoperative complications after laparoscopic surgery for colon cancer.
[Ann Surg Treat Res 2020;99(3):153-160]

Key Words: Colonic neoplasms, Laparoscopy, Prognosis, Sarcopenia

INTRODUCTION

Frailty is defined as a biological syndrome characterized by decreased reserve and resilience to stress factors across multiple physiological systems, and has been shown to be associated with adverse health outcomes [1]. A hallmark of frailty is sarcopenia, defined as the involuntary, progressive, and generalized loss of skeletal muscle mass with aging [2]. Sarcopenia has been known to have a negative impact on surgical complications and survival [3,4]. These negative impacts have also been noted in patients with colorectal cancer [5-7].

In colorectal cancer surgery, abdominal CT is routinely performed for staging work-up. In addition, abdominal CT imaging enables evaluation of patients' body composition and allows for identification of sarcopenia [7,8]. Sarcopenia was defined by using sex-specific cut-off points for the third lumbar vertebra (L3) skeletal muscle index (SMI). L3 level is used for evaluating sarcopenia due to its accuracy reflecting the real muscle mass and fat volume [3]. So far, previous studies regarding colorectal resection have demonstrated that

Received May 6, 2020, **Revised** June 19, 2020, **Accepted** July 16, 2020

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sarcopenia has a negative impact on postoperative morbidity and survival [5-9]. However, these studies included mostly patients undergoing open resection and those with metastases.

Recently, laparoscopic surgery has been used worldwide since the oncologic stability and clinical benefits were reported by several international, multicenter, randomized, and controlled trials [10-12]. However, few studies have investigated the association of body composition with clinical outcomes after laparoscopic colorectal surgery. One previous study showed that laparoscopic surgery could reduce the negative impact of sarcopenia on short-term outcomes in patients with colorectal cancer, contrary to traditional open surgery [13]. However, the study only evaluated perioperative outcomes and did not assess oncologic results.

The aim of this study was to analyze the preoperative CT images of patients who underwent laparoscopic surgery for colon cancer, and to analyze the impact of sarcopenia on short-term and oncologic outcomes after laparoscopic surgery.

METHODS

Patients

This retrospective study was approved by the Institutional Review Board (IRB) of Chungnam National University Hospital (NO. 2018-05-002) and the informed consent was waived by IRB. The medical records and preoperative CT images of patients who underwent laparoscopic surgery for colon cancer with curative intent between November 2010 and October 2014 at our institution were reviewed retrospectively. Exclusion criteria were as follows: (1) distant metastases at initial diagnosis, (2) previous radiotherapy or chemotherapy, (3) no available CT examination at initial diagnosis, and (4) conversion to open surgery. Nine patients were converted to open surgery because of duodenal invasion during right hemicolectomy (n = 2), huge tumor size (n = 3), and uncontrolled bleeding (n = 4).

Preoperative work-up included a complete history taking, a physical examination, complete blood count, liver function tests, colonoscopy, and CT scanning. Curative laparoscopic surgery was performed after mechanical bowel preparation and followed the principle of primary tumor excision. The completeness of resection was defined based on the operative and pathologic reports. All operative specimens had negative gross and microscopic margins.

Body composition analysis

Contrast-enhanced abdominal CT scan was performed as routine staging work-up. One axial portal-phase image at the level of L3 was analyzed by a radiologist using commercial imaging software (TeraRecon Aquarius Workstation, TeraRecon, Foster City, CA, USA). According to the different Hounsfield units radiodensities of different tissue types, the software automatically calculates the skeletal muscle area (–29 to +150), abdominal fat area (–50 to –150), and subcutaneous fat area (–190 to –30) (Figs. 1 and 2) [14]. The SMI was calculated by dividing the muscle area (m^2) by the square of the patient's height (cm^2). Sarcopenia was defined as an SMI <41 cm^2/m^2 in women and <43 cm^2/m^2 in men with a body mass index (BMI) <25 kg/m^2, and <53 cm^2/m^2 in men with a BMI >25 kg/m^2 [15].

Outcome parameters

All patients were divided into 2 groups based on presence or absence of sarcopenia. Outcome measures included functional recovery parameters, length of hospital stay, postoperative complications, and survival data. Overall survival was defined

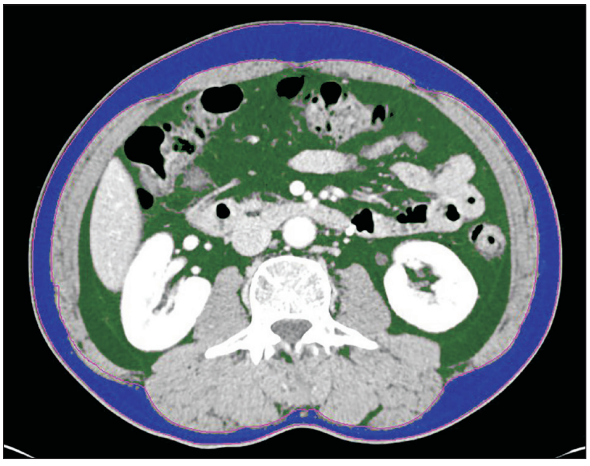

Fig. 1. Measurement of the subcutaneous and visceral adiposity. Axial computed tomography obtained at the level of the third lumbar vertebra showing the region colored blue represent the subcutaneous fat area and green represented the visceral fat area.

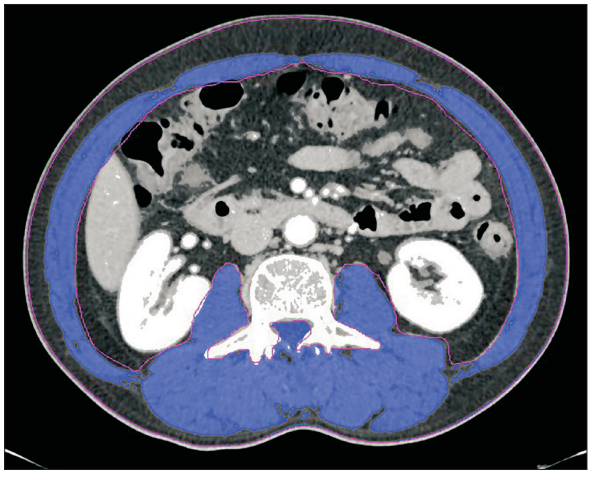

Fig. 2. Measurement of the skeletal muscle. Axial computed tomography obtained at the level of the third lumbar vertebra showing the region colored blue represent the skeletal muscle area.

as the time from surgery to death from any other causes or the last follow-up for alive status. Disease-free survival was defined as the time from surgery to the time of recurrence.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics ver. 24.0 (IBM Corp., Armonk, NY, USA). The Mann-Whitney test was used for continuous parameters and a chi-squared test and/or Fisher exact test for categorical parameters were utilized for comparison of the differences between the 2 groups. Univariate logistic regression analyses for postoperative complications was performed to assess the influence on outcomes. Sex, BMI, sarcopenia, and laboratory parameters potentially predictive of postoperative complications were entered into multivariate logistic regression analyses. Univariate overall and disease-free survival rates were calculated using the Kaplan-Meier method, while multivariate overall and disease-free survival rates were calculated using Cox regression analysis. A P-value of <0.2 was adopted as the limit for inclusion of a covariant. A P-value of <0.05 was considered statistically significant.

RESULTS

A summary of the demographics characteristics of patients with and without sarcopenia is shown in Table 1. Fifty-four patients had sarcopenia, while 369 patients did not. No significant differences were observed regarding age, sex, BMI, or presence of comorbidities between groups. Type of operation, histology, T and N stage, and pathologic stage were also similar between groups. Table 2 summarizes the differences in the variables between patients with and without sarcopenia. The skeletal muscle area was smaller in patients with sarcopenia, whereas the subcutaneous fat area was not different between groups in body composition analysis. It is noteworthy that functional recovery parameters, such as median time to first flatus (3 days), median time to tolerable soft diet (4 days), and median length of hospital stay (7 days) were not significantly different between the 2 groups. However, there were 46 patients (12.5%) without sarcopenia and 15 patients (27.8%) with sarcopenia who developed postoperative complications (P = 0.006). In particular, complications of Clavien-Dindo classification III were more frequent in patients with sarcopenia (P = 0.001). Types of complications according to presence or absence of sarcopenia are described in detail in Table 3.

Clinical factors predicting postoperative complications

Table 4 identified potentially related factors predicting postoperative complications. Univariate logistic regression analyses showed that low BMI (P = 0.036), sarcopenia (P = 0.004), lower hemoglobin (P = 0.025), lower albumin (P = 0.005), and higher carcinoembryonic antigen level (P = 0.007) were significant factors associated with postoperative complications. Sarcopenia remained the most significant factor related to postoperative complications after multivariate regression analyses (P = 0.015).

Table 1. Demographic analysis of patients according to sarcopenia

Characteristic	Sarcopenia		
	No (n = 369)	Yes (n = 54)	P-value
Age (yr)			0.657
<65	151 (40.9)	20 (37.0)	
≥65	218 (59.1)	34 (63.0)	
Sex			0.285
Male	235 (63.7)	39 (72.2)	
Female	134 (36.3)	15 (27.8)	
Body mass index (kg/m^2)			0.169
<25	235 (63.7)	40 (74.1)	
≥25	134 (36.3)	14 (25.9)	
Presence of comorbidities			>0.999
No	174 (47.2)	25 (46.3)	
Yes	195 (52.8)	29 (53.7)	
Type of operation			0.294
Right hemicolectomy	93 (25.2)	19 (35.2)	
Transverse colectomy	5 (1.4)	1 (1.9)	
Left hemicolectomy	34 (9.2)	2 (3.7)	
Anterior resection	237 (64.2)	32 (59.3)	
Histology			0.230
WD/MD	343 (93.0)	53 (98.1)	
PD/mucinous	26 (7.0)	1 (1.9)	
Pathologic T stage			0.097
T1–2	140 (37.9)	14 (25.9)	
T3–4	229 (62.1)	40 (74.1)	
Pathologic N stage			0.879
N0	239 (64.8)	34 (63.0)	
N positive	130 (35.2)	20 (37.0)	
Pathologic TNM stage			0.195
I	121 (32.8)	12 (22.2)	
II	118 (32.0)	23 (42.6)	
III	130 (35.2)	19 (35.2)	
Adjuvant chemotherapy			0.661
No	165 (44.7)	22 (40.7)	
Yes	204 (55.3)	32 (59.3)	

Values are presented as number (%).
WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

Survival analysis

After a median follow-up of 48.7 months, the 5-year overall survival and disease-free survival rates, respectively, were in 85.9% and 93.7% in patients without sarcopenia, and 72.8% and 88.1% in patients with sarcopenia (P = 0.120 and P = 0.112, respectively). According to univariate analysis of factors affecting overall survival and disease-free survival, age (≥65

Table 2. Clinical characteristics according to sarcopenia

Characteristic	Sarcopenia		
	No (n = 369)	Yes (n = 54)	P-value
Area of skeletal muscle (cm^2)	145.0 (89.6–227.0)	120.0 (72.8–156.0)	<0.001
Area of subcutaneous fat (cm^2)	10.9 (2.4–70.3)	10.5 (3.9–50.3)	0.176
Level of hemoglobin (g/dL)	13.1 (7.3–17.8)	12.7 (6.1–16.6)	0.190
Level of albumin (g/dL)	4.1 (2.5–5.1)	4.1 (2.87–4.8)	0.184
Level of CEA (ng/mL)	3.0 (0.5–99.4)	2.4 (0.5–48.9)	0.078
Time to first flatus (day)	3.0 (1.0–13.0)	3.0 (1.0–11.0)	0.840
Time to tolerable soft diet (day)	4.0 (2.0–16.0)	3.0 (2.0–16.0)	0.437
Length of hospital stay (day)	7 (3–50)	7 (5–154)	0.159
Postoperative complications	46 (12.5)	15 (27.8)	0.006
Clavien-Dindo classification, III–IV	7 (1.9)	5 (9.3)	0.001

Values are presented as median (range) or number (%).

Table 3. Types of complications according to sarcopenia

Complication	Sarcopenia		P-value
	No (n = 369)	Yes (n = 54)	
Surgical site infection	10 (2.7)	3 (5.6)	0.223
Postoperative ileus	14 (3.8)	2 (3.7)	>0.999
Postoperative bleeding	2 (0.5)	0 (0.0)	>0.999
Chyle drainage	1 (0.3)	1 (1.9)	0.239
Bladder dysfunction	6 (1.6)	0 (0.0)	>0.999
Intraabdominal abscess	2 (0.5)	3 (5.6)	0.016
Anastomotic leakage	5 (1.4)	0 (0.0)	>0.999
Intestinal obstruction	2 (0.5)	2 (3.7)	0.081
Cardiovascular	2 (0.5)	2 (3.7)	0.081
Renal	1 (0.3)	0 (0.0)	>0.999
Pulmonary	1 (0.3)	2 (3.7)	0.239
Total	46 (12.5)	15 (27.8)	0.006

Values are presented as number (%).

years) and pathologic TNM stage were significant prognostic factors for overall survival, while pathologic TNM stage was also a significant factor for disease-free survival (Table 5). Multivariate analysis of these factors showed that older age (≥65 years, P = 0.003) was a significant predictor for overall survival, while pathologic TNM stage showed a tendency to negatively affect overall survival (P = 0.050). There was no significant independent factor for disease-free survival (Table 6).

DISCUSSION

Previous studies regarding colorectal resection have shown that sarcopenia has a negative impact on postoperative morbidity and prolonged length of hospital stay after colorectal surgery [5-9,16]. However, these studies included mostly patients undergoing open resection. One previous study evaluated the impact of sarcopenia on laparoscopic surgery for colorectal cancer, and reported that there was no negative impact of sarcopenia on treatment results [13].

So far, prospective, randomized, controlled trials comparing open surgery and laparoscopic surgery for colon cancer have demonstrated that laparoscopic surgery is more advantageous for reduced hospital stay and fast recovery [12,17,18]. Therefore, we postulated that laparoscopic surgery might eliminate the deleterious prognostic impact of sarcopenia with respect to not only short-term results, but also oncologic outcomes in patients with colon cancer. Indeed, in our study, sarcopenia did not affect functional recovery parameters (time to first flatus, time to tolerable soft diet, and length of hospital stay) after laparoscopic surgery. In particular, median length of hospital stay after surgery did not differ between patients with and without sarcopenia (7 days, P = 0.159). A similar study conducted by Pędziwiatr et al. [13] also showed that functional recovery after laparoscopic colorectal cancer surgery was similar regardless of presence or absence of sarcopenia. However, in our results, sarcopenia was revealed as an independent risk factor influenced postoperative complications (P = 0.015), even though demographic differences were not significant between groups. These results suggests that the amount of muscle of patients at the time of diagnosis is an important factor for short-term outcomes after laparoscopic surgery, whereas functional recovery may not be influenced by sarcopenia. Sarcopenia may associated with functional impairment and disability by affecting mobilization, impairing breathing, and decreasing physical performance [19]. The mechanism of sarcopenia is multifactorial. It can alter systemic inflammatory response, endocrine function, nutritional status, and insulin resistance [20]. These mechanisms may play a role increasing postoperative morbidity.

Although sarcopenia was negatively associated with postoperative complications, it did not affect oncologic outcomes after laparoscopic colon cancer surgery in our

Table 4. Univariate and multivariate analysis of clinical parameters affecting postoperative complications

Parameter	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Old age, ≥65 yr	1.2 (0.71–2.18)	0.454		
Male sex	1.6 (0.89–3.0)	0.114	1.8 (0.92–3.42)	0.086
Low BMI, <25 kg/m^2	2.0 (1.05–3.72)	0.036	1.6 (0.84–3.14)	0.148
Presence of comorbidity	1.2 (0.71–2.13)	0.455		
Sarcopenia	2.7 (1.38–5.28)	0.004	2.4 (1.19–4.84)	0.015
Histology, PD/mucinous	1.0 (0.35–3.10)	0.952		
TNM stage				
I	-			
II	2.0 (0.97–4.07)	0.600		
III	1.7 (0.82–3.48)	0.158		
Level of hemoglobin (g/dL)	0.9 (0.75–0.98)	0.025	0.9 (0.77–1.07)	0.247
Level of albumin (g/dL)	0.5 (0.26–0.79)	0.005	0.6 (0.3–1.19)	0.142
Level of CEA (ng/mL)	1.0 (1.0–1.05)	0.007	1.0 (1.0–1.05)	0.062

OR, odds ratio; CI, confidence interval; BMI, body mass index; PD, poorly differentiated.

Table 5. Univariate analysis of factors associated with 5-year overall and disease-free survival

Variable	No.	Overall survival		Disease-free survival	
		%	P-value	%	P-value
Age (yr)			0.001		0.120
<65	171	93.2		95.7	
≥65	252	77.1		90.9	
Sex			0.253		0.092
Male	274	81.6		91.7	
Female	149	88.6		95.4	
Body mass index (kg/m^2)			0.249		0.337
<25	275	82.6		92.1	
≥25	148	86.7		94.7	
Presence of comorbidity			0.071		0.203
No	199	90.0		94.4	
Yes	224	79.3		91.7	
Initial CEA (ng/mL)			0.121		0.069
<5	323	85.3		94.3	
≥5	100	79.2		88.7	
Histology			0.629		0.221
WD/MD	396	83.6		93.3	
PD/mucinous	27	88.4		88.7	
Pathologic TNM stage			0.004		0.001
Stage I	133	93.8		99.2	
Stage II	141	80.1		93.0	
Stage III	149	78.3		87.3	
Adjuvant chemotherapy			0.986		0.212
No	187	83.0		95.4	
Yes	236	84.5		91.3	
Sarcopenia			0.120		0.112
No	369	85.9		93.7	
Yes	54	72.8		88.1	

WD, well differentiated; MD, moderately differentiated; PD, poorly differentiated.

Table 6. Multivariate analysis factors associated with 5-year overall and disease-free survival

Variable	No.	Overall survival		Disease-free survival	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Age (yr)			0.003		0.135
<65	171	1		1	
≥65	252	2.64 (1.40–4.97)		1.96 (0.81–4.76)	
Presence of omorbidity			0.171		0.222
No	199	1		1	
Yes	224	1.48 (0.86–2.55)		1.67 (0.73–3.81)	
Initial CEA (ng/mL)			0.258		0.281
<5	323	1		1	
≥5	100	1.38 (1.79–2.41)		1.55 (0.70–3.47)	
Pathologic TNM stage			0.050		0.100
I	133	1		1	
II	141	2.31 (1.02–5.28)		7.05 (0.88–56.80)	
III	149	3.62 (1.64–7.8)		15.64 (2.05–119.17)	
Sarcopenia			0.115		0.125
No	369	1		1	
Yes	54	1.38 (0.79–2.41)		1.55 (0.70–3.47)	

HR, hazard ratio; CI, confidence interval.

study. To the best of our knowledge, this is the first report to demonstrate the clinical impact of sarcopenia in patients with colon cancer undergoing laparoscopic surgery in terms of short-term and oncologic outcomes simultaneously.

Only few studies have described the association of sarcopenia with oncologic outcomes after colorectal cancer surgery [8]. Van Vledder et al. [21] reported that patients with sarcopenia showed worse survival than nonsarcopenic patients after resection of colorectal liver metastasis. Jung et al. [16] showed that the SMI had an adverse effects on mortality in older and obese patients who received adjuvant chemotherapy after colon cancer surgery. As patients with advanced stage of cancer should endure more challenging treatment, such as major hepatectomy and chemotherapy, those with sarcopenia might be associated with higher mortality. In addition, sarcopenia may reflect the increased metabolic activity of a more aggressive tumor biology, leading to systemic inflammation and muscle wasting [22]. These may explain why sarcopenia is a poor prognostic factor especially in advanced stage of disease. On the contrary, one study including patients with stage III colon cancer, instead of stage IV disease, showed that overall survival was not associated with sarcopenia [16]. In our study, excluding stage IV colon cancer, sarcopenia was not a significant prognostic factor for overall (P = 0.120) or disease-free (P = 0.112) survival. It can be inferred that sarcopenic patients who underwent laparoscopic surgery may not be affected by survival rate at relatively early stage of disease.

Routine preoperative CT has been suggested as a useful tool for body composition analysis [3,5,15]. The prevalence of sarcopenia has been reported to range from 17.0% to 79% according to the cancer type and studied population [4,8]. It has been observed that patients with sarcopenia are in general older and have a low BMI [5,6]. The percentage of patients with sarcopenia in our study was 12.8%. The reason for the lower percentage compared with other studies may be the different value used for defining sarcopenia as well as the relatively healthy patients who could undergo laparoscopic surgery in our study.

The present study has several limitations, which are common for single-center, retrospective studies. First, we excluded patients with stage IV colon cancer. As we evaluated colon cancer treated by laparoscopic surgery and excluded cases of conversion to open surgery, these 2 conditions might have eliminated advanced-stage tumors. Further studies might be necessary to assess the impact of sarcopenia on short-term and/or oncologic outcomes after laparoscopic surgery including advanced-stage tumors such as other-organ invasive (T4) cancer and multiple liver metastases. Second, the definition of sarcopenia was different from other studies. We used cut-off values proposed by Martin et al. [15] for defining sarcopenia. However, different values may be used in other studies and this may influence the interpretation of the results [4].

The strength of our study is that we demonstrated the clinical impact of sarcopenia in patients with colon cancer undergoing laparoscopic surgery. As abdominal CT is routinely performed in staging work-up, CT-based body composition analysis is an efficient tool to assess a patient's function and frailty. Furthermore, we provided prognostic value in the Asian population, with a relatively large number of patients, even though cut-off values corresponding to Western populations

were used in our study. More standardized measurement for body composition analysis based on CT scan is needed in the future.

In conclusion, patients with sarcopenia were not compromised functional recovery and median hospital stay after laparoscopic surgery for colon cancer although more frequent postoperative complications were observed. In addition, laparoscopic surgery may reduce the negative impact of sarcopenia on oncologic outcomes in colon cancer.

ACKNOWLEDGEMENTS

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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