의학석사 학위논문

비전이성 대장직장암 환자에서 수술 후의 근육감소증의 변화가 예후에 미치는 영향

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이 논문을 의학석사 학위 논문으로 제출함

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이충엽의 의학석사 학위 논문을 인준함

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Influence of postoperative changes of sarcopenia on long-term survival in non-metastatic colorectal cancer patients

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Abstracts

Purpose/Background : Body composition is modifiable in the perioperative period. There are many indicators of body composition, such as body mass index, sarcopenia, and visceral obesity. Among them, sarcopenia gained increasing attention recently. We evaluate the association of changes in sarcopenia in the perioperative period with oncologic outcomes in non-metastatic colorectal cancer.

Methods : We enrolled 2,333 patients with stage 0-III colorectal cancer who were treated at Asan Medical Center between January 2009 and December 2012. The body composition at diagnosis was measured using 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 averaged for each patient. Sarcopenia was defined using CT-measured parameters such as total abdominal muscle area (TAMA) and skeletal muscle index (SMI, TAMA/height2). Patients underwent CT scans at preoperative, postoperative 6 months-1 year, and postoperative 2nd year-3rd year. Cox proportional hazard analysis was performed to evaluate the association between survival and changes in body composition.

Results: Among the 2,333 patients, 1,728 (74.1%) had colon and 605 (25.9%) had rectal cancer. A total of 1387 (59.5%) patients received adjuvant chemotherapy. According to sarcopenic criteria, 1,155 (49.5%), 890 (38.2%), and 893 (38.3%) patients had sarcopenia at preoperative, postoperative 6th month-1st year, and postoperative 2nd-3rd year, respectively. The 5-year overall survival (OS) rate (95.8% vs. 92.1%, hazard ratio [HR]= 2.234, $p<0.001$) and 5-year recurrence-free survival (RFS) rate (93.2% vs. 86.2%, HR = 2.251, $p<0.001$) were significantly lower in patients with preoperative sarcopenia. The 5-year OS and RFS rates were different according to postoperative changes in sarcopenia. Both OS and RFS were lower in patients with persistent sarcopenia at postoperative 2nd-3rd year than in those who recovered (recovered vs. persistent sarcopenia; OS: 96.2% vs .90.2%, p=0.001; RFS: 91.1% vs. 83.9%, p=0.002). In multivariate analysis, persistent sarcopenia, age, and pathologic stage were confirmed as independent factors associated with poorer OS and RFS.

Conclusions: Preoperative and postoperative sarcopenia as well as changes in this condition during surveillance were associated with oncologic outcomes.

Contents

Lists of figures, tables & abbreviations

Introduction

The stress imposed by surgery affects the metabolic state of patients' body. Among different surgery types, gastrointestinal surgery shortens small bowel or remnant stomach, which results in decreased ability of containing food and nutrient absorption, in turn causing changes in body composition.[1] Surgery also affects patients' basic physical activity due to postoperative pain, fatigue and lethargy, and other surgery-related stress.[2] As a result, the body condition of patients who underwent gastrointestinal surgery is affected in terms of weight, muscle mass, and body fat distribution and overall composition.[3-6]

There are many parameters that reflect the body condition, such as body weight, body mass index (BMI), total fat area (TFA), visceral obesity, and total psoas muscle area (TPA).[7,8] These parameters are used to define obesity, sarcopenia, and sarcopenic obesity. A number of studies have demonstrated that many diseases were associated with indicators of body composition.[4-8] Indicators of body composition affect not only the incidence of a disease but also the outcomes of the disease. Obesity and sarcopenia are risk factors for esophageal cancer,[9] colon cancer,[10] and cardiovascular disease.[11] Indeed, body composition has been reported to influence oncologic outcomes in variable cancers.[8]

However, there is a disagreement concerning the method for measuring body composition. BMI is defined as weight divided by square of height (kg/m^2). Universally, BMI is used to evaluate the risk of obesity. In addition, many studies using BMI showed that obesity was associated with many other diseases. Specifically, high BMI increases cancer risk[12] and postoperative complications after lung cancer[6], colorectal cancer (CRC),[13] and esophageal cancer.[14] However, BMI does not reflect body composition accurately.[15] Indeed, the body is made of protein, water and fat, and other components, but BMI takes into consideration only body weight and height. Therefore, the percentage of muscle and fat is missing when evaluating body composition.[16,17] Because BMI cannot accurately represent body composition, various indicators such as sarcopenia, TFA, and TPA that can reflect it more precisely have been studied. Among these, studies on sarcopenia, an indicator of muscle

status, are being published steadily.

Sarcopenia refers to muscle depletion. There are various methods used to measure muscle mass and strength. Many methods have been proposed for body composition measurement, including assessments at the atomic, molecular, and whole-body levels. Techniques used include bioelectrical impedance analysis, dilution techniques, magnetic resonance imaging, and computed tomography (CT).[18] However, many centers generally use CT for measuring muscle mass. Because CT scans are easily utilized with cross-sectional imaging and enable measurements at the tissue-system level, they are considered highly accurate in evaluating levels of fat, fat-free mass, and skeletal muscle.[19, 20, 21] Psoas muscle is usually employed to measure skeletal muscle status in patients.[22, 23] Recently, many studies provided evidence of the negative impact of sarcopenia in patients with various types of cancer such as cancer of the lung[24], esophagus[9], and pancreas.[7, 25]

Cancer induces abnormal metabolic alterations in lipid mobilization and carbohydrate and protein metabolism. These alterations contribute to skeletal muscle breakdown. Inflammatory cytokines increase in response to these change. Cancer cachexia is a complex metabolic syndrome associated with underlying illness, loss of muscle with or without loss of fat. Thus, cancer causes muscle degradation and inflammatory status. [26-28] In addition, loss of skeletal muscle induces postoperative complications and increases mortality and hospital costs.[29-32] Therefore, muscle status would influence postoperative cancer care and long-term outomes.

Advances in chemotherapy strategies and surgical procedured are the key for longer survival in cancer patients. Surgical procedures such as total mesorectal excision and central vessel ligation help in achieving improved oncologic outcomes.[33] Preoperative chemotherapy and concorrunt chemotherapy also improve patients' survival and quality of life. In addition to surgical intervetions, postoperative health care and follow-up are emerging because of the improved survival in patients with cancer. However, longer survival time results in increased chance for complications and secondary disease. Therefore, more patients are in need of postoperative care. Changes in body composition and sedentary lifestyle have been shown consistently to increase the risk of developing CRC[34-36]

Until recently, only few studies had addressed whether these factors influence the outcomes in patients with CRC. Increased levels of circulating insulin and free insulin-like growth factor 1 have been associated with obesity and physical inactivity.[37-39] Furthermore, both insulin and insulin-like growth factor 1 promote cell proliferation and inhibit apoptosis in colon cancer cells.[40, 41] One could hypothesize that such lifestyle factors may influence the risk of colon cancer recurrence by promoting growth of micrometastases through insulin-related growth factors.

In CRC patients, body composition has emerged as an indicator for postoperative complications or overall survival (OS).[13, 15, 20, 22, 29, 42] Many other studies addressed the association of muscle parameteres with CRC. Low muscular stucture correlated with postoperative morbidity.[15, 20, 22, 43]

We previously reported that body composition affected the long-term survival in patients with non-metastatis rectal cancer.[44] Patients who had rectal cancer with sarcopenic obesity and low BMI at diagnosis had negative association with OS. Although we showed that body composition was associated with OS, it could not reflect postoperative changes in body composition. Therefore, in this study, we evaluated changes in body composition measured by sarcopenia at diagnosis, and postoperatively at 6-12 monts and 2-3 year time periods.

We aimed to investigate the changes in body composition and how these affected prognosis.

Materials and methods

Study population

We enrolled CRC patients with stage 0-III who underwent curative resection at Asan Medical Center between January 2009 and December 2012. Cancer staging was based on the most updated American Joint Committee on Cancer (AJCC) manual at the time of surgery.

Patients who underwent radical resection and elective surgery for primary CRC were included. Those who were treated with preoperative chemoradiotherapy followed by radical resection were also included.

Patients with synchronous distant metastasis, synchronous cancer at other organ, cancer diagnosed within 5 years, inflammatory disease associated CRC, underwent local excision, or had unknown staging status were excluded. We also excluded patients who did not have record of preoperative height and weight and were unable to calculate skeletal muscle index (SMI) at postoperative 6 months-1 year, and 2 year-3 year. Patients were also excluded if they did not undergo CT scan at preoperation, postoperative 6-12 months, and postoperative 2-3 year; we also excluded those who were lost to follow-up observation. Therefore, 2333 patients who met the inclusion criteria were included in the final analysis.

Using medical records, data of patients' sex, age, height, weight, pathologic stage, and CT images were obtained. We used these data to calculate BMI and body composition.

Treatment and Surveillance

Open and minimally invasive approach including laparoscopic or robotic surgery were performed. Radical resection for rectal cancer was performed according to principles of tumor-specific mesorectal excision.

Adjuvant chemotherapy was initiated 1-2 months after operation. Adjuvant chemotherapy was recommended in colon cancer with pathologic stage III, and stage II with risk factors such as preoperative obstruction, lympho-vascular invasion, perineural invasion, high tumor budding, and less than 12 lymph nodes obtained. In patients with rectal cancer, adjuvant chemotherapy was recommended in patients with pathologic stage II and III or those treated with preoperative chemo-radiotherapy (PCRT) regardless of pathologic stage. PCRT was indicated for patients who had clinical stage II or III disease. In addition, even in the case of clinical stage I, PCRT was chosen when sphincter savings could be expected with PCRT due to low-lying rectal cancer or reluctant to perform surgery due to medical comorbidity.

Chemotherapy regimens used for the adjuvant setting included XELOX (oxaliplatin +

capecitabine), FOLFOX (5-fluorouracil + leucovorin + oxaliplatin), and LF (5-fluorouracil + leucovorin). XELOX was composed of oxaliplatin 130 mg/m^2, capecitabine 100 mg/m^2 administered in 8-16 cycles. FOLFOX was composed of oxaliplatin 85 mg/m^2, capecitabine 2400 mg/m^2 and leucovorin 200 mg/m^2 administered in 8-12 cycle. LF was composed of 5-fluorouracil 375 mg/m^2 and leucovorin 20 mg/m^2. These regimens were administered according to the patient's pathologic stage and general condition.

All patients were followed up for approximately 5 years after surgery. All patients underwent surveillance every 3-6 months at the outpatient clinic. Physical examination and carcinoembryonic antigen (CEA) evaluations were performed every 3-6 months. Abdominopelvic and chest CT was performed every 6-12 months. Colonoscopy was conducted at an interval of 2-3 years. For patients with preoperative obstruction and who could not be evaluated for the full length of colon, colonoscopy was performed at 3-6 months after surgery. Recurrences were identified based on imaging modality and confirmed pathologically by biopsy if possible. When pathologic confirmation was not possible, diagnosis of recurrence was made combining more than two imaging modality diagnoses or serial change on the same imaging method. Local recurrence was defined as the presence of a suspicious lesion in the pelvis (the site of anastomosis, the bed of the primary resection, etc.) identified using colonoscopy or imaging modalities such as abdominopelvic CT, MRI, or positron emission tomography (PET). Distant metastasis was defined as the presence of recurrence beyond the pelvis.

Measurements and definitions of body composition parameters

All CT scans were retrieved from the Picture Archiving and Communication System (PACS) at Asan Medical Center. The presence of sarcopenia was evaluated according to on abdominal CT scans 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 Asan-J software, the total abdominal muscle area (TAMA, cm^2), including all muscles on the

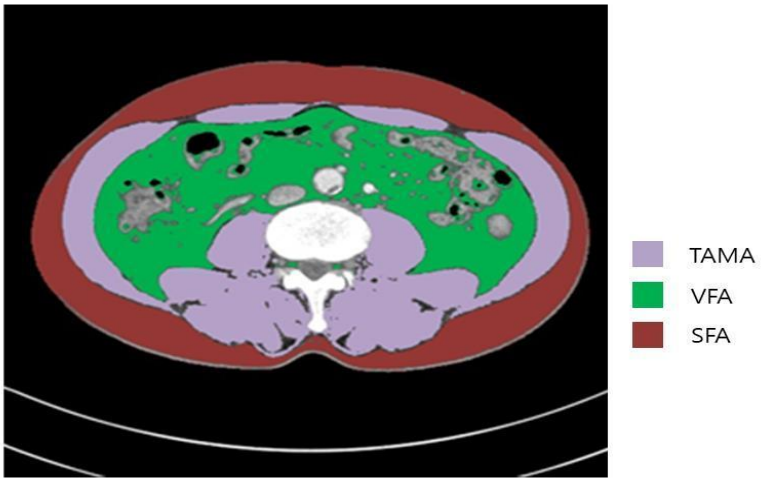
selected axial images, i.e., psoas, paraspinals, transversus abdominus, rectus abdominus, quadratus lumborum, and internal and external obliques, were demarcated using predetermined thresholds for the HU on CT or the signal intensity (SI) on pre-contrast. The visceral fat area (VFA, cm^2) and the subcutaneous fat area (SFA, cm^2) were also demarcated using the adipose tissue thresholds on CT (Figure 1).

Sarcopenia was defined based on the skeletal muscle index (SMI), which was calculated as TAMA/height^2. In our previous study, we selected Western criteria, which were used in a large population-based study of Prado et al. With these criteria, cut-off values for sarcopenia were SMI<38.5 cm^2/m^2 in women, and <52.4 cm^2/m^2 in men.[3]

All patients had CT scans for the analysis of body composition at diagnosis, postoperative 6-12 months, and postoperative 2-3 year.

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 computed tomography (CT) image was segmented into the total abdominal muscle area (TAMA), visceral fat area (VFA), and superficial fat area (SFA).



Statistical analysis

All continuous variables are presented as the mean±standard deviation (SD). OS was determined from the time of the 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, loss to follow-up, or death from any cause.

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 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.

All tests were established using the 2-sided test at $p < 0.05$ were considered statistically significant. All statistical analyses were performed using PASW Statistics 21 (SPSS Inc., Chicago, IL)

Results

Clinical characteristics

The clinical characteristics of the patients are shown in Table 1. There were 1373 men (58.85%) and 960 women (41.15%). There were 1728 (74.07%) patients with colon cancer and 605 (25.93%) with rectal cancer. We divided patients into pathologic Stage 0-II (66.27%) and Stage III (33.73%). A total of 1387 (59.45%) patients were administered adjuvant chemotherapy. Among 605 rectal cancer patients in our cohort, 261 (43.14%) underwent preoperative chemoradiotherapy. With regard to surgery, 687 (29.45%) patients underwent right hemicolectomy; 146 (6.26%), left hemicolectomy; 867 (37.16%), anterior resection; 419 (17.96%), low anterior resection; 155 (6.64%), ultra-low anterior resection;

57 (2.44%), abdominoperineal resection; and 2 (0.09%), Hartmann's operation. There were 1155 (49.51%) patients who had sarcopenia preoperatively; 128 (5.49%), had <12 harvested lymph nodes; and 2205 (94.51%) had ≥12 harvested lymph nodes. Lympho-vascular invasion was detected in 476 (20.41%) patients and perineural invasion in 380 (16.29%).

Preoperative skeletal muscle index (SMI) and proportion of sarcopenic patients according to age and sex are shown in Table 2. Average male SMI was 51.13±0.21, and average female SMI was 40.57±0.21. Preoperative sarcopenia was found in 799 (58.19%) male patients and in 356 (37.08%) female patients. In both sexes, the proportion of sarcopenic patients was the lowest in those under 40 years of age.

Table 1. Clinical characteristics of the study patients

Variables	**Mean ± SD, or No (%)**
Age, years, mean ± SD	60.43 ± 10.70
Sex	
Male	1373 (58.85%)
Female	960 (41.15%)
Location	
Colon	1728 (74.07%)
Rectum	605 (25.93%)
Pathologic stage	
Stage 0-Ⅱ	1546 (66.27%)
Stage Ⅲ	787 (33.73%)

Adjuvant chemotherapy	
Yes	1387 (59.45%)
No	946 (40.55%)
PCRT in rectal cancer patients	
Yes	261 (43.14%)
No	344 (56.86%)
Preoperative Sarcopenia	
Yes	1155 (49.51%)
No	1178 (50.49%)
Surgery classification	
Rt. hemicolectomy	687 (29.45%)
Lt. hemicolectomy	146 (6.26%)
Anterior resection	867 (37.16%)
Low anterior resection	419 (17.96%)
Ultra low anterior resection	155 (6.64%)
Abdominoperineal resection	57 (2.44%)
Hartmann's operation	2 (0.09%)
Harvested lymph node (number)	
<12	128 (5.49%)
≥12	2205 (94.51)

Lympho-vascular invasion	
Yes	476 (20.41%)
No	1857 (79.59%)
Perineural invasion	
Yes	380 (16.29%)
No	1953 (83.71%)

Lt., Left; Rt., Right; SD, standard deviation;

Table 2. Preoperative Skeletal muscle index and proportion of sarcopenic patients according to age and sex

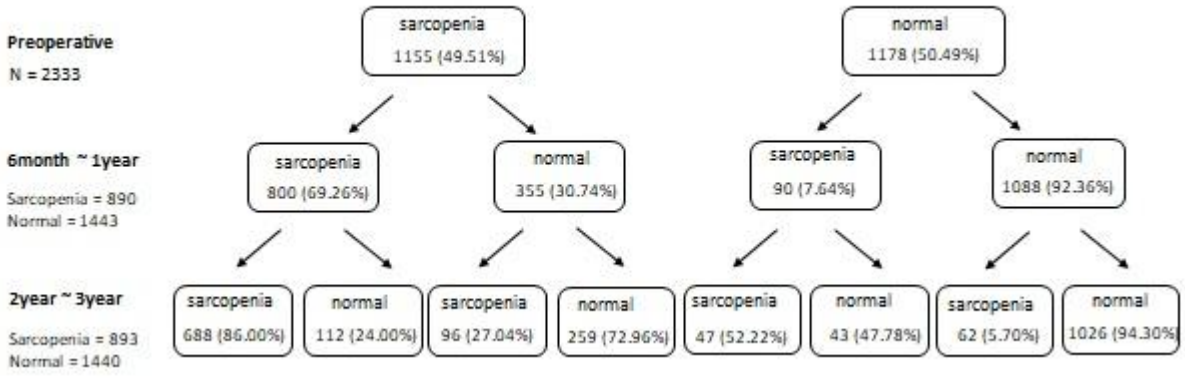
Age group	Number	Skeletal muscle index, mean ± SD	Sarcopenia
Male, yrs	1373	51.13±0.21	799 (58.19%)
≤40s	193	53.48±0.61	83 (43.01%)
50s	403	53.03±0.37	198 (49.13%)
60s	457	50.35±0.34	280 (61.27%)
≥70s	320	48.43±0.38	238 (80.63%)
Female, yrs	960	40.57±0.21	356 (37.08%)
≤40s	142	40.54±0.49	56 (39.44%)
50s	313	40.58±0.34	123 (39.30%)
60s	303	41.15±0.34	98 (32.34%)

≥70s	202	39.69±0.54	79 (39.11%)

Changes in SMI during surveillance

There were the following proportions of sarcopenia and normal body composition during surveillance (Figure 2). Among preoperative patients, 1155 had sarcopenia and 1178 had normal body composition. Furthermore, we found that there were changes in the proportion of sarcopenia and normal body composition among patients at postoperative 6-12 months and 2-3 year periods. Among the sarcopenic patients, 371 (32.12%) had recovered from preoperative sarcopenia at postoperative 2-3 years. However, there were 109 (9.7%) patients with newly develop sarcopenia at postoperative 2-3 years among those who had normal preoperative body composition. (Figure 2)

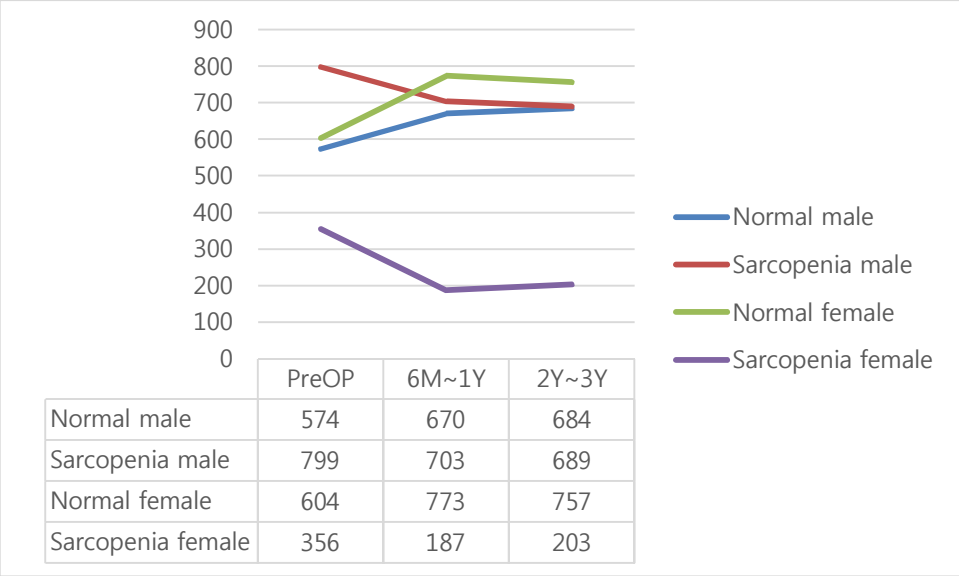
Figure 2. Proportions of sarcopenia and normal body composition during surveillance.



In Figure 3, changes in SMI during surveillance according to sex are shown. Among male patients, the number of patients with normal body composition was increased over time. The number of sarcopenic male patients was decreased over time. There were 604 female

patients who had normal body composition preoperatively, 773 postoperatively in 6-12 months, and 757 postoperatively in 2-3 year, respectively. Among sarcopenic female patients, there were 356 who had it preoperatively, 187 postoperatively in 6-12 months, and 203 postoperatively at 2-3 year, respectively. There was the highest number of female patients with normal body composition postoperative at 6-12 months period. In addition, the number of sarcopenic patients decreased postoperatively at 2-3 year (Figures 4a and b).

Figure 3. Changes in SMI during surveillance according to sex



	PreOP	6M~1Y	2Y~3Y
Normal male	574	670	684
Sarcopenia male	799	703	689
Normal female	604	773	757
Sarcopenia female	356	187	203

PreOP, preoperative; 6-12M, postoperative 6-12 months; 2-3Y, postoperative 2-3 years

Figure 4. Proportions of patients with sarcopenia under a specific condition

Figure 4a. Proportions of patients with sarcopenia among male (preoperative to postoperative 2-3 years)

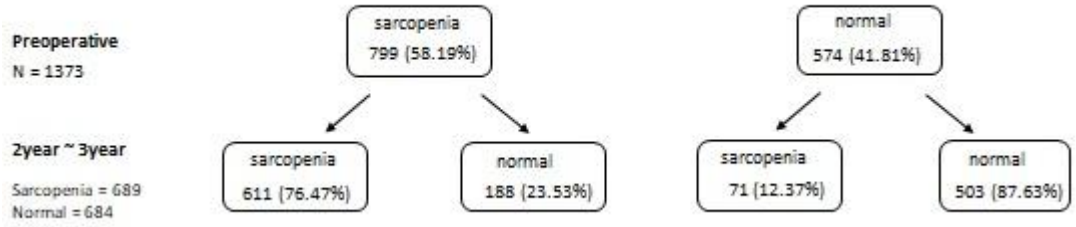
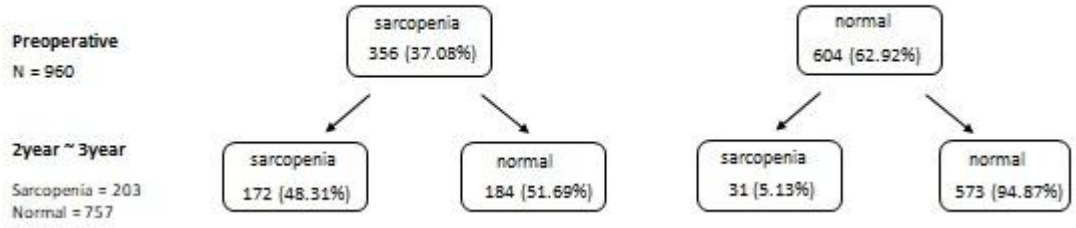


Figure 4b. Proportions of patients with sarcopenia among females (preoperative to postoperative 2-3 years)



We then studied specific conditions that affected the proportions of patients with sarcopenia and normal body composition. Patients were divided into groups based on age. In those under 70 years of age, among 838 preoperative patients, 538 (65.20%) had sarcopenic status, while among 973 preoperative patients who had normal body composition, 890 (91.47%) had normal body composition postoperatively at 2-3 year. Among patients older than 70 years of age, when, 317 patients had sarcopenia preoperatively and 246 (77.60%) postoperatively at 2-3 year. Furthermore, 205 patients, had normal body composition preoperatively and 179 (87.32%) postoperatively at 2-3 year. In our study, at older ages, there was had a higher

percentage of patients retaining sarcopenic status and a lower percentage of those retaining normal body composition (Figure 4c, 4d).

Figure 4c. Proportions of patients with sarcopenia among those under 70 years of age (preoperative to postoperative 2-3 years)

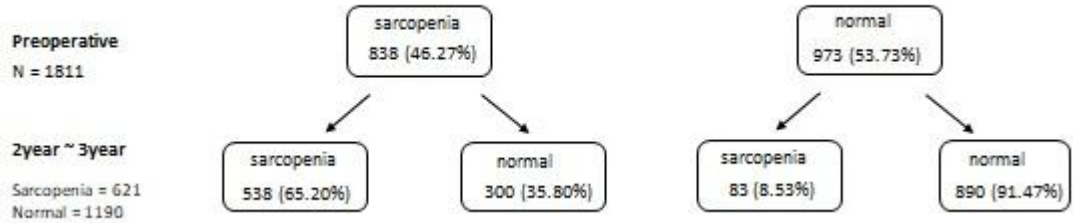
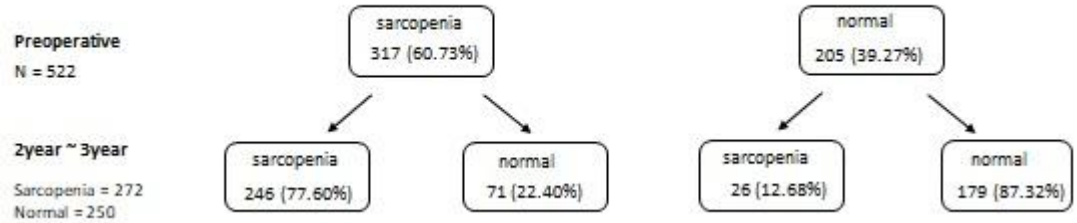


Figure 4d. Proportions of patients with sarcopenia among those above 70 years of age (preoperative to postoperative 2-3 years)

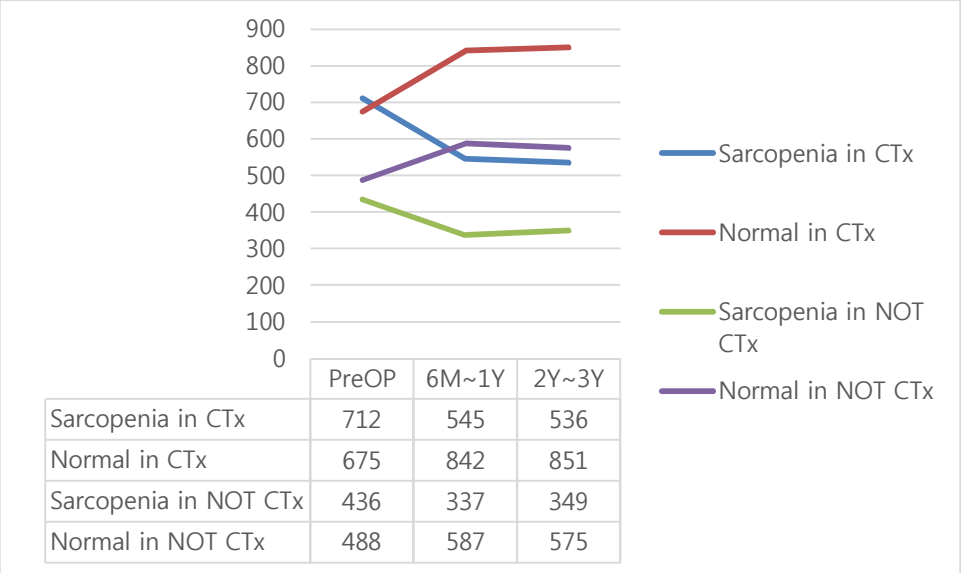


We further divided patients based on pathologic stage into stage 0-II and III groups. Among patients with stage 0-II, 766 (49.55%) had sarcopenia, and 780 (50.45%) had normal body composition preoperatively. Among 766 preoperative patients with sarcopenia, 520 (67.89%) had sarcopenia status postoperatively at 2-3 year. Among 780 preoperative patients with normal body composition, 713 (91.41%) retained it postoperatively at 2-3 year. In the stage III group, 389 (49.43%) patients had sarcopenia, and 398 (50.57%) had normal body composition preoperatively Among 389 patients with preoperative sarcopenia, 264 (67.87%)

had sarcopenia postoperatively at 2-3 year. Among 398 patients with preoperative normal body composition, 356 (89.45%) retained it postoperatively at 2-3 year. There was no difference in the proportions of sarcopenic to sarcopenic or normal to normal in between stage 0-II and stage III groups.

Sarcopenic status was further evaluated according to the administration of adjuvant chemotherapy (CTx). In our cohort, 924 (39.61%) patients were NOT administered adjuvant CTx, 1387 (59.45%) were administered adjuvant CTx, and 22 (0.94%) patients had unknown status of CTx. In both the CTx and non-CTx groups, the proportion of patients with sarcopenia was decreased in postoperative 6-12 months, while it was similar between postoperative 6-12 months and postoperative 2-3 year (Figure 4e). In the non-CTs group, 436 patients had sarcopenia preoperatively and 308 (70.64%) postoperatively at 2-3 year (Figure 4f). The CTx group, 712 patients had sarcopenia preoperatively and 470 (66.01%) postoperatively at 2-3 year (Figure 4g). Comparing all the graphs corresponding to the entire patient cohort presented in Figure 3, we found the decrease in the proportion of patients with sarcopenia at postoperative 6-12 months, and similar proportions between postoperative 6-12 months and 2-3 year.

Figure 4e. Changes in SMI during surveillance according to CTx



	PreOP	6M~1Y	2Y~3Y
Sarcopenia in CTx	712	545	536
Normal in CTx	675	842	851
Sarcopenia in NOT CTx	436	337	349
Normal in NOT CTx	488	587	575

CTx, chemotherapy, 6-12M, 6-12 months, postoperative 6 months-1 year; 2-3Y, postoperative 2-3 years

Figure 4f. Proportions of patients with sarcopenia among those NOT under Adjuvant CTx (preoperative to postoperative 2 year-3 year)

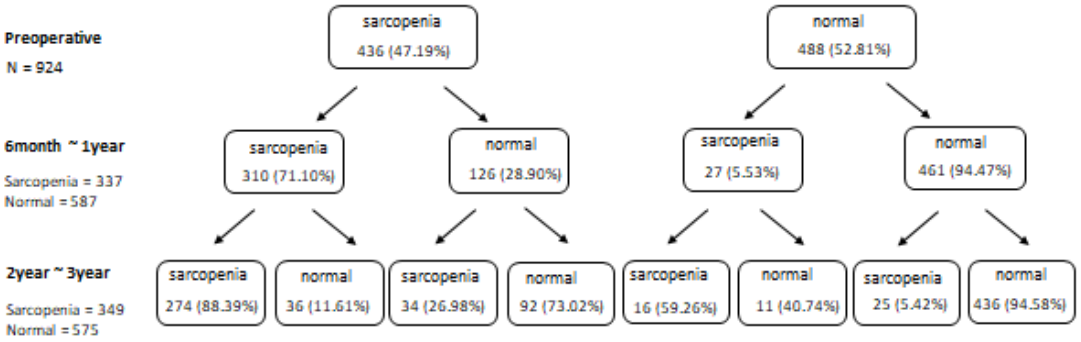
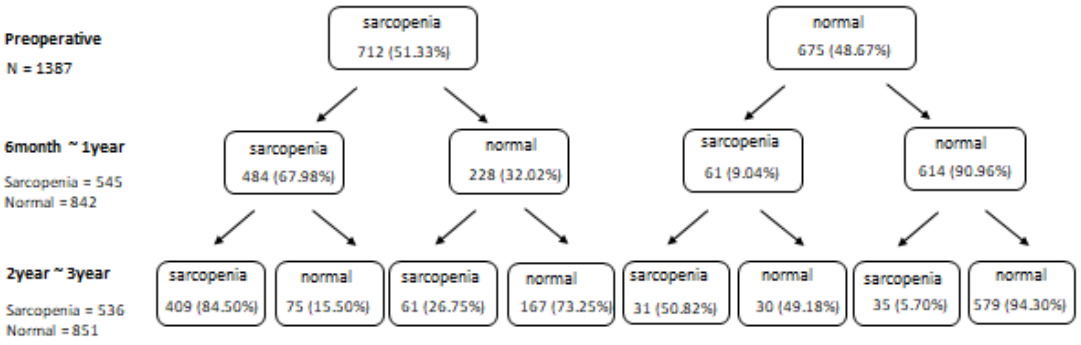


Figure 4g. Proportions of patients with sarcopenia among those under Adjuvant CTx (preoperative to postoperative 2 years-3 years



Among the 605 patients with rectal cancer, 427 had sarcopenia and 178 had normal body composition preoperatively, while there were 274 patients with sarcopenia and 331 with normal body composition at postoperative 2-3 year.

Among the 1728 patients with colon cancer, 728 had sarcopenia and 1000 had normal body composition preoperatively, while 619 had sarcopenia and 1109 normal body composition at postoperative 2-3 year.

Oncologic outcomes according to SMI and its changes

We evaluated oncologic outcomes according to SMI. We analyzed the association of OS and RFS with preoperative sarcopenic status. Patients with preoperative sarcopenia had poor oncologic outcomes than those with normal body composition ($p<0.001$) (Figure 5a, 5b).

For an analysis by sub-stage, patients with sarcopenic conditions had poorer oncologic prognosis than those with normal body composition in both stage 0-II and stage III groups ($p<0.001$). At stage III, the sarcopenia group had HR=2.014 for OS, and HR=2.034 hazard for RFS (both $p<0.001$). In stage 0-II, the sarcopenia group had HR=2.722 for OS, and HR=2.748 for RFS (both $p<0.001$).

We further analyzed the dynamic changes in normal body composition to sarcopenia,

sarcopenia to normal body composition, normal to normal, or sarcopenia to sarcopenia between preoperative and postoperative 2-3 year groups. The best prognosis was found in the normal to normal group, the sarcopenia to sarcopenia group had the worst prognosis, and the normal to sarcopenia group had also poor prognosis than the sarcopenia to normal group (all $p<0.001$) (Figure 6). There was no significant difference in the prognosis between the sarcopenia to normal group and the normal to sarcopenia groups.

The association of OS and RFS with sarcopenia, normal body composition in the postoperative 2-3 year group revealed that patients with sarcopenia in the postoperative 2-3 year group had poorer prognosis than others ($p<0.001$).

Figure 5a. Association between overall survival and preoperative sarcopenia

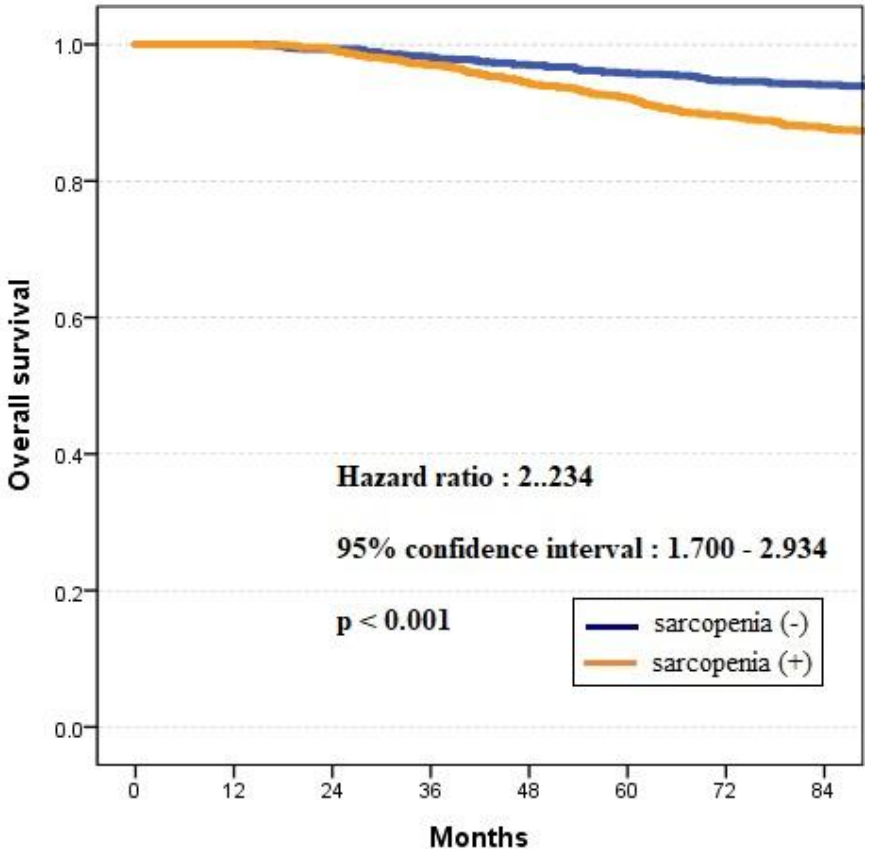


Figure 5b. Association between recurrence-free survival and preoperative sarcopenia

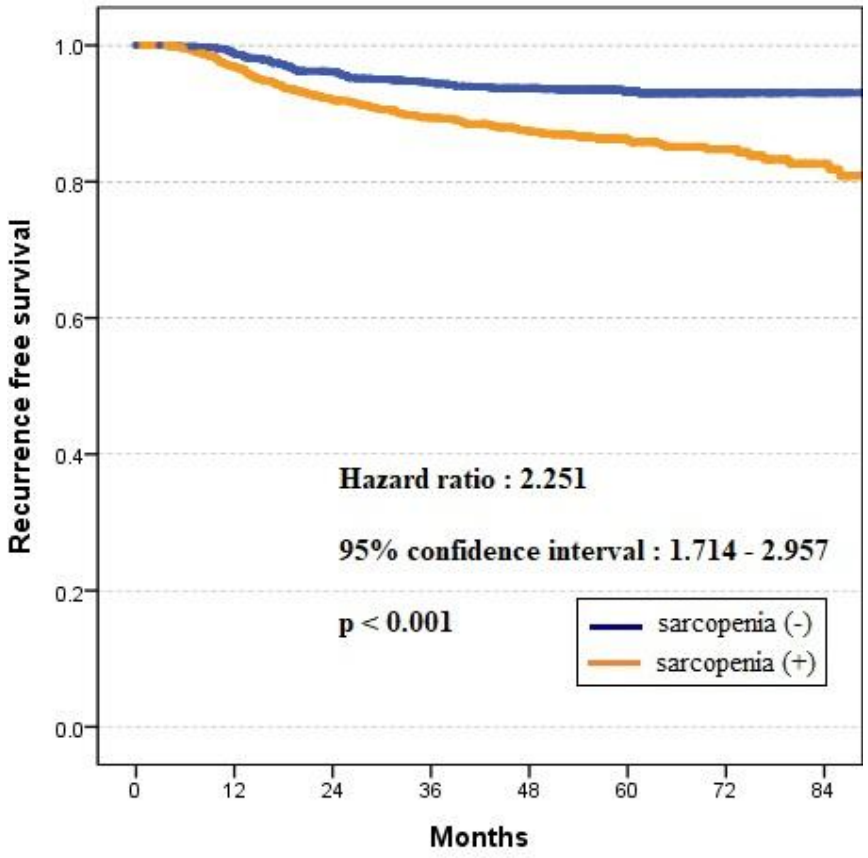
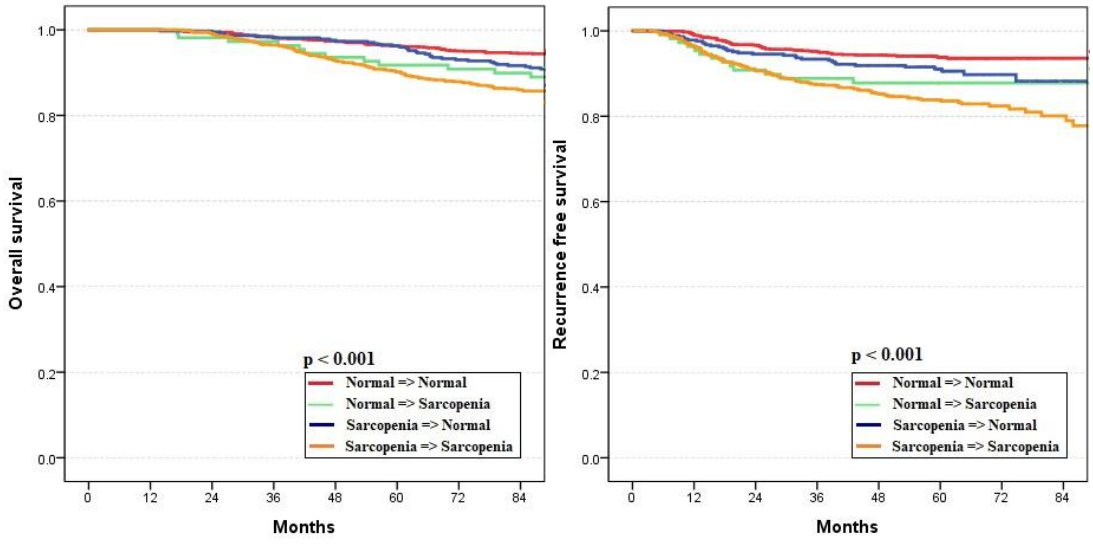


Figure 6. Association of overall survival and recurrence-free survival with normal body composition and sarcopenia change



Among the changes in preoperative to postoperative 2-3 year conditions, we focused on the sarcopenia to normal group and the sarcopenia to sarcopenia groups. We evaluated the associations of OS and RFS with changes in sarcopenia to normal and sarcopenia to sarcopenia in various subgroup analysis (Figure 7). Among 1155 patients, 371 were in the sarcopenia to normal group, and 784 in the sarcopenia to sarcopenia group, with 356 male and 799 female patients. The sarcopenia to normal group had better OS (p=0.001) and RFS (p=0.002) than the sarcopenia to sarcopenia group (Figure 7). There were no correlations of OS and RFS with changes in the sarcopenia to normal group or the sarcopenia to sarcopenia group among female patients (Figure 8a). However, there was such correlation with OS (p=0.013) and RFS (p=0.010) among male patients (Figure 8b).

In patients above 70 years of age, SMI changes were not associated with prognosis, either OS or RFS (Figure 8c), while among those under 70 years of age, patients in the sarcopenia to normal group had better OS and RFS than those in the sarcopenia to sarcopenia group (p = 0.013 and p = 0.015, respectively) (Figure 8d).

We divided patients into two groups by pathologic stage 0-II and III. In stage 0-II, OS was not associated with SMI changes (p= 0.060), while RFS was associated with SMI changes (p = 0.049) (Figure 8e). In the stage III group, both OS and RFS were associated with SMI changes (Figure 8f).

Patients who underwent CTx had an association with SMI changes and prognosis (Figure 8g). Patients who did not undergo CTx showed no association between SMI changes and prognosis (Figure 8h).

Figure 7. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia

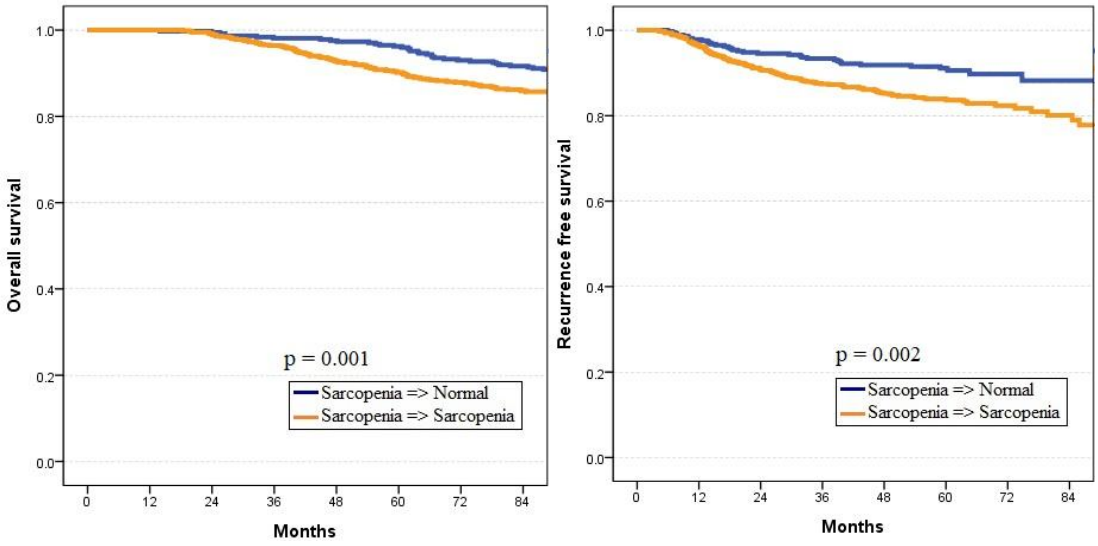


Figure 8a. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among females

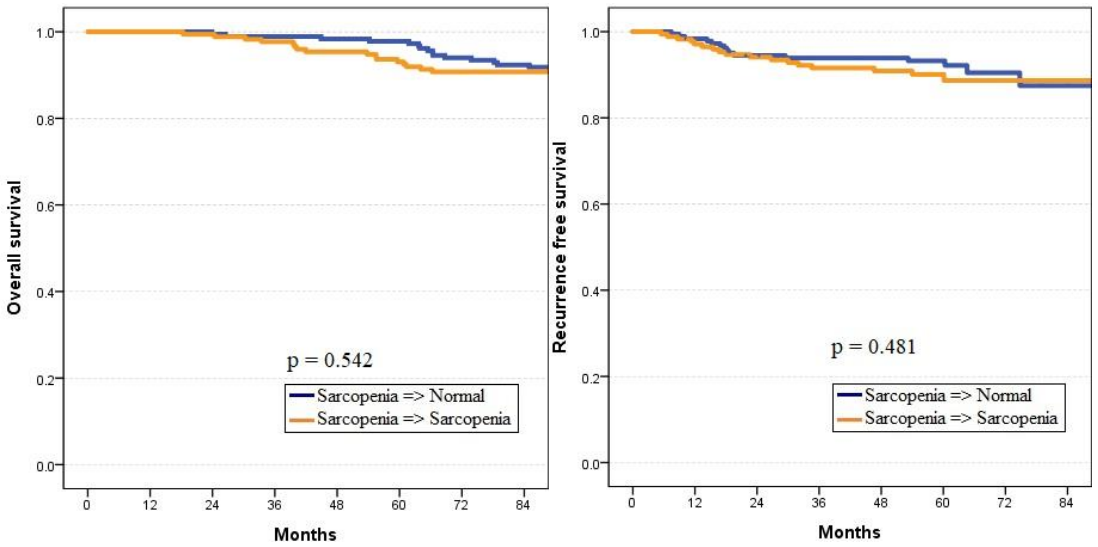


Figure 8b. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among males

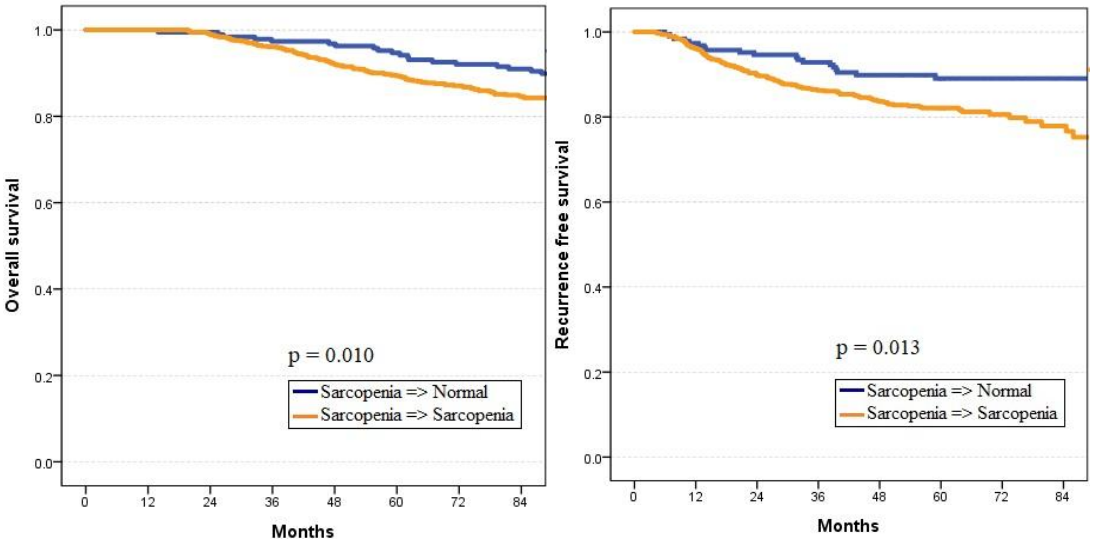


Figure 8c. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among patients older than 70 years

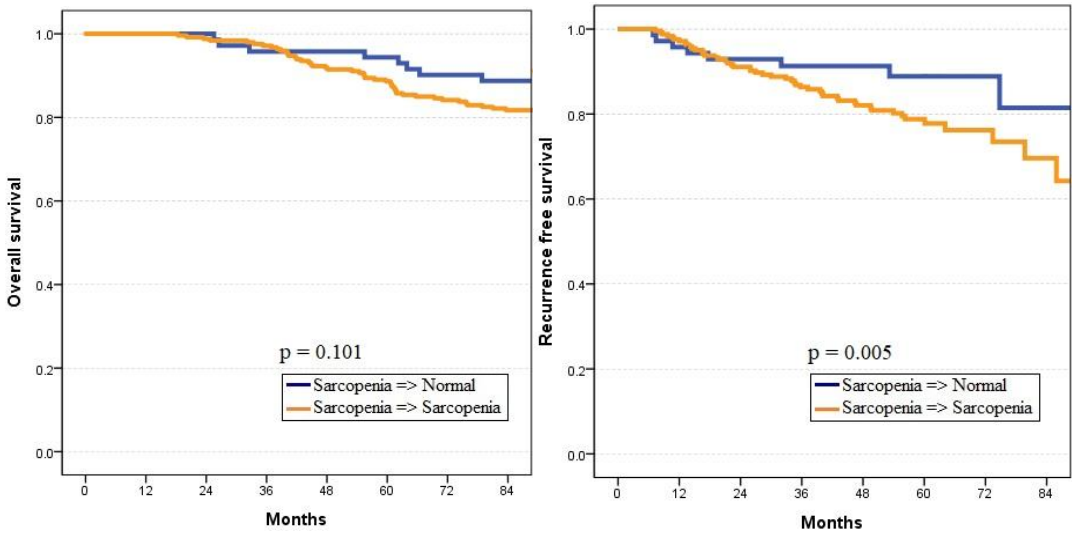


Figure 8d. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among patients under 70 years

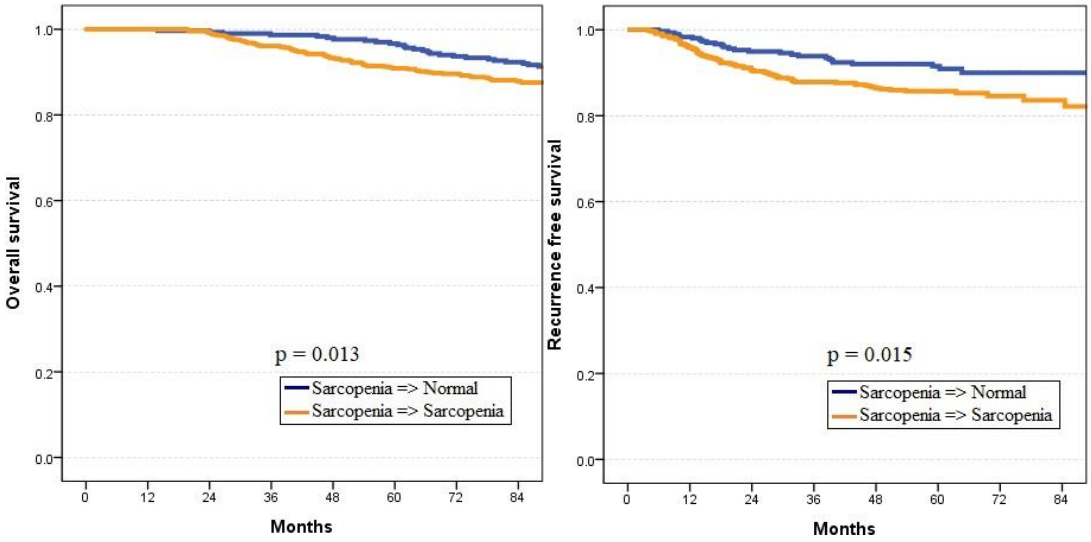


Figure 8e. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among patients with pathologic stage 0-II

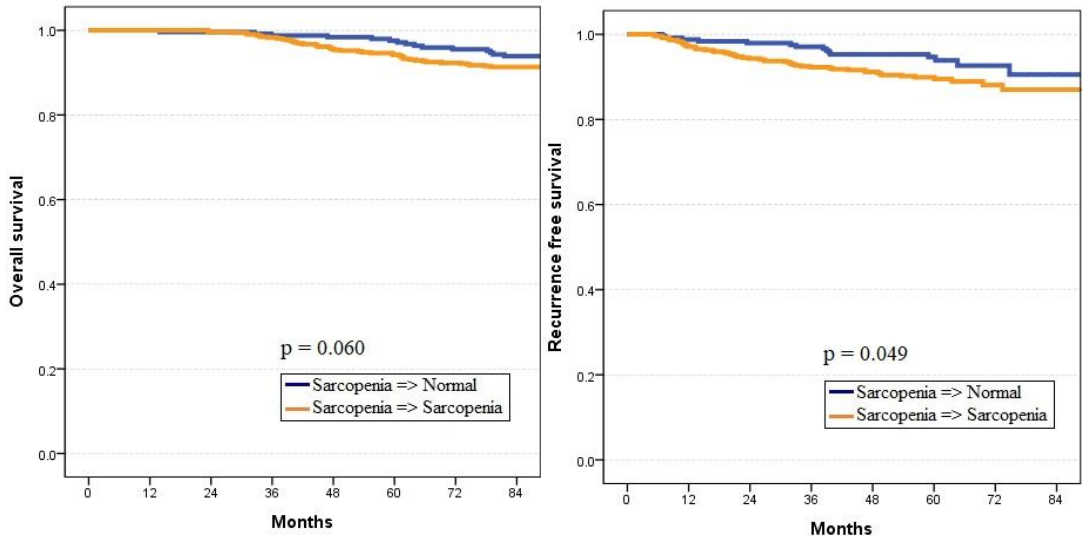


Figure 8f. Association of overall survival and recurrence-free survival with changes with sarcopenia to normal, and sarcopenia to sarcopenia in pathologic stage III

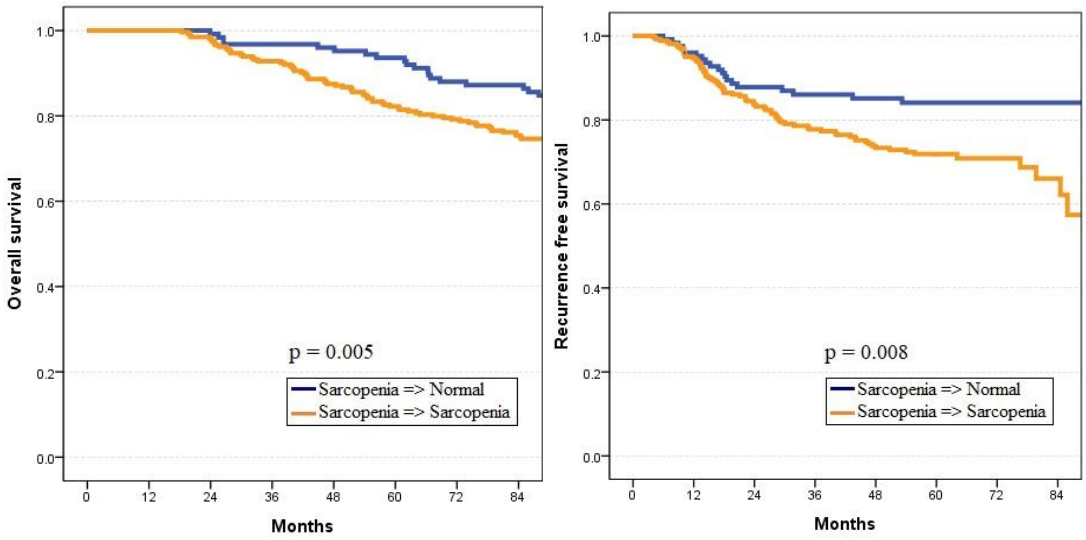


Figure 8g. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among those under CTx

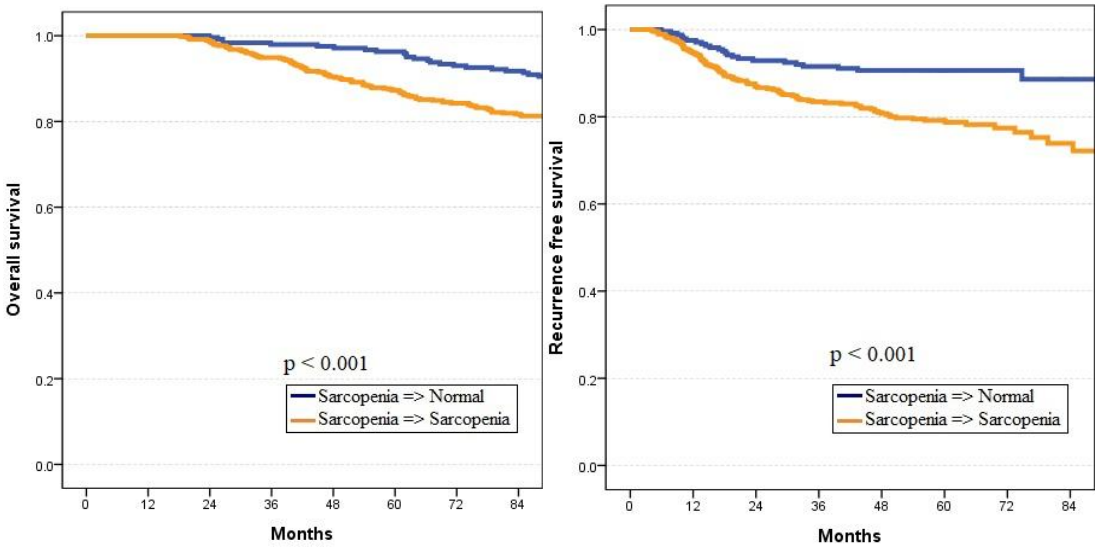
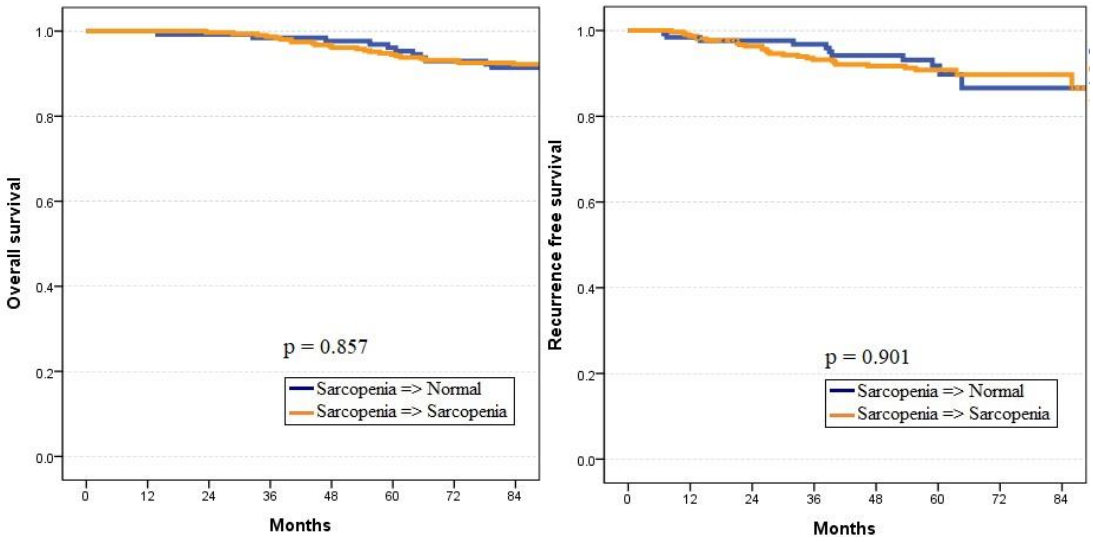


Figure 8h. Association of overall survival and recurrence-free survival with changes in sarcopenia to normal, and sarcopenia to sarcopenia among those not under CTx



Preoperative postoperative 2-3 year sarcopenia were the factors associated with RFS in multivariate analysis. Age, pathologic stage, sex, and receipt of adjuvant chemotherapy history were associated with RFS by risk factors in univariate analysis. Among these, age and pathologic stages were confirmed as risk factors for RFS in multivariate analysis (Table 3).

For OS, preoperative and postoperative 2-3 year sarcopenia, age, and pathologic stage were significant risk factors in multivariate analysis (Table 4).

Table 3. Risk factors associated with recurrence-free survival (N = 2333, Recurrence = 296)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p
PreOP Sarcopenia				
No	1		1	
Yes	2.251 (1.714-2.957)	<0.001	1.604 (1.118-2.302)	0.010
6-12M Sarcopenia				
Normal	1		1	
Sarcopenia	1.982 (1.535-2.559)	<0.001	0.825 (0.565-1.206)	0.321
2-3Y Sarcopenia				
Normal	1		1	
Sarcopenia	2.450 (1.891-3.174)	<0.001	1.934 (1.322-2.829)	0.001
Age, years				
<70	1		1	
≥70	1.629 (1.235-2.150)	0.001	1.401 (1.057-1.855)	0.019
Stage				
Stage 0-II	1		1	
Stage III	3.254 (2.508-4.222)	<0.001	3.253 (2.484-4.261)	<0.001
Gender				
Male	1		1	
Female	1.465 (1.116-1.923)	0.006	1.196 (0.895-1.599)	0.226
CTx				
No	1		1	
Yes	1.145 (1.048-1.250)	0.003	1.042 (0.920-1.180)	0.518

CI, confidence interval; CTx, chemotherapy; PreOP, preoperative; 6-12M, postoperative 6-12 months; 2-3Y, postoperative 2-3 years

Table 4. Risk factors associated with overall survival (N = 2333, Death = 237)

Variables	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	p	Hazard ratio (95%CI)	p
PreOP Sarcopenia				
No	1		1	
Yes	2.234 (1.700-2.934)	<0.001	1.603 (1.118-2.298)	0.010
6-12M Sarcopenia				
Normal	1		1	
Sarcopenia	1.965 (1.522-2.536)	<0.001	0.809 (0.554-1.181)	0.273
2Y-3Y Sarcopenia				
Normal	1		1	
Sarcopenia	2.444 (1.887-3.167)	<0.001	1.958 (1.342-2.856)	<0.001
Age, years				
<70	1		1	
≥70	1.340 (1.087-1.653)	0.006	1.341 (1.012-1.776)	0.041
Stage				
Stage 0-II	1		1	
Stage III	3.200 (2.467-4.151)	<0.001	3.219 (2.457-4.216)	<0.001
Gender				
Male	1		1	
Female	1.473 (1.122-1.933)	0.005	1.220 (0.913-1.629)	0.179
CTx				
No	1		1	
Yes	1.141 (1.045-1.245)	0.003	1.038 (0.917-1.175)	0.555

CI, confidence interval; PreOP, preoperative; 6M-1Y, postoperative 6 months-1 year; 2Y-3Y, postoperative 2 year-3 year; CTx, chemotherapy

Discussion

This study showed that either preoperative or postoperative 2-3 year sarcopenic status together with age and pathologic stage were independent negative prognostic factors for OS and RFS. In addition, patients who recovered from sarcopenia to normal status had better OS and RFS than those who retained sarcopenia.

Many studies have reported that sarcopenia was a poor prognostic factor in CRC.[45, 46] However, only few studies evaluated the association between postoperative muscle mass changes and oncologic outcomes.[23,47] We evaluated whether postoperative changes in sarcopenic status affected long-term oncologic outcomes in non-metastatic CRC. Sarcopenia in patients was evaluated at postoperative 6-12 months, when adjuvant treatment was completed, and at postoperative 2-3 year, when recurrences occur most commonly. After 2-3 years post-surgery, body composition status rarely changed, suggesting that postoperative care including nutrition and exercise might influence prognosis. This hypothesis was important because postoperative care is a manageable factor. The survival of cancer patients increases with advances in cancer treatment. Therefore, there is an overall prevalence of patients with cancer and chances of second cancer increase.[48] Under current circumstances, we need to invest in postopetative care to improve oncologic outcomes and decrease secondary cancer.

Many studies showed that sarcopenia was a risk factor for morbidity and mortality. Sarcopenia was had worse impact for morbidity in patients with cancer such as esophagus[9], lung[24], pancreas[7, 25, 49], and colon and rectum[45, 46].

The cost of sarcopenic patients care is higher than that of other patients because sarcopenic patients stay longer in the hospital.[31] The effects of sarcopenia on health care costs are in the immediate postoperative period. Sarcopenic patients tend to have more postoperative

complications than others and they also attend other hospitals after being discharged.[31] However, there was no association between sarcopenia and re-admission rate. Sarcopenia is associated with high costs and negative margins after major surgery. Given that sarcopenia may be manageable, efforts to reduce costs associated with major surgery should focus on targeted preoperative interventions.[32] In addition, postoperative rehabilitation is also important.

Sarcopenia also affects poor prognosis for survival.[50] It is not clear how sarcopenia affects patient prognosis. There is a hypothesis that sarcopenia induces systemic inflammation.[19, 42] Systemic inflammatory status is also known to increase the risk of cancer and diminish treatment efficacy.[51] Miyamoto et al. reported that sarcopenia negatively affected survival in patients undergoing curative resection for stage I-III CRC.[43] They conducted a retrospective analysis of 220 consecutive patients with stage I–III CRC who underwent curative resection of whom 55 (25%) had sarcopenia. The median follow-up duration was 41.4 months. RFS and OS were significantly shorter in patients with sarcopenia than in those without (5-year RFS, 56% vs. 79%, log-rank p=0.006; 5-year OS, 68% vs. 85%, log-rank p=0.015). Multivariate Cox regression analysis revealed that sarcopenia was independently associated with shorter RFS (HR=2.176; 95% CI 1.200–3.943; p=0.010) and OS (HR 2.270; 95% CI 1.147–4.494; p=0.019). Moreover, they showed that sarcopenia was associated with a poor prognosis, especially in young patients (log-rank p<0.001). Like in our study, sarcopenia had been shown to adversely affect the OS and RFS. Furthermore, they also used SMI by measuring patient muscle mass. However, this study differed from our study because the muscle mass was measured using CT only preoperative. In our study, a significant difference was shown in younger but not in older age when compared based on the changes in sarcopenia (Figure 8c, 8d). This study chose the SMI using sex-specific category variable that Q1 (male: 62.0–85.0, n=34; female: 51.7–65.4, n=21), Q2 (male: 52.2–61.8, n=34; female: 46.9–51.3, n=21), Q3 (male: 49.9–54.9, n=33; female: 42.1–46.8, n=22), and Q4 (male: 32.6–49.5, n=34; female: 15.6– 42.1, n=21). They used this category divided into two

groups by Q1-Q3 and Q4. This division had the smallest muscle mass quartile and the others. They used other standards that were different from those used in our study, but it showed that sarcopenia induced worse prognosis, which is in accordance with our results. Feliciano et al. studied that prospective cohort of 2470 patients with stage I-III CRC diagnosed from 2006 through 2011.[42] They used CT scans to calculate SMI by measuring muscle status. Among 2470 patients, 1219 (49%) were female; mean (SD) age was 63 (12) years. A neutrophil-to-lymphocyte ratio (NLR) of 3 or greater and sarcopenia were common (1133 [46%] and 1078 [44%], respectively). Over a median of 6 years of follow-up, they observed 656 deaths, 357 from CRC. An NLR of 3 or greater and sarcopenia independently predicted overall (HR, 1.64; 95% CI, 1.40-1.91 and HR, 1.28; 95% CI, 1.10-1.53, respectively) and CRC-related death (HR, 1.71; 95% CI, 1.39-2.12 and HR, 1.42; 95% CI, 1.13-1.78, respectively). Patients with both sarcopenia and NLR of 3 or greater had the risk of death, overall (HR, 2.12; 95% CI, 1.70-2.65) and CRC related (HR, 2.43; 95% CI, 1.79-3.29). Similar to our previous study, this study evaluated NLR and sarcopenia together and also showed that sarcopenia lead to a higher mortality rate.

There are other studies on perioperative body composition changes and patients prognosis.[47] Zarinsefat et al reported that 425 patients who underwent inpatient general surgery were identified to have both within 90-day preoperative and within 90-day postoperative abdominal CT that were used to calculate changes in trunk muscle size. The primary outcome was 1-year survival. A total of 351 (82.6%) patients experienced a decrease in trunk muscle size in the time between their scans. The adjusted mortality rate for the tertile of the greatest rate loss was 24.0% compared with 13.3% for the tertile of the least decrease. They also reported that trunk muscle size may be a critical target for interventional programs focusing on perioperative optimization of the surgical patient. Differences from our study is that they evaluated changes in trunk muscle by TPA, compared only to the 1-year survival rate, and analyzed in terms of not only colorectal surgery but also general surgery such as the liver, stomach, and bladder. However, similar to our study, the decrease

in patient muscle size was associated with worse prognosis.

In addition to sarcopenia, other types of body composition indicator such as BMI, sarcopenic obesity, and visceral obesity were also studied for evaluating the association with postoperative and oncologic outcomes in CRC or other cancers. Sarcopenia is not the only measure of patient body composition. Body composition parameters include BMI, sarcopenic obesity (SO), and visceral obesity (VO). BMI at the time of diagnosis and that following diagnosis of CRC were associated with mortality risk.[10] However, Kroenke et al, reported that recommendations for weight loss in the immediate postdiagnosis period among patients with CRC who are overweight may be unwarranted. The prognosis was poor for those who lost weight >20% or more after surgery, and those who were obese at the time of surgery also had poor prognosis in esophageal cancer.[14] These reports only focused BMI not the "muscle mass." Therefore, weight loss also includes muscle loss, which justifies their result. In lung cancer patients, those with either high or low BMI showed poor prognosis.[6] High BMI implies obesity. A low BMI means no obesity, but it is an index that focuses only on the weight, suggesting that muscle mass is low. Therefore, it can be seen that body weight is not an important indicator in evaluating patient prognosis, but muscle is an indicator. As such, studies have shown that sarcopenia was more specific than BMI in predicting patient prognosis.

Visceral obesity (VO) is determined with higher precision if the direct visceral fat area (VFA) is measured using CT.[52] A VFA of >100 cm^2 was associated with the metabolic syndrome and was a risk factor for poor outcome and longer hospital stay after colorectal operations[53]. Cakir et al reported that association of VO with worse outcome after colon cancer surgery was most pronounced in patients with a BMI <25 kg/m^2.[54]

Some studies reported that sarcopenia was not associated with morbidity or mortality.[55, 56] Visceral obesity predicted fewer lymph node metastases and better overall survival in CRC patients.[55] Park et al reported that metastatic lymph node ratio (MLR) was defined as the number of involved nodes by tumor divided by the total number of resected lymph nodes.

Visceral (VFA) and subcutaneous fat areas (SFA) were determined by measuring abdominal fat volume distribution via CT scan, and visceral obesity (VO) was defined as the VFA-to-total fat area ratio (VFA/TFA) >0.29. In multivariate analysis, among 186 patients, there were inverse associations between VFA/TFA and MLR (OR=0.413, 95% CI=0.216–0.789, p=0.007). Mean OS was 69.71±3.97 months in the not VO subgroup vs. 80.02±2.17 months in the VO subgroup. Patients with visceral obesity tended to have significantly better OS than patients with non-visceral obesity. This study used VO as an indicator of body composition. The above paper was missing some parts. First of all, in the case of visceral obesity, lymphadenectomy may not be performed properly because there is a lot of fat. Therefore, visceral obesity predicted fewer lymph node metastases. However, the fact of better OS in CRC patients requires more accurate studies because VO did not reflect muscle status, and comorbidity.

Van Roekel et al reported that although visceral obesity and sarcopenia were relatively common at CRC diagnosis, they found no significant associations of these parameters with long-term high quality of life in stage I–III CRC survivors[56]. A cross-sectional study was conducted in 104 stage I–III CRC survivors diagnosed at Maastricht University Medical Center, the Netherlands (2002–2010). Diagnostic CT images at the level of the third lumbar vertebra were analyzed to retrospectively determine VFA and SMI as measure of muscle mass and for deter- mining sarcopenia. Participants showed a large variation in body composition parameters at CRC diagnosis with a mean VFA of 136.1 cm^2 (SD: 93.4) and SMI of 47.8 cm^2/m^2 (SD: 7.2); 47% was classified as being viscerally obese, and 32% as sarcopenic. In multivariable linear regression models, associations of the body composition parameters with long-term global quality of life, physical, role and social functioning, disability, fatigue, and distress were not significant, and observed mean differences were below predefined minimal important differences. They chose the category of quality of life based on the International Classification of Functioning, Disability and Health (ICF) of the World Health Organization. These criteria adopt a broad biopsychosocial definition of

human functioning, including physical health components (body perspective) and the ability to perform daily activities and societal roles (individual and societal perspectives). However, the notion that sarcopenia was not associated with quality of life was limited to episodes at diagnosis. If patients with sarcopenia are managed after surgery, the prognosis is good as in our work. Evidently, there was no correlation with prognosis, so more research is needed.

E. H. Kim et al suggest the standard of sarcopenia in Koreans in a study of 11,845 people.[57] Divided by Korean standards, sarcopenic males are <39.8cm^2/m^2 and sarcopenic females are <28.4cm^2/m^2. When analyzing by applying Korean standards, OS (HR: 1.848, 95% CI; 1.128-3.026, p=0.013) and RFS (HR; 1.829, 95% CI: 1.116-2.997, p= 0.017) were showed significantly poor outcome in preoperative sarcopenic patients. Postoperative 2~3year sarcopenia was also related to both OS (HR; 3.902, 95% CI :2.382-6.392, p<0.001). and RFS (HR; 3.900, 95% CI :2.380-6.391, p<0.001) and the difference was greater than that of preoperative sarcopenia. In multivariate analysis, sarcopenia at postoperative 2~3year was found to be a significant associative factor in RFS and OS. However, when Korean standards were applied, the number of sarcopenic patients were very small, accounting for only 4.2% of the total group. Therefore, it was difficult to analyze the difference in oncological results according to changes in sarcopenia before and after surgery. In the future, it is necessary to analyze the effect of sarcopenia on the prognosis of colorectal cancer in Koreans through a large-scale study applying Korean sarcopenic standards.

There were some limitations in our study. First, this study was retrospective cohort study. Therefore, selection bias little intervened that we collected patients who had CT scan at preoperative necessarily. Second, we chose the definition of sarcopenia by Prado et al.[3] among variable criteria of sarcopenia,[43, 58] because many 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 cm^2/m^2, sarcopenia in men, SMI <52.4 cm^2/m^2).[13, 42, 59, 60] Other limitation was surveillance. Patients in our cohort were traced until postoperative 2-3 year. If the follow-up period was longer, it is unknown whether sarcopenia would have had

different efficacy effects. Additionally, we did not take into account patient medical comorbidity and their medications that could affect their body composition.

Conclusion

In conclusion, postoperative sarcopenia as well as its changes affect oncologic outcomes. This result suggests that 'patient care' is needed to maintain positive body composition after surgery and may also affect oncological outcomes. Therefore, a large-scale study is needed to verify the results of our study. In addition, it will be possible to develop this research further to a prospective study to evaluate the role of intervention such as life style modification coaching in oncological outcome.

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국문 요약

연구목적

수술 전 후 기간동안 체 성분을 조절할 수 있다. 체질량지수, 근육감소증 및 내장 비만과 같은 체성분을 나타내는 많은 지표들이 있다. 그 중 최근에 근육감소증이 주목을 받고 있다. 비전이성 대장직장암 환자에서 수술 전 후 근육 감소증의 변화와 종양학적 결과의 연관성을 평가한다.

연구방법

2009 년 1 월부터 2012 년 12 월까지 서울아산병원에서 치료받은 0-III 기 대장직장암 환자 2,333 명을 대상으로 했다. 진단 당시의 체성분은 Asan-J 소프트웨어를 사용하여 복부-골반 컴퓨터 단층 촬영(CT)을 사용하여 측정했다. L3 요추 수준에서 두 개의 연속적인 축 방향으로 CT 이미지를 처리하고, 각 환자에 대해 평균을 냈다. 근육 감소증은 총 복근 면적 (TAMA) 및 골격근 지수 (SMI, TAMA / 높이^2) 와 같은 CT 측정 매개 변수를 사용하여 정의하였다. 환자들은 수술 전, 수술 후 6 개월 -1 년, 수술 후 2 년 -3 년에 CT 촬영을 받았 다. 생존율과 체성분 변화 사이의 연관성을 평가하기 위해 Cox 비례 위험 분석을 수행했다.

연구결과

2,333 명 중 1,728 명 (74.1 %)이 결장암, 605 명 (25.9 %)이 직장암이었다. 총 1387 명 (59.5 %)의 환자가 보조 화학 요법을 받았다. 근육감소증 기준에 따르면 수술

전 1,155 명 (49.5 %), 890 명 (38.2 %), 893 명 (38.3 %)에서 수술 전, 수술 후 1 년, 수술 후 2 ~ 3 년에 근육감소증을 보였다. 5 년 OS 비율 (95.8 % vs 92.1 %, [HR] = 2.234, p <0.001) 및 5 년 RFS 비율 (93.2 % vs 86.2 %, HR = 2.251, p <0.001)은 수술 전 근육감소증 환자에서 유의하게 낮았다. 5 년 OS와 RFS 비율은 수술 후 근육감소증의 변화에 따라 달랐다. OS와 RFS는 모두 회복 된 환자보다 수술 후 2 ~ 3 년 에 근육감소증이 지속된 환자에서 더 낮았다 (회복 vs. 지속성 근육감소증; OS : 96.2 % vs. 90.2 %, p = 0.001; RFS : 91.1 % vs. 83.9 % , p = 0.002). 다변량 분석에서 지속적인 근육감소증, 연령 및 병리학적 단계가 OS 및 RFS의 감소와 관련된 독립적인 요인으로 확인되었다.

결론 및 제언

수술 전 및 수술 후의 감시기간동안 근육감소증과 근육감소증 상태의 변화는 종양학적 결과와 관련이 있다.