Negative impact of sarcopenia on survival in elderly patients with colorectal cancer receiving surgery: A propensity-score matched analysis

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Received September 14, 2023; Accepted December 1, 2023

DOI: 10.3892/ol.2024.14224

Abstract. Sarcopenia is a prognostic factor for patients with colorectal cancer and is commonly seen in elderly patients. The purpose of the present study was to demonstrate the impact of preoperative sarcopenia on the short- and long-term outcomes of curative surgery for treating colorectal cancer in elderly patients. Between 2016 and 2020, patients aged ≥80 years with colorectal cancer were investigated. The total muscle cross-sectional area was calculated using computed tomography imaging at the mid-3rd lumbar vertebra. Elder sarcopenia was identified using sex-specific cut-offs. Out of 106 elderly colorectal cancer patients, 27 patients were diagnosed with elder sarcopenia. Patients with elder sarcopenia had a reduced body mass index (19.7±2.5 vs. 22.5±2.9 kg/m^2; P<0.01), an advanced pN stage (P<0.01) and an advanced stage (stage 3) (P=0.029). Elder sarcopenia had a negative impact on relapse-free survival (3-year, 78.4 vs. 91.1%; P=0.049) and overall survival (3-year, 73.0 vs. 93.9%; P=0.022). Propensity score-matched analysis was performed, matching 27 patients in each group to remove selection bias, which demonstrated elder sarcopenia had a negative impact on overall survival (3-year, 73.0 vs. 100%; P<0.01). Overall, elder sarcopenia was prevalent in 25% of elderly patients with colorectal cancer that received curative surgery, and it was a poor prognostic indicator in this patient population.

Introduction

Colorectal cancer is the third most common malignancy and the second leading cause of cancer-related deaths worldwide (1). Surgical treatment is the only method enabling a potential cure for patients with Stage 1-3 colorectal cancer. Along with the aging of the population, the number of elderly patients who receive surgical treatment for colorectal cancer has gradually increased. The incidence rate of colorectal cancer escalates rapidly with age, increasing by approximately 30% with each 5-year age increase aged 55 years and older (2). The median age at diagnosis of colorectal cancer is 69-72 years, with 70% of colorectal cancer diagnosed in patients over 65 years (3-5). Approximately 17.5% of colorectal cancer patients are diagnosed when they are over 80 years (6). Unfortunately, most elderly patients have comorbidities, such as cardiovascular or pulmonary diseases, and reduced functional reserve, which may increase their risks of postoperative morbidity, mortality, and prognosis and subsequently influence the treatment choice (e.g., avoiding curative resection).

Sarcopenia was first described in 1988 as a condition in which muscle mass decreases with age (7). It was reported that more than half of people aged 80 years or older was sarcopenia (8). Among colorectal cancer patients, the number of patients with sarcopenia is increasing due to the aging population (9). Recently, preoperative sarcopenia has attracted attention as a predictor of postoperative complications and prognosis. In a recent meta-analysis, sarcopenia was prevalent in 37% of colorectal cancer patients, significantly prolonging hospital stay and increasing postoperative complications and mortality rates (10,11). Sarcopenia has also been linked with poor long-term outcomes in patients receiving curative resection for stage 1-3 colorectal cancer (12) and in patients with rectal cancer who underwent preoperative chemoradiotherapy (13,14). Despite increased awareness, a preventative treatment strategy remains unclear (15).

Although the incidence of colorectal cancer and the proportion of sarcopenia, in which muscle mass decreases and muscle strength and physical function decline, increases with aging, the impact of sarcopenia on short- and long-term outcomes in patients with colorectal cancer aged 80 years or older who received curative surgery remains still unclear. The purpose of this study was to demonstrate the impact of preoperative elder sarcopenia on the short- and long-term outcomes of curative surgery for treating colorectal cancer in patients older than 80 years.

Materials and methods

Patients. Between January 2016 and December 2020, a retrospective investigation was conducted on 106 consecutive

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Key words: sarcopenia, colorectal cancer, elderly patients, skeletal muscle index, overall survival

colorectal cancer patients aged 80 years or older who were intended to receive curative resection at Saitama cancer center in Saitama, Japan. Patients with recurrent colorectal cancers, patients who received palliative surgery from the beginning, and patients with synchronous metastases (Stage 4) were excluded.

Skeletal Muscle Tissue Measurement. The total muscle cross-sectional area (skeletal muscles, including psoas, paravertebral, and abdominal wall muscles) at the middle level of the third lumbar (L3) vertebra was assessed using SYNAPSE VINCENT software (Fujifilm Co., Tokyo, Japan) before surgery. An intensity window was used from -29 to 150 Hounsfield units for skeletal muscle selection. The skeletal muscle index (SMI) (cm^2/m^2) was calculated as follows:

SMI (cm^2/m^2)=L3 total muscle cross-sectional area (cm^2)/height^2 (m^2)

Sarcopenia was defined as SMI <52.4 cm^2/m^2 for the men and <38.5 cm^2/m^2 for the women (16). Elder sarcopenia was defined as SMI <38.3 cm^2/m^2 for the men and <29.9 cm^2/m^2 for the women, below the range of SMI in the previous report (16), which nearly a quartile of this study population. Histogram of SMI according to sex was demonstrated in Fig. 1

Outcomes. The clinicopathological and operative data, as well as the short-term outcomes (including morbidity, mortality, postoperative oral intake, and postoperative hospital stay), and long-term outcomes (such as relapse-free survival (RFS) and overall survival (OS)), were investigated. Robotic rectal surgery was considered a laparoscopic technique and included in laparoscopic surgery. The results of the pathological examination were classified according to the TNM classification of The International Union Against Cancer (UICC) (17). The resumption of oral intake was decided by the operating surgeon according to the patient's general condition, including factors such as good bowel movement, no abdominal distention, no fever, and laboratory data. Patients were discharged when they had demonstrated sufficient oral intake, no complications or well-controlled complications, and did not exhibit excessive anxiety about leaving the hospital. The Clavien-Dindo (CD) classification was used to classify postoperative complications. CD classification grade 3 and 4 are major complications (18). Short-term morbidity and mortality were defined as 30-day or in-hospital morbidity and mortality. As the follow-up, blood tests were performed every three months after the surgery, and a CT of the abdomen combined with imaging of the pelvis and chest was performed every six months after the surgery. Recurrence was defined as the presence of locoregional recurrence, distant metastases, or death from colorectal cancer. The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Saitama Cancer Center (No. 1071). The need for informed consent was waived because of the retrospective nature of this study.

Statistical analysis. For categorical variables, data were presented as frequencies and percentages, and Fisher's exact probability test or chi-square test was applied to evaluate the significance of differences in proportions. Continuous variables were shown as mean ± standard deviation (SD) and were estimated using the unpaired Student t-test. To investigate and compare the relapse-free survival and the overall survival, a Kaplan-Meier analysis was used, and the log-rank test was used to compare different curves. Propensity score-matching was performed to reduce imbalances between patients at baseline. A ratio of 1:1 nearest neighbor matching method with confounding covariates including gender, age, ASA-PS (American Society of Anesthesiologists physical status), comorbidities, procedure, tumor location, pT stage, pN stage, Stage, and morbidity was used for matching. And matching with a predefined caliper width equal to 0.2 of the standard deviation of the logit model yielded the final matched pairs. Statistical analyses were performed using R software (version 4.3.1: http://www.R-project.org). Associations were considered significant when P<0.05.

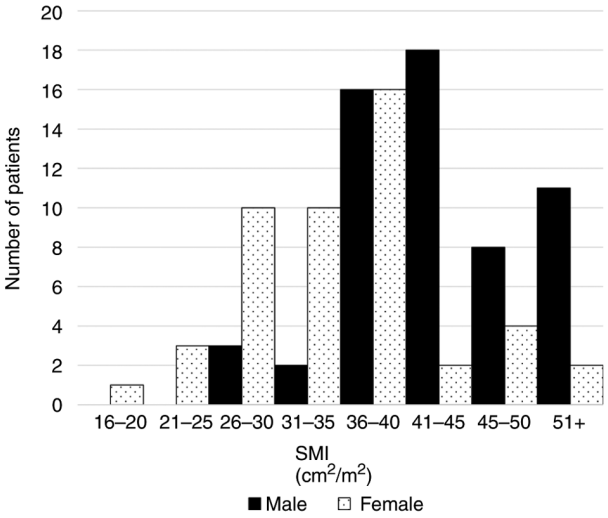

Figure 1. Histogram of SMI according to sex. Elder sarcopenia was defined as SMI <38.3 cm^2/m^2 for the men and <29.9 cm^2/m^2 for the women. SMI, skeletal muscle index.

Results

Out of 106 elderly patients with colorectal cancer intended to receive curative resection, there were 82 patients with sarcopenia (77.4%) and the remaining 24 patients without sarcopenia. There were 58 men and 48 women. OS rates of patients with or without sarcopenia are shown in Fig. 2. Three-year OS rates of elderly patients with sarcopenia was 86.1%, and that of those without was 100%. There was no significant difference between the two groups (P=0.28). Next, to investigate whether or not sarcopenia affected the prognosis of elderly colorectal cancer patients who were intended to receive curatively resected surgery, we examined elderly colorectal cancer patients with elder sarcopenia.

There were 27 patients (25.5%) with elder sarcopenia and the remaining 79 patients without elder sarcopenia. About a quarter of elderly colorectal cancer patients had elder sarcopenia. Table I summarizes differences in characteristics of patients with and without elder sarcopenia. BMI was significantly smaller in patients with elder sarcopenia (P<0.01). And

Table I. Patient characteristics.

Characteristic	Elder sarcopenia (n=27)	Non-elder sarcopenia (n=79)	P-value
Sex			1.0
Male	15	43	
Female	12	36	
Mean age, years (range)	84.0 (80-91)	83.1 (80-90)	0.15
Mean ± SD Body mass index, kg/m^2	19.7±2.5	22.5±2.9	<0.01
Albumin	3.8±0.44	3.8±0.53	0.97
ASA-PS			1.0
2	25	72	
3	2	7	
Comorbidities			
Overall, n (%)	16 (59.2)	61 (77.2)	0.08
Cardiovascular	3	13	0.76
Pulmonary	5	22	0.45
Renal	1	4	1
Cerebrovascular	2	16	0.15
Diabetes mellitus	5	18	0.79
Has a history of other malignancies, n (%)	7 (25.9)	28 (35.4)	0.64

ASA-PS, American Society of Anesthesiologists Physical Status; SD, standard deviation.

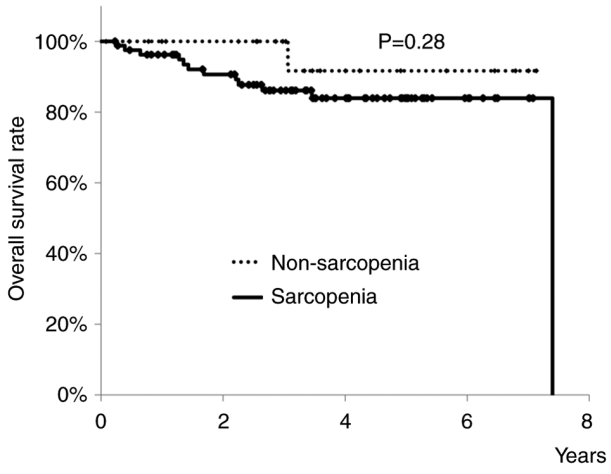

Figure 2. Overall survival rates of elderly patients with colorectal cancer and with or without sarcopenia: 5-year overall survival rate of elderly patients with sarcopenia was 84.0%, and that of those without was 91.7%. There was no significant difference between the two groups (P=0.28).

there was a tendency for a higher frequency of comorbidities in patients without elder sarcopenia (P=0.084). Pulmonary comorbidity was the most common in elderly colorectal cancer patients. There were no significant differences in gender, age, preoperative plasma albumin concentration, and ASA-PS. More than a quarter of elderly patients had a history of other malignancies.

Operative and pathological data are shown in Table II. There was a tendency for patients with elder sarcopenia to receive laparoscopic surgery (P=0.072). Operative time and the amount of blood loss were not statistically different between the two groups. As for pathological data, tumor location, pT stage, and number of harvested lymph nodes were not statistically different between the two groups. Significantly, more patients with elder sarcopenia had advanced stages (P=0.029) because of the higher number of lymph node metastasis cases.

Postoperative events are shown in Table III. Day until oral intake (4.6±2.2 days vs. 6.0±4.2 days, respectively) and postoperative hospital stay (11.3±4.1 days vs. 12.9±10.0 days, respectively) in patients with and without elder sarcopenia were similar (P=0.12, P=0.42, respectively). Postoperative complications occurred in about a quarter of elderly patients, and bowel obstruction was the most common in both groups. CD classification of more than grade 3 was observed in one case in the patients with elder sarcopenia and 3 cases in those without elder sarcopenia. There was no mortality in both groups.

As for the long-term outcomes, RFS rates of patients with or without elder sarcopenia are shown in Fig. 3A. Three-year RFS rates of elderly patients with elder sarcopenia was 78.4%, and that of those without was 91.1%. Patients with elder sarcopenia had a significantly worse RFS rate than those without (P=0.049). OS rates of patients with or without elder sarcopenia are shown in Fig. 3B. Three-year OS rates of elderly patients with elder sarcopenia was 73.0%, and that of those without was 93.9%. Patients with elder sarcopenia had a significantly worse OS rate than those without (P=0.022). However, the high rate of advanced Stage in patients with elder sarcopenia may have caused the group's worse RFS rate and OS rate.

Therefore, a 1-to-1 propensity score matching was performed to achieve balance between elderly patients with and without elder sarcopenia. After the matching, 27 patients were successfully matched in each group. Except for BMI, no statistically significant differences were found between the two groups in terms of the measured parameters (Table IV).

Table II. Operative and pathological data.

Parameter	Elder sarcopenia (n=27)	Non-elder sarcopenia (n=79)	P-value
Procedure			0.07
Open	3	24	
Laparoscopic/Robotic	24	55	
Mean ± SD operative time, min	251.1±128.7	243.9±91.5	
Mean ± SD blood loss, ml	174.9±465.5	135.4±225.1	
Tumor location			0.61
Colon	20	62	
Rectum	7	17	
Histology			1.0
Well/moderately differentiated	26	75	
Others	1	4	
pT stage			0.64
Tis	2	3	
T1	1	19	
T2	6	9	
T3	17	41	
T4	1	7	
pN stage			<0.01
N0	13	62	
N1	9	11	
N2	5	6	
Stage (TNM classification)			0.03
0	2	3	
1	4	24	
2	7	34	
3	14	18	
Mean ± SD no. of harvested lymph nodes	19.8±9.7	22.5±13.8	0.35
Cancer cells at the proximal and distal margins of the specimen			1.0
Cancer negative	27	79	
Cancer positive 0	0		
R stage			1.0
R0	27	79	
R1/2	0	0	

RFS rates of patients with or without elder sarcopenia are shown in Fig. 4A. Three-year RFS rates of elderly patients with elder sarcopenia was 78.4%, and that of those without was 96.3%. There was a tendency for patients with elder sarcopenia to have a worse RFS rate than patients without elder sarcopenia (P=0.069). OS rates of patients with or without elder sarcopenia are shown in Fig. 4B. Three-year OS rates of elderly patients with elder sarcopenia was 73.0%, and that of those without was 100%. Patients with elder sarcopenia had a significantly worse OS rate than those without (P<0.01).

Discussion

We demonstrated in this study that elderly colorectal cancer patients with elder sarcopenia who received curative surgery had worse results in terms of decreased relapse-free survival and overall survival. However, these results might have been influenced by more advanced colorectal cancer cases in elderly patients with elder sarcopenia, so we performed a propensity score matching analysis. Consequently, we found that elderly colorectal cancer patients with elder sarcopenia who received curative surgery had worse overall survival, even after propensity score matching. Regarding postoperative complications, there were no significant differences observed between elderly patients with and without elder sarcopenia. Additionally, no mortality was recorded in this study.

To the best of our knowledge, this is the first study to report that elder sarcopenia has a negative impact on long-term survival in elderly colorectal cancer patients aged 80 years or older after curative resection. Previously, Miyamoto *et al*

Table III. Postoperative events.

Events	Elder sarcopenia (n=27)	Non-elder sarcopenia (n=79)	P-value
Mean ± SD time until oral intake, days	4.6±2.2	6.0±4.2	0.12
Mean ± SD postoperative hospital stay, days	11.3±4.1	12.9±10.0	0.42
Morbidity (CD classification grade 1-5)			
Overall (%)	6 (22.2)	22 (27.8)	0.62
Wound infection	1	5	1.0
Intraabdominal abscess	1	0	0.26
Urinary tract infection	0	1	1.0
Pneumonia	1	3	1.0
Enterocolitis	0	1	1.0
Bowel obstruction	3	11	1.0
Bleeding	0	2	1.0
Urinary retention	0	2	1.0
CD classification grade3≦	1	3	1.0
Mortality (%)	0 (0)	0 (0)	1.0

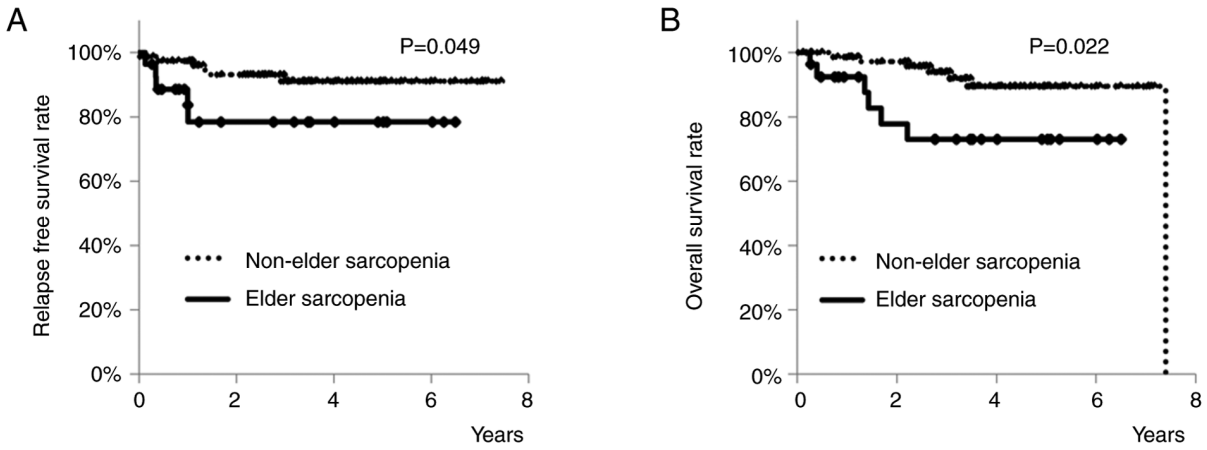

Figure 3. (A) Relapse-free survival rates of elderly patients with colorectal cancer and with or without elder sarcopenia: 5-year relapse-free survival rate of elderly patients with elder sarcopenia was 78.4%, and that of those without was 91.1%. Patients with elder sarcopenia had a significantly worse RFS rate than those without (P=0.049). (B) Overall survival rates of elderly patients with colorectal cancer and with or without elder sarcopenia: 5-year overall survival rate of elderly patients with elder sarcopenia was 72.3%, and that of those without was 89.5%. Patients with elder sarcopenia had a significantly worse overall survival rate compared with those without (P=0.022).

revealed that sarcopenia had a negative impact on both RFS and OS in colorectal cancer patients aged 30-93 years receiving potentially curative resection (12). Choi *et al* demonstrated that sarcopenia was negatively associated with OS in locally advanced rectal cancer patients who underwent neoadjuvant chemoradiation therapy followed by surgical resection (19). van Vledder *et al* demonstrated that sarcopenia in colorectal cancer patients had a negative impact on cancer outcomes following resection of colorectal liver metastasis (20). The precise mechanisms by which sarcopenia impacts survival rates in patients with colorectal cancer have not been fully determined (21). Sarcopenia may reflect the increased metabolic activity of a more aggressive tumor biology, leading to systemic inflammation and muscle wasting (22). This might explain why skeletal muscle depletion is a poor prognostic factor. Miyamoto *et al* reported that the effect of skeletal muscle depletion on prognosis appeared to differ with age. This effect is particularly prominent among young patients, and little difference in skeletal muscle mass may be seen among older patients (12). So, in our study, although sarcopenia did not reveal the worse prognosis in elderly colorectal cancer patients, elder sarcopenia, a quartile of this study population, has a negative impact on OS in elderly colorectal cancer patients aged 80 years or older.

This study found no difference in morbidity and mortality between patients with and without elder sarcopenia. Postoperative complications are often reported to be strongly correlated with both disease recurrence and shorter survival in patients with colorectal cancer (23-25). Previously, Traeger *et al* demonstrated sarcopenia had a significant association with postoperative bowel obstruction and complications (11). And Trejo-Avila *et al* also demonstrated in their meta-analysis that sarcopenia had an association with total postoperative complications, postoperative infection, postoperative cardiopulmonary

Table IV. Patient data after propensity score matching.

Characteristic	Propensity-matched groups		P-value
	Elder sarcopenia (n=27)	Non-elder sarcopenia (n=27)	
Sex			0.78
Male	15	17	
Female	12	10	
Mean age, years (range)	84.0 (80-91)	83.7 (80-90)	0.7
Mean ± SD Body mass index, kg/m^2	19.7±2.5	22.8±2.5	<0.01
Mean ± SD albumin, g/dl	3.8±0.44	3.7±0.46	0.45
ASA-PS			
2	25	25	1.0
3	2	2	
Comorbidities			
Overall (%)	16 (59.2)	21 (77.8)	0.24
Cardiovascular	3	3	1.0
Pulmonary	5	5	1.0
Renal	1	2	1.0
Cerebrovascular	2	6	0.25
Diabetes mellitus	5	7	0.74
History of other malignancies			
Yes	7	8	1.0
Procedure			0.47
Open	3	6	
Laparoscopic/Robotic	24	21	
Mean ± SD operative time, min	251.1±128.7	230.7±95.8	0.51
Mean ± SD blood loss, ml	174.9±465.5	76.3±98.8	0.29
Tumor location			1.0
Colon	20	21	
Rectum	7	6	
Histology			0.61
Well/moderately differentiated	26	24	
Others	1	3	
pT stage			0.68
Tis	2	2	
T1	1	1	
T2	6	7	
T3	17	17	
T4	1	0	
pN stage			0.67
N0	13	15	
N1	9	7	
N2	5	5	
Stage (TNM classification)			0.68
0	2	2	
1	4	6	
2	7	6	
3	14	13	
Mean ± SD no. of harvested lymph nodes	19.8±9.7	26.2±14.3	0.06
Proximal margin, Distal margin			1.0
Negative	27	27	
Positive	0	0	

Table IV. Continued.

Characteristic	Propensity-matched groups		P-value
	Elder sarcopenia (n=27)	Non-elder sarcopenia (n=27)	
R stage			1.0
R0	27	27	
R1/2	0	0	
Mean ± SD time until oral intake, days	4.6±2.2	4.8±2.8	0.83
Mean ± SD postoperative hospital stay, days	11.3±4.1	12.0±14.7	0.78
Morbidity (CD classification grade 1-5)			
Overall (%)	6	4	0.73
Wound infection	1	1	1.0
Intraabdominal abscess	1	0	1.0
Urinary tract infection	0	1	1.0
Pneumonia	1	2	1.0
Enterocolitis	0	0	1.0
Bowel obstruction	3	2	1.0
Bleeding	0	0	1.0
Urinary retention	0	0	1.0
CD classification grade 3≦	1	2	1.0
Mortality (%)	0 (0)	0 (0)	1.0

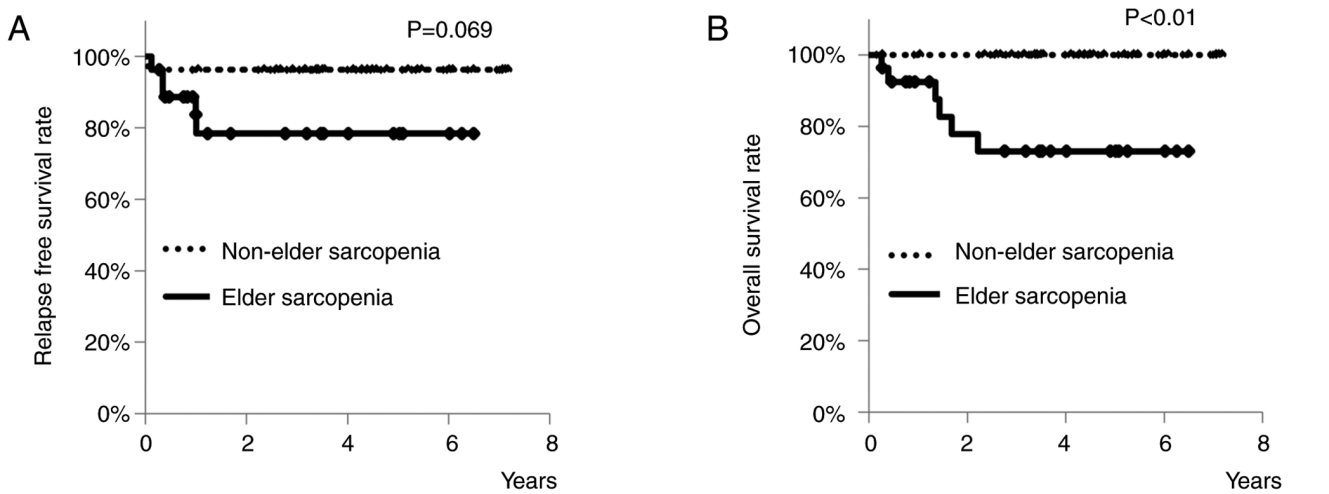

Figure 4. (A) Relapse-free survival rates of elderly patients with colorectal cancer and with or without elder sarcopenia after propensity score matching: 5-year relapse-free survival rates of elderly patients with elder sarcopenia was 78.4%, and that of those without was 96.3%. There was a tendency for patients with elder sarcopenia to have a worse relapse-free survival rate compared with patients without elder sarcopenia (P=0.069). (B) Overall survival rates of elderly colorectal cancer patients with or without elder sarcopenia after propensity score matching: 5-year overall survival rates of elderly patients with elder sarcopenia was 72.3%, and that of those without was 100%. Patients with elder sarcopenia had a significantly worse overall survival rate compared with those without (P<0.01).

complications, postoperative mortality, and prolonged hospital stay after colorectal surgery, and patients with sarcopenia had significantly shorter overall survival (10). The precise mechanisms by which sarcopenia impact on surgical morbidity in patients with colorectal cancer have not been fully determined (21). Trejo-Avila *et al* described in the previous report that one potential mechanism proposed was the hyper-inflammatory response to surgery in patients with sarcopenia, which might decrease wound healing, increase sepsis, and prolong the hospital length of stay (10). In this study, bowel obstruction was the most common prevalent postoperative complication in both groups, and some infectious complications also found in both groups. Above mentioned, little difference in skeletal muscle mass is often seen among older patients. Therefore, the difference in complication rates did not exhibit statistical significance, even among elderly colorectal cancer patients with elder sarcopenia. Additionally, no mortality was recorded in this study. However, Nishikawa *et al* reported cases of postoperative mortality due to pneumonia in elderly patients aged 80 years or older with colorectal cancer who underwent curative surgery (26). Special

attention should be given to postoperative complications, especially infections in elderly patients aged 80 years or older with colorectal cancer, regardless of the presence of sarcopenia.

Sarcopenia is the age-related loss of skeletal muscle mass and strength and impaired muscle function. And sarcopenia has been increasingly investigated for its predictive value in cancer patients over the past decade. But the objective definition of sarcopenia is still controversial (27). Although most reports define sarcopenia as loss of total skeletal muscle cross-sectional area at the L3 level, cut-offs differ among reports (16,28,29). In this study, we chose to use gender-specific cut-off values rather than quartiles to define the levels of sarcopenia because the study population was elderly colorectal cancer patients aged 80 years or older. Prado *et al* demonstrated that a skeletal muscle index of 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women was associated with mortality (16). Many reports cited this definition of sarcopenia (14,19,30-32). Therefore, in this study, we chose to use this index of 52.4 cm^2/m^2 in men and 38.5 cm^2/m^2 in women for defining sarcopenia which could not have significant difference as for OS rates of elderly patients with colorectal cancer, and defined numerical value below the lower limit of the range in Prado's report (SMI <38.3 cm^2/m^2 for the men and <29.9 cm^2/m^2 for the women) as elder sarcopenia, which nearly a quartile of this study population and showed significant difference as for OS rates of elderly patients with colorectal cancer. This time, the cut-off value from the Western population was applicable, but a more standardized body composition index is needed based on not only gender but also ethnicity. There are some studies that defined sarcopenia in the Japanese population (13,33). Fujiware *et al* defined sarcopenia as 36.2 cm^2/m^2 in male and 29.6 cm^2/m^2 in female (33). Further studies with a more comprehensive definition of sarcopenia are needed to reach more reliable conclusions.

The present study had some limitations. First, this study was not a large-scale multicenter randomized trial but a retrospective study conducted at a single institute with a limited sample size. We demonstrated the significant differences between elder sarcopenia patients and non-elder sarcopenia patients as for overall survival after propensity score matching, although the number of patients in this study might be small. And regarding population bias after the PSM method, the remaining patients without severe sarcopenia are expected to have a better prognosis due to the low late of advanced stage. Although we employed propensity score matching to eliminate bias and confounding factors as much as possible, propensity score matching itself has limitations, and the influence of some unknown confounding factors may not be fully excluded. Additionally, selection bias remains a concern. There is the possibility that some elderly colorectal cancer patients did not receive curative surgery.

In conclusion, elder sarcopenia is prevalent in a quarter of elderly patients with colorectal cancer aged 80 years or older receiving curative surgery. And elder sarcopenia is a poor prognostic indicator in elderly colorectal cancer patients.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

TNi, TT, NK, RO and TNa contributed to the study conception and design. Material preparation, data collection and analysis were performed by TNi and TT. TNi and TT confirm the authenticity of all the raw data. The first draft of the manuscript was written by TNi and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Saitama Cancer Center (approval no. 1071). The need for informed consent was waived because of the retrospective nature of this study.

Patient consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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