의학박사 학위논문

전이성 직결장암 환자에서 항암치료 중 신체 구성의 변화와 예후

Longitudinal changes in body composition during palliative chemotherapy and survival outcomes in metastatic colorectal cancer

울산대학교 대학원

의 학 과

정 혜 현

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이 논문을 의학박사 학위 논문으로 제출함

2022년 8월

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국문요약

연구 배경: 고형암 환자에서 근감소증과 불량한 예후와의 연관성은 잘 알려져 있다. 최근 영상 기술의 발전으로 CT 영상을 분석하여 골격근의 양 뿐 아니라 골격근의 질 (골격근 내 지방의 침윤), 그리고 체지방의 분포 등에 대한 평가가 가능해져, 근감소증 뿐 아니라 근지방증, 복부 비만, 피하 비만 등의 신체 구성에 대한 통합적인 평가가 가능해졌다. 직결장암에서 신체 구성에 대한 이전 연구는 주로 전이가 없는 환자를 대상으로 하거나 한 시점에 측정된 신체 구성만으로 예후 분석이 이루어진 경우가 많아, 전이성 직결장암 환자에서 항암치료 중 신체 구성의 변화 양상과, 이에 따른 예후에 대해서는 잘 알려져 있지 않다.

연구 방법: 본 연구에서는 2008년부터 2017년까지 서울아산병원에서 고식적 항암화학요법을 시행받은 재발성/전이성 직결장암 환자를 후향적으로 확인하였다. 이들 중 고식적 항암치료 시작 전과, 치료 종결 이후 시행한 CT 영상이 모두 있는 경우를 분석에 포함하였으며, 전체 치료 기간 중 시행한 여러 시점의 연속적 CT 영상을 수집하였다. 딥러닝 프로그램을 이용하여, 근감소증, 근지방증, 복부 비만, 피하 비만의 빈도와 이들의 치료 중 변화 및 생존 기간과의 연관성을 평가하였다. 사망에 대한 위험비는 시간-의존 콕스 회귀분석을 시행하여 구하였으며, 예후와 연관된 임상 인자로 보정하였다.

연구 결과: 총 1805명의 환자가 분석에 포함되었다. 진단 시 연령의 중위값은 57세였으며, 62% 의 환자가 남성이었다. 고식적 항암화학요법 시행 전 근감소증의 빈도는 4.7% 이었으며, 근지질증은 30.9%, 내장 비만은 36.5%, 복부 비만은 37.1%의 환자에서 확인되었다. 항암화학요법 시행 중 약 54.5% 환자에서 중대한 신체 구성의 변화를 겪었으며, 새로운 근감소증과 근지질증이 각각 9.1% 와 19.2% 의 환자에서 발생하였다. 약 21.5% 와 18.1% 환자에서 각각 기존의 내장 비만과 피하 비만이 소실되거나 새로 발생하는 변화를 경험하였다. 치료 기간 중의 신체 구성의 이러한 변화는, 치료 시작 시 상태와 무관하게 치료 종결 이후 여명과 유의한 연관성을 보여 치료 중 근육의 양 또는

질이 감소하거나, 내장 또는 피하지방이 감소한 환자는 치료 종결 후 더 짧은 생존 기간을 보였다. 치료기간 전반에 걸쳐 근감소증과 근지질증은 짧은 전체 생존기간과 연관성을 보였다(근감소증의 위험비, 2.55 [95% 신뢰구간(CI), 2.06−3.16, $p < 0.001$; 근지질증의 위험비, 2.37 [95% CI, 2.00−2.82], $p < 0.001$). 반면 내 비만과 피하 비만은 모두 긴 전체 생존기간과 연관성을 보였다 내장 비만의 위험비, 0.69 [95% CI, 0.57−0.82], $p < 0.001$; 피하 비만의 위험비, 0.78 [95% CI, 0.64−0.95], $p = 0.015$). 비만과 전체 생존 기간에 대한 유리한 연관성은 높은 내장 및 피하지방 값에서도 반대 관계를 보이지 않았다. 이러한 신체 구성 값들은 서로간 그리고 체질량 지수나 혈액검사 결과와 낮은 연관도를 보였다.

결론: 고식적 항암치료 시행을 받는 직결장암 환자에서, 신체 구성의 이상 소견은 흔하고, 항암치료 시행 중 변화 역시 흔하게 발생하며 이들 중 근지질증의 증가가 가장 두드러졌다. 이러한 신체 구성과 그 변화가 모두 예후와 유의한 연관성을 보였고, 임상에서 암 환자 진료 시 CT 스캔이 정기적으로 이루어 지는 점을 고려할 때, 본 연구에서와 같이 CT 영상을 통해 신체 구성과 그 변화를 평가하면 추가적인 검사를 시행하지 않고도 이들 환자의 예후에 대한 유용한 정보를 줄 수 있을 것으로 생각된다.

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Introduction

Cancer is a systemic disease that is accompanied by changes in the body's metabolism and composition. [1, 2] Recently, there has been a growing interest regarding the abnormalities in body composition and their clinical implication in patients with cancer. Studies have repeatedly shown poor prognoses in patients with sarcopenia, a loss of muscle mass across various types and stages of cancers.[3] Although many of these studies on body composition had focused mostly on sarcopenia, the recent development of imaging techniques has aided a more comprehensive assessment of the body composition beyond muscle quantity alone, such as the muscle quality or the distribution of body fat.[4] These developments have led to reports showing an association between myosteatosis (infiltration of fat in skeletal muscles) and poor survival outcomes,[5] and leading to a more accurate assessment of obesity rather than simply determining it by body weight.

In colorectal cancer, the presence of sarcopenia at diagnosis has been associated with poor survival outcomes, higher postoperative morbidity and mortality, and toxicity to chemotherapy.[6] However, many of these studies included baseline values only, and did not show changes during treatment. Some studies included chronological data, but the majority of them included patients with non-metastatic colorectal cancers and compared pre-and post-operative values or included various stages of cancers. In addition, their analysis was limited to sarcopenia alone among all the abnormalities in body composition markers.[5, 6] Data analysis assessing comprehensive changes in the body composition, including quantity and quality of skeletal muscle and body fat distribution during palliative chemotherapy in metastatic colorectal cancer, is limited.

In addition, conflicting results have been reported regarding the

prognostic implication of obesity in patients with cancer, including colorectal cancer.[7, 8] This is partly attributed to a methodological limitation as many previous studies used anthropometric methods, such as body mass index (BMI) or abdominal circumference for defining obesity, whereas some argued that obesity can have different prognostic implications according to the type and stage of cancer,[7, 9] suggesting the need for an accurate measurement of the body fat area and homogeneous patient selection.

Here, we selected a homogeneous group of patients with recurrent/metastatic colorectal cancer treated with palliative chemotherapy and assessed the abnormalities in muscle quantity (sarcopenia), quality (myosteatosis), and distribution of fat (visceral and subcutaneous obesity) using serially collected computed tomography (CT) images. All measurements were performed using a deep-learning software. By implementing these methods, we aimed for a comprehensive evaluation of abnormalities in body composition, their serial changes during systemic chemotherapy, and their prognostic implications in a real-world patient population with advanced colorectal cancer.

Methods

1. Patients

Patients with recurrent or metastatic colorectal cancer aged 18 years and older who received palliative chemotherapy between January 2008 and November 2017 in Asan Medical Center, a tertiary referral center in Republic of Korea, were retrospectively identified. Patients were eligible for analysis if they were followed up until the cessation of palliative chemotherapy and had at least two or more abdominal CT scans for the measurement of body composition markers. Abdominal CT scan at two time points, at the start of

palliative chemotherapy and after the last chemotherapy, were required. This study was approved by the institutional review board of Asan Medical Center and performed following the ethical standards of the institutional research committee and the Declaration of Helsinki. The institutional review board granted a waiver of informed consent for this retrospective study.

2. Measurement and definition of body composition markers

Multiple abdominal CT images for each patient obtained during routine practice were retrospectively collected. The time points for CT images analyzed for this study included the start of each line of chemotherapy (palliative first-, second-, and third-line chemotherapy) and the last CT image obtained after discontinuation of all chemotherapy. Information on BMI and laboratory markers known to be associated with malnutrition or systemic inflammation, including serum albumin level, total cholesterol level, absolute lymphocyte count (ALC), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), measured at the time of each CT scan, was also collected.[10-12]

We measured the areas of fat and muscle and their quality using a deep-learning software described previously.[13] Briefly, the convolutional network-based software automatically selected axial CT images at the L3 vertebra level and demarcated the areas of skeletal muscle, visceral fat, and subcutaneous fat using predetermined thresholds (-29 to +150 and -190 to -30 Hounsfield units for muscles and fat tissues, respectively). For the assessment of sarcopenia, the skeletal muscle area (SMA) was measured and adjusted for BMI (SMA/BMI, in cm^2/m^2), and the T-scores for SMA/BMI were calculated using reference values in a young, healthy Korean population.[14] For the assessment of myosteatosis, areas of normal attenuation

muscle area (NAMA) were divided by the total abdominal muscle area (TAMA), where TAMA comprised NAMA, representing areas of good quality muscle, low attenuation muscle area (LAMA), representing areas of poor quality muscle, and intermuscular adipose tissue area (IMAT), representing the apparent fat tissue between muscle groups and muscle fibers. The T-scores for NAMA/TAMA were calculated using values measured in the young reference group of Koreans.[15]

Four categories of body composition abnormalities were defined in this study as follows: 1) sarcopenia, which represents low muscle mass in terms of muscle quantity, was defined as a T-score <-2.0 calculated from the SMA/BMI index;[14] 2) myosteatosis, which represents fatty infiltration of muscle in terms of muscle quality, was defined as a T-score <-2.0 calculated from the LAMA/TAMA index;[15] 3) visceral obesity, which represents an excessive amount of visceral fat, was defined as the visceral fat area (VFA) ≥ 100 cm^2;[16] 4) subcutaneous obesity, which represents an "excess amount of subcutaneous fat," was defined as the height-adjusted subcutaneous fat area index (SFAI) ≥ 50.0 cm^2/m^2 in men and ≥ 42.0 cm^2/m^2 in women.[17] The status of these four body composition markers was assessed for every CT image collected for analysis. Lastly, BMI ≥ 25 kg/m^2 was defined as obese, and BMI < 18.5 kg/m^2 was defined as underweight according to the world's health organization guidelines for the Asia-Pacific region.[18]

3. Statistical analysis

Overall survival (OS) was defined as the time from the date of the first palliative chemotherapy to the date of death of any cause. Survival after the last chemotherapy was defined as the time from the date of the last CT

scan after stopping chemotherapy to the date of death. Baseline characteristics were analyzed using descriptive methods. Changes in the body composition markers during the treatment course were compared using a linear mixed model. For survival analyses, time-dependent Cox regression was used to estimate the effect of body composition markers measured at multiple time points on OS. A restricted cubic spline model with four knots was used to estimate the non-linear associations of body composition markers as continuous values with OS. Pearson's R was used to assess the correlation among body composition markers, BMI, and laboratory values measured at each time point. All statistical analyses were carried out using R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

1. Patients and incidence of abnormal body composition at baseline

From January 2008 to November 2017, a total of 2960 patients with recurrent/metastatic colorectal cancer who received palliative chemotherapy were identified. Among those, patients without adequate abdominal CT scan either at the start of or after stopping palliative chemotherapy (n = 1100), patients who were on chemotherapy (n = 52), and patients without survival data (n = 3) were excluded. As a result, a total of 1805 patients were included in the analysis (Fig.1).

Baseline characteristics of the patients are summarized in Table 1. Overall, the median age at diagnosis was 57 years (range: 18-86), with men comprising 62.1% (n = 1121) of the patients. At baseline, 4.7% (n = 85) of patients had sarcopenia, 30.9% (n = 558) had myosteatosis, 36.5% (n = 659) had visceral obesity, and 37.1% (n = 670) had subcutaneous obesity. Regarding BMI, 68.3% of the patients (n = 1233) had BMI within the normal

range, and 24.8% (n = 447) were obese. None of them had "severe" obesity (BMI ≥ 40 kg/m^2). Of note, the median BMI of the sarcopenic patients at diagnosis was higher than that of the non-sarcopenic patients (22.7 vs. 24.8 in non-sarcopenic vs. sarcopenic patients, $p < 0.001$). Sarcopenia, myosteatosis, and visceral obesity were associated with age. The median age at diagnosis was higher in patients with sarcopenia, myosteatosis, and visceral obesity compared with patients without them (Table 1). The median T-scores for sarcopenia and myosteatosis were decreased and the median VFA was increased with age. However, subcutaneous obesity was not associated with age (Supplementary Figure S1). The incidence of sarcopenia did not differ by sex (5.0% [n = 56] vs. 4.2% [n = 29] in men and women, respectively; $p = 0.535$). However, compared with women, men had higher rates of visceral obesity (44.4% [n = 498] vs. 23.5% [n = 161], $p < 0.001$), but lower rates of myosteatosis (22.1% [n = 248] vs. 45.3% [n = 310], $p < 0.001$) and subcutaneous obesity (15.8% [n = 177] vs. 72.1% [n = 493], $p < 0.001$).

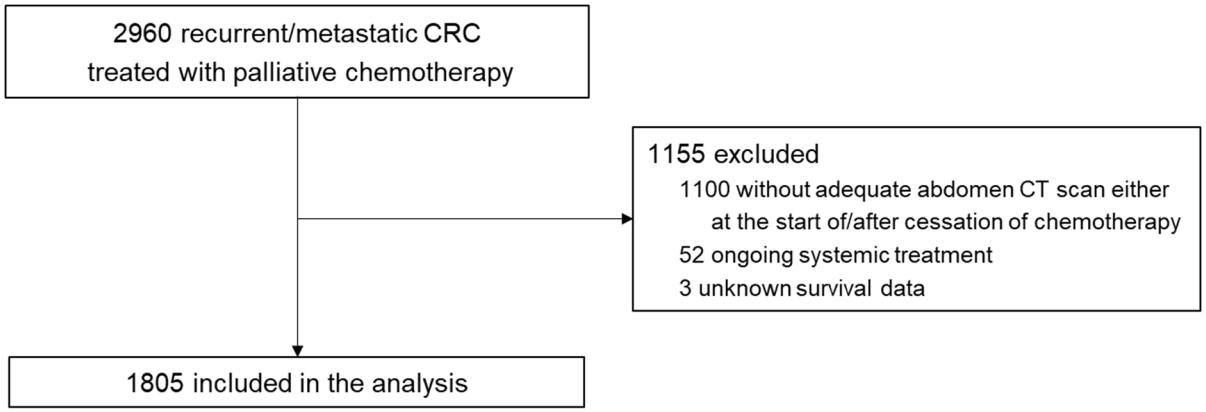


Figure 1. Flow diagram

Abbreviations: CRC, colorectal cancer; CT, computed tomography

Table 1. Baseline characteristics

	All patients N = 1805	No sarcopenia N = 1720	Sarcopenia N = 85	*p* value	No myosteatosis N = 1247	Myosteatosis N = 558	*p* value	No visceral obesity N = 1146	Visceral obesity N = 659	*p* value	No subcutaneous obesity N = 1135	Subcutaneous obesity N = 670	*p* value
Age at diagnosis													
Median (range)	57 (18–86)	57 (18–86)	65 (20–81)	< 0.001	55 (18–82)	63 (32–86)	< 0.001	56 (18–82)	60 (30–86)	< 0.001	57 (19–82)	57 (18–86)	0.494
Sex				0.535			< 0.001			< 0.001			< 0.001
Male	1121 (62.1)	1065 (61.9)	56 (65.9)		873 (70.0)	248 (44.4)		623 (54.4)	498 (75.6)		944 (83.2)	177 (26.4)	
Female	684 (37.9)	655 (38.1)	29 (34.1)		374 (30.0)	310 (55.6)		523 (45.6)	161 (24.4)		191 (16.8)	493 (73.6)	
BMI (kg/m^2)													
Median (IQR)	22.8 (20.8–25.0)	22.7 (20.7–24.8)	24.8 (22.6–28.0)	< 0.001	22.4 (20.4–24.3)	24.0 (21.9–26.1)	< 0.001	21.5 (19.8–23.2)	25.1 (23.7–27.0)	< 0.001	22.0 (20.0–23.9)	24.4 (22.2–26.7)	< 0.001
Normal (18.5–24.9)	1233 (68.3)	1188 (69.1)	45 (52.9)	< 0.001	908 (72.8)	325 (58.2)	< 0.001	920 (80.3)	313 (47.5)	< 0.001	852 (75.1)	381 (56.9)	< 0.001
Obese (≥ 25.0)	447 (24.8)	407 (23.7)	40 (47.1)		231 (18.5)	216 (38.7)		101 (8.8)	346 (52.5)		160 (14.1)	287 (42.8)	
Underweight (< 18.5)	125 (6.9)	125 (7.3)	0 (0.0)		108 (8.7)	17 (3.0)		125 (10.9)	0 (0.0)		123 (10.8)	2 (0.3)	
Disease status				0.727			0.986			0.646			0.291
Recurrent	551 (30.5)	527 (30.6)	24 (28.2)		380 (30.5)	171 (30.6)		345 (30.1)	206 (31.3)		336 (29.6)	215 (32.1)	
Initially metastatic	1254 (69.5)	1193 (69.4)	61 (71.8)		867 (69.5)	387 (69.4)		801 (69.9)	453 (68.7)		799 (70.4)	455 (67.9)	
Primary site				0.729			0.046			0.012			< 0.001
Right colon	407 (22.6)	389 (22.6)	18 (21.2)		266 (21.3)	141 (25.3)		279 (24.3)	128 (19.4)		225 (19.8)	182 (27.2)	
Left colon	676 (37.5)	644 (37.4)	32 (37.6)		459 (36.8)	217 (38.9)		411 (35.9)	265 (40.2)		417 (36.7)	259 (38.7)	
Rectum	698 (38.7)	665 (38.7)	33 (38.8)		502 (40.3)	196 (35.1)		436 (38.0)	262 (39.8)		478 (42.1)	220 (32.8)	
Multifocal/unknown	24 (1.3)	22 (1.3)	2 (2.4)		20 (1.6)	4 (0.7)		20 (1.7)	4 (0.6)		15 (1.3)	9 (1.3)	

Table 2. Baseline characteristics (continued)

MSI/MMR status				0.266			< 0.001			0.260			0.430
MSS/pMMR	1203 (66.6)	1151 (66.9)	52 (61.2)		871 (69.8)	332 (59.5)		762 (66.5)	441 (66.9)		769 (67.8)	434 (64.8)	
MSI-H/dMMR	57 (3.2)	56 (3.3)	1 (1.2)		39 (3.1)	18 (3.2)		42 (3.7)	15 (2.3)		35 (3.1)	22 (3.3)	
Unknown	545 (30.2)	513 (29.8)	32 (37.6)		337 (27.0)	208 (37.3)		342 (29.8)	203 (30.8)		331 (29.2)	214 (31.9)	
Lines of chemotherapy given				0.031			0.001			0.089			0.929
1	540 (29.9)	504 (29.3)	36 (42.4)		341 (27.3)	199 (35.7)		323 (28.2)	217 (32.9)		338 (29.8)	202 (30.1)	
2	730 (40.4)	704 (40.9)	26 (30.6)		514 (41.2)	216 (38.7)		470 (41.0)	260 (39.5)		457 (40.3)	273 (40.7)	
≥3	535 (29.6)	512 (29.8)	23 (27.1)		392 (31.4)	143 (25.6)		353 (30.8)	182 (27.6)		340 (30.0)	195 (29.1)	
Duration of palliative chemotherapy, median (95% CI)	11.9 (11.2-12.6)	12.0 (11.3-12.6)	10.2 (6.0-14.4)	0.143	12.5 (11.6-13.6)	10.7 (9.7-11.9)	0.003	11.9 (10.9-12.7)	12.0 (10.6-13.0)	0.631	11.9 (10.8-12.6)	12.1 (10.9-13.1)	0.392
Palliative first-line regimen				0.489			0.895			0.038			0.504
Bevacizumab-containing	433 (24.0)	415 (24.1)	18 (21.2)		297 (23.8)	136 (24.4)		260 (22.7)	173 (26.3)		263 (23.2)	170 (25.4)	
Cetuximab-containing	130 (7.2)	126 (7.3)	4 (4.7)		92 (7.4)	38 (6.8)		74 (6.5)	56 (8.5)		80 (7.0)	50 (7.5)	
Chemotherapy only	1242 (68.8)	1179 (68.5)	63 (74.1)		858 (68.8)	384 (68.8)		812 (70.9)	430 (65.3)		792 (69.8)	450 (67.2)	
Metastasectomy after palliative chemotherapy	249 (13.8)	236 (13.7)	13 (15.3)	0.803	175 (14.0)	74 (13.3)	0.715	160 (14.0)	89 (13.5)	0.842	148 (13.0)	101 (15.1)	0.254

Note: Values indicate no. of patients (%) if not specified.

Abbreviations: BMI, body mass index; CI, confidence interval; dMMR, deficient mismatch repair; IQR, interquartile range; MSI-H, microsatellite instability-high; MSS, microsatellite stable; pMMR, proficient mismatch repair.

2. Changes in the body composition during treatment and survival after the last chemotherapy

Changes in the body composition markers from baseline until after stopping palliative chemotherapy are summarized in Table 2 and Fig. 2. Overall, about 54.5% (n = 984) of the patients experienced changes in their body composition (in terms of sarcopenia, myosteatosis, visceral and subcutaneous obesity) from the start to the cessation of palliative chemotherapy. The prevalence of sarcopenia and myosteatosis was increased, with 9.1% and 19.2% of patients developing new sarcopenia and myosteatosis, respectively. Additionally, 12.9% and 10.5% of the patients developed new visceral and subcutaneous obesity, respectively, whereas 8.6% and 7.6% had pre-existing visceral and subcutaneous obesity, respectively, resolved during treatment (Fig. 2A).

Survival after the last chemotherapy was associated with dynamic changes in the body composition markers. Fig. 2B-D shows the survival after the last chemotherapy according to the baseline body composition status and changes during treatment. Using cutoffs determined by sensitivity analyses (data not shown), patients who experienced a decrease in the muscle mass (sarcopenia T-scores < −0.5 [n = 732, 41.0%]), muscle quality (myosteatosis T-scores < −0.5 [n = 944, 52.3%]), visceral fat (VFAT < −20% [n = 419, 23.2%]), subcutaneous fat (SFAI < −15% [n = 447, 24.8%]) during treatment showed shorter survival after the last chemotherapy compared with those who did not, irrespective of the baseline status. For instance, inferior survival was observed in patients with decreased subcutaneous fat area with and without baseline subcutaneous obesity. Additionally, the median duration between the last chemotherapy and the last CT scan was 0.5 months (interquartile range, 0.2–0.9 months), and the

median OS after the last chemotherapy was 8.7 months (95% CI, 7.9–9.8) in the entire study population.

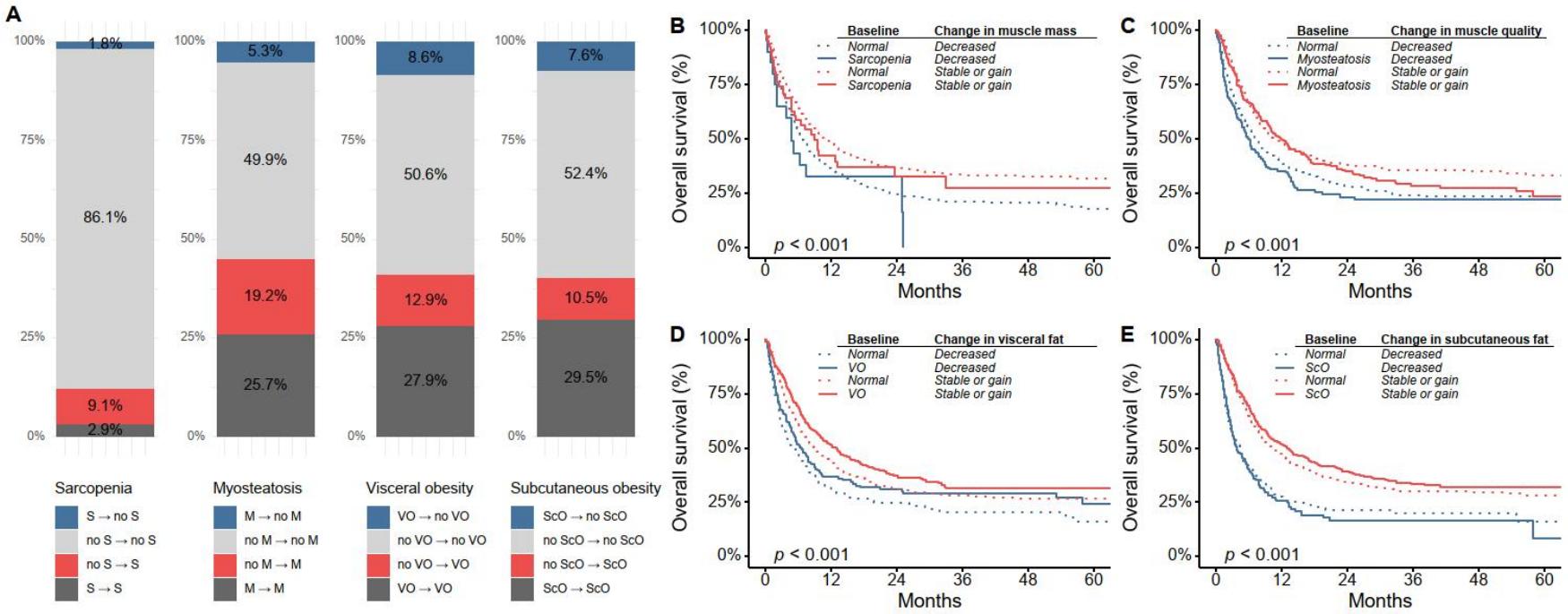


Figure 2. Changes in the body composition and its association with survival after the last chemotherapy

(A) Percent changes in the abnormalities in body composition from baseline to after last chemotherapy, and survival after last chemotherapy according to the baseline values and the changes in the (B) muscle quantity, (C) muscle quality, (D) visceral fat area, and (E) subcutaneous fat area during treatment.

Abbreviations: CI, 95% confidence interval; S, sarcopenia; ScO, subcutaneous obesity; M, myosteatosis; mo, months; VO, visceral obesity. Note: Decrease in muscle mass, muscle quality, visceral fat, and subcutaneous fat were defined as sarcopenia T−scores < −0.5, myosteatosis T−scores < −0.5, visceral fat area < −20%, subcutaneous fat area index < −15%.

Table 3. Incidence of sarcopenia at baseline, during treatment, and after last chemotherapy

Status	At baseline N=1805	At starting second-line chemotherapy N=1131	At starting third-line chemotherapy N=477	After last chemotherapy N=1805	Changes †	*p* value ‡
Sarcopenia	85 (4.7%)	70 (6.2%)	40 (8.4%)	215 (12.0%)*	+7.3%*	< 0.001
SMI T-score, mean ± SD	−0.4 ± 1.0	−0.6 ± 1.0	−0.7 ± 1.0	−0.8 ± 1.0*	−0.4 ± 0.8*	< 0.001
Myosteatosis	558 (30.9%)	409 (36.2%)	185 (38.8%)	809 (44.8%)	+13.9%	0.009
NAMA/TAMA T-score, mean ± SD	−1.4 ± 1.7	−1.6 ± 1.7	−1.7 ± 1.6	−2.1 ± 1.9	−0.7 ± 1.4	< 0.001
Visceral obesity	659 (36.5%)	461 (40.8%)	203 (42.6%)	736 (40.8%)	+4.3%	< 0.001
VFA (cm^2), mean ± SD	87.0 ± 55.5	94.0 ± 55.4	98.7 ± 58.2	94.5 ± 57.8	7.5 ± 42.7	< 0.001
Subcutaneous obesity	670 (37.1%)	489 (43.2%)	218 (45.7%)	723 (40.1%)	+2.9%	< 0.001
SFAI (cm^2/m^2), mean ± SD	43.3 ± 23.8	48.2 ± 25.3	49.4 ± 24.5	46.0 ± 25.9	2.6 ± 16.5	< 0.001
BMI						< 0.001
Normal (18.5-24.9 kg/m^2)	1233 (68.3%)	720 (63.7%)	300 (62.9%)	1107 (61.9%) **	−6.5%**	
Obese (≥ 25.0 kg/m^2)	447 (24.8%)	358 (31.7%)	149 (31.2%)	533 (29.8%)**	+5.1%**	
Underweight (< 18.5 kg/m^2)	125 (6.9%)	53 (4.7%)	28 (5.9%)	149 (8.3%)**	+1.5%**	
BMI (kg/m^2), mean (SD)	23.0 ± 3.2	23.5 ± 3.3	23.6 ± 3.4	23.2 ± 3.4**	0.3 ± 2.2**	< 0.001

† From the start of first-line chemotherapy to after stopping the last chemotherapy. ‡ P values were calculated using linear mixed models. * Excluding 20 patients with missing data; ** Excluding 16 patients with missing data

Abbreviations: NAMA, normal-attenuation muscle area; SD, standard deviation; SFAI, subcutaneous fat area index; SMA, skeletal muscle area; SMI, skeletal muscle index; VFA, visceral fat area.

3. Overall prognostic effect of body composition on survival

The median OS was 32.0 months (95% CI, 29.8−34.2) in the entire population. Overall hazard ratios (HRs) estimated by the time−dependent Cox regression analyses are summarized in Table 3. Sarcopenia and myosteatosis were associated with poor OS (HR for sarcopenia, 2.64 [95% CI, 2.16–3.23], $p < 0.001$; HR for myosteatosis, 1.91 [95% CI, 1.67–2.18], $p < 0.001$), whereas visceral and subcutaneous obesity were associated with better OS (HR for visceral obesity, 0.74 [95% CI, 0.65–0.85], $p < 0.001$; HR for subcutaneous obesity, 0.75 [95% CI, 0.66–0.86], $p < 0.001$). After adjustment for clinical factors, including BMI, age at diagnosis, initial stage, sidedness, metastasectomy, first−line treatment regimens, and lines of treatment, the body composition markers consistently showed an independent association with survival (HR for sarcopenia, 2.55 [95% CI, 2.06–3.16], $p < 0.001$; HR for myosteatosis, 2.37 [95% CI, 2.00–2.82] $p < 0.001$; HR for visceral obesity, 0.69 [95% CI, 0.57–0.82], $p < 0.001$; HR for subcutaneous obesity, 0.78 [95% CI, 0.64–0.95], $p = 0.015$).

Regarding the continuous values, higher T−scores for sarcopenia (representing higher areas of muscle mass) and myosteatosis (representing better quality muscle), higher VFA (representing higher areas of abdominal fat), SFAI (representing higher areas of subcutaneous fat), and BMI were associated with a favorable OS (Table 3). In addition, the restricted cubic spline curve analyses did not show an inverse relationship with OS at the highest levels of VFAT, SFAI, or BMI (Fig. 3C−E).

Table 4. Univariable and multivariable time-dependent cox regression analysis

	Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Body composition (categorical)				
Sarcopenia	2.64 (2.16-3.23)	< 0.001	2.55 (2.06-3.16)	< 0.001
Myosteatosis	1.91 (1.67-2.18)	< 0.001	2.37 (2.00-2.82)	< 0.001
Visceral obesity	0.74 (0.65-0.85)	< 0.001	0.69 (0.57-0.82)	< 0.001
Subcutaneous obesity	0.75 (0.66-0.86)	< 0.001	0.78 (0.64-0.95)	0.015
BMI (vs. Normal)				
Obese	0.66 (0.57-0.77)	< 0.001	0.68 (0.56-0.83)	< 0.001
Underweight	2.26 (1.74-2.94)	< 0.001	2.26 (1.75-2.91)	< 0.001
Other clinical variables				
Age ≥ 60	1.20 (1.06-1.36)	0.004	0.80 (0.69-0.93)	0.004
Female sex (vs. Male)	1.03 (0.91-1.17)	0.650	0.89 (0.74-1.07)	0.229
Initially metastatic (vs. Recurrent)	1.28 (1.11-1.47)	0.001	1.43 (1.23-1.66)	< 0.001
Primary site (vs. Left/Rectum)				
Right	1.25 (1.08-1.45)	0.003	1.40 (1.17-1.67)	< 0.001
Multifocal/Unknown	2.25 (1.41-3.59)	0.001	2.26 (1.54-3.31)	< 0.001
Metastasectomy	0.36 (0.29-0.46)	< 0.001	0.35 (0.28-0.45)	< 0.001
First-line chemotherapy with targeted agent (vs. chemotherapy only)	0.44 (0.37-0.52)	< 0.001	0.45 (0.37-0.54)	< 0.001
Lines of treatment (vs. 1)				
2	1.51 (1.28-1.78)	< 0.001	1.50 (1.24-1.82)	< 0.001
≥ 3	1.29 (1.09-1.53)	0.004	1.20 (0.99-1.46)	0.063
Body composition (continuous)				
Sarcopenia T-score	0.69 (0.64-0.74)	< 0.001		
Myosteatosis T-score	0.80 (0.77-0.84)	< 0.001		
Visceral fat area/100	0.76 (0.67-0.86)	< 0.001		
Subcutaneous fat index/10	0.89 (0.86-0.92)	< 0.001		
Body mass index/5	0.60 (0.53-0.67)	< 0.001		

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio.

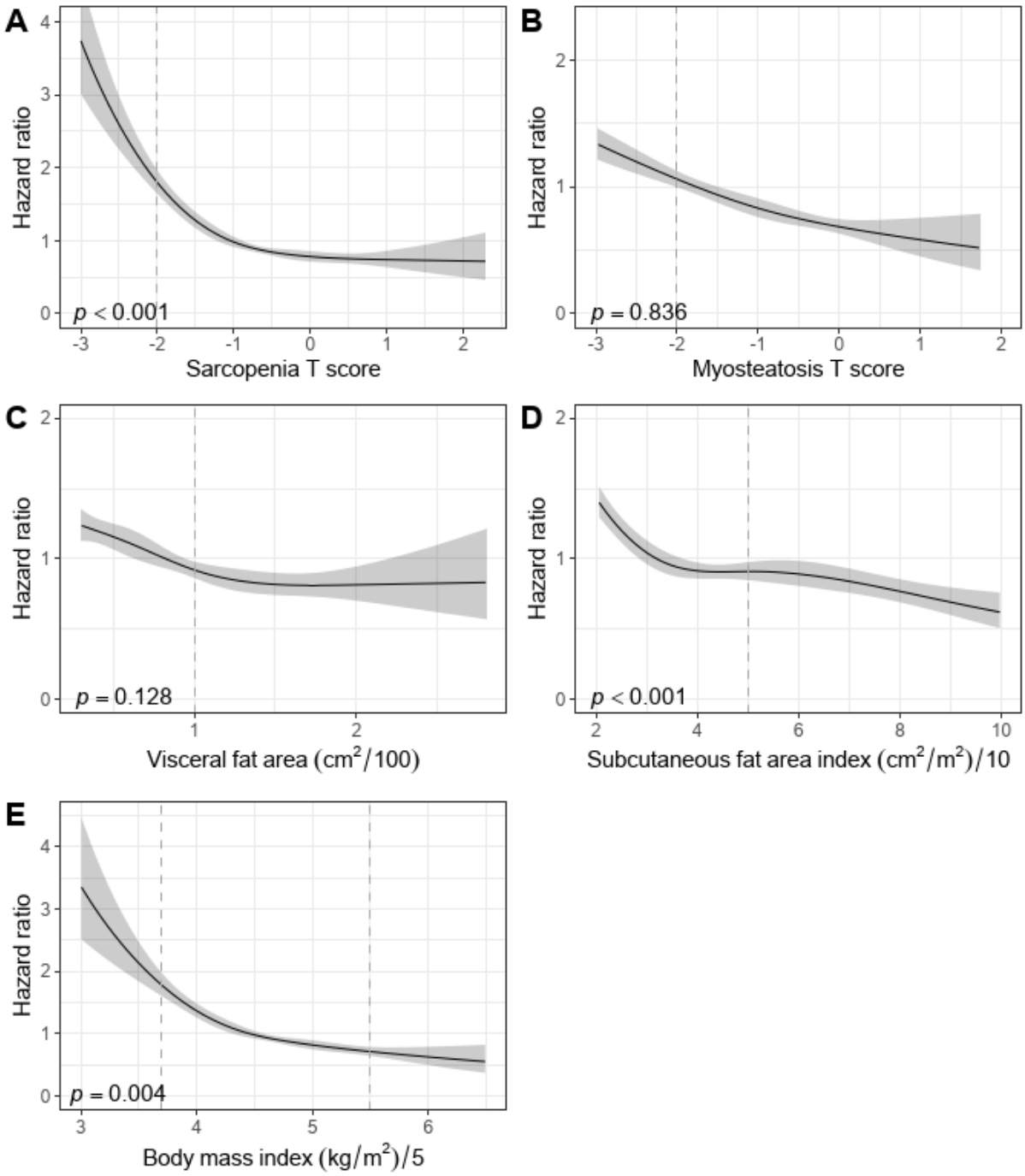


Figure 3. Restricted cubic spline curve showing hazard ratios of the body composition markers and survival

Note: *p* values are for nonlinearity.

4. Correlations with body composition, body mass index, and laboratory tests

Correlations among each body composition marker and correlations of the body composition markers with BMI or laboratory are shown as correlation matrices in Fig. 4 (Fig. 4A, at the start of chemotherapy, and Fig. 4B, after stopping chemotherapy). Body mass index showed only a weak negative correlation with sarcopenia or myosteatosis (Pearson's R, −0.34 to −0.19), whereas it showed a moderate positive correlation with VFA or SFAI (Pearson's R, 0.65–0.72) at both time points. Overall, all laboratory markers analyzed showed weak correlations with the body composition markers.

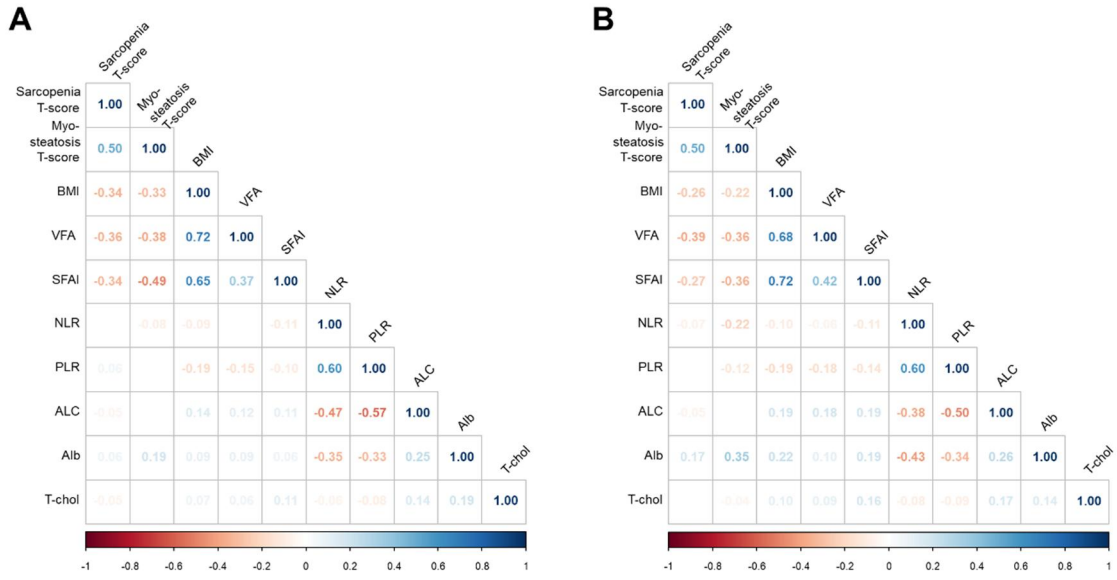


Figure 4. Correlation matrix

(A) at starting chemotherapy, (B) after stopping chemotherapy.†

†The numbers shown are Pearson's correlation coefficients with p values < 0.05. Negative and positive values indicate negative and positive correlations, respectively. Absolute values from 0 to 0.10, 0.10 to 0.39, 0.40 to 0.69, 0.70 to 0.89, and 0.90 to 1.00 indicates negligible, weak, moderate, strong, and very strong correlations, respectively.[19]

Discussion

In this study, we evaluated the comprehensive landscape of the body composition during palliative chemotherapy and their changes in metastatic colorectal cancer. We found that myosteatosis affected the largest proportion of the patients and that it was the most prevalent change during chemotherapy, rather than sarcopenia. Survival analysis using serial data acquired at multiple time points showed that sarcopenia and myosteatosis were associated with poor survival outcomes, whereas obesity, regardless of the distribution of fat (subcutaneous or visceral), was associated with a favorable survival outcome. Moreover, the dynamic changes in the fat and muscle component during chemotherapy were associated with survival in the last months of life after stopping chemotherapy. Although these body composition markers showed prognostic significance, they were only weakly correlated with BMI or other laboratory blood tests, suggesting the need for separate assessments for the body composition. To the best of our knowledge, this is the largest study to evaluate a comprehensive, longitudinal landscape of body composition and its prognostic implication in a homogenous set of palliative chemotherapy–treated metastatic colorectal cancer.

Interestingly, the prevalence of sarcopenia at baseline in our cohort (5%) was similar to that of the healthy Korean population (4–9%).[14] Even after the last chemotherapy, most patients remained non–sarcopenic. In contrast, the prevalence of myosteatosis (31%) was higher than that of the healthy population (17–22%),[15] and 19% of the patients developed new myosteatosis during treatment. These data suggest that although the decline in muscle mass is undoubtedly an important change in patients with cancer, qualitative changes in muscle are more prevalent in colorectal cancer and require clinical attention. Previous studies reported the prevalence of

sarcopenia and myosteatosis among patients with colorectal cancer in the wide ranges of 12–60% and 19–78%, respectively,[6, 20] as different methodologies and cutoffs had been used among various studies. We used healthy Koreans as a reference rather than implementing data from Western countries to reflect differences in muscle mass by ethnicity and not to overestimate the prevalence of sarcopenia in the Asian population.[14, 21]

The dynamic changes in the muscle quantity and quality during palliative chemotherapy were associated with survival after stopping chemotherapy. Patients who lost muscle mass or had increased fat infiltration in muscles during chemotherapy showed shorter survival after the last chemotherapy, irrespective of the presence of baseline sarcopenia or myosteatosis. These findings suggest that monitoring body composition during treatment can provide prognostic information on the patients' prognosis in the last months of life, which can help to prepare end-of-life care plans.

We also observed that sarcopenia and myosteatosis were independently associated with poor survival with more than two-fold HRs for OS throughout the treatment course, consistent with previous findings.[6, 20] Of note, we included all longitudinal body composition data measured at multiple time points and estimated overall hazards, rather than using data acquired at a single time point. By doing so, we sought to reflect changes during treatment in the survival analyses and to improve methodological limitations observed in previous studies.[8]

Another noteworthy finding is that obesity was associated with favorable survival outcomes, irrespective of its distribution, i.e., visceral or subcutaneous. This contrasts with previous studies that showed poor survival outcomes in obese patients with colorectal cancer.[22-24] However, these studies mostly included non-metastatic patients treated with curative

resection. It has been suggested that obesity may play different roles according to the disease stage, and a protective effect of obesity has also been shown in the prospective patients' cohort with metastatic colorectal cancer, consistent with our findings.[9, 25] In addition, although it should be taken into account that none in our patients' cohorts had severe, i.e. class III obesity (BMI ≥ 40 kg/m^2), we did not observe inverse trends for increased hazards for OS at the highest values of the visceral and subcutaneous fat area. Furthermore, the inferior survival outcome observed in patients who lost body fat (both visceral and subcutaneous) during chemotherapy, irrespective of the baseline obesity status, further support the protective effect of obesity in these patients. Potential mechanistic explanations for these observations include that fat tissues may serve as a nutritional reserve, or treatment toxicity or pharmacokinetic profiles might differ in obese patients, which requires further studies.[8] We also found that visceral or subcutaneous obesity showed a weak correlation with myosteatosis. Therefore, myosteatosis might be a better surrogate for a poor metabolic phenotype, rather than visceral obesity.[26, 27]

Lastly, body composition markers, especially myosteatosis and sarcopenia, showed only weak correlations with BMI or laboratory nutritional/inflammatory markers. The prognostic importance of the abnormal body composition, along with their low correlation with other measures, highlight the need for separate evaluations for body composition in patients with metastatic colorectal cancer. The benefit of CT-based body composition analysis, especially in cancer patients, is that additional testing is not required given that most of the patients undergo regular CT evaluation. Moreover, our deep-learning based system enabled automated segmentation along with qualitative/quantitative assessment of body muscle and fat area, which helped to minimize manual work, additional cost, and time.[13, 28]

Our work is limited by its single-centered, retrospective nature. This study included patients of Asian ethnicity only, which may limit its generalizability, while reducing the potential confounding effects of ethnicity. However, the strengths of our study include the inclusion of a large number of homogeneous patients and the collection of longitudinal data for each patient. Furthermore, we evaluated multiple aspects of body composition and analyzed their changes during palliative chemotherapy comprehensively, which has been rarely reported. Moreover, longitudinal data acquisition with time-dependent survival analyses with further adjustment for other important clinical characteristics helped to improve methodological limitations in previous studies,[8] and to understand the overall independent effect of the body composition during treatment. We believe that our study can shed light on the landscape of the body composition in patients with metastatic colorectal cancer and their clinical implications. Further investigation is warranted to determine whether measuring the body composition can help treatment decision-making, such as the decision to administer chemotherapy at later lines or to enroll a patient in a clinical trial. Future studies that investigate the efficacy of therapeutic interventions on body composition, especially myosteatosis, and the mechanistic background of the body composition changes, are needed.[29-31]

Conclusion

In conclusion, abnormalities and changes in body composition were common during palliative chemotherapy in patients with advanced colorectal cancer, most notably, myosteatosis. Whereas sarcopenia and myosteatosis were poor prognostic factors, obesity, both visceral and subcutaneous, had a protective effect on survival. Computed tomography-based assessment of

these body composition markers during systemic treatment can provide valuable prognostic information without requiring additional testing.

References

1. Petruzzelli M, Wagner EF. Mechanisms of metabolic dysfunction in cancer-associated cachexia. *Genes Dev*. Mar 1 2016;30(5):489-501. doi:10.1101/gad.276733.115

2. Fouladiun M, Korner U, Bosaeus I, Daneryd P, Hyltander A, Lundholm KG. Body composition and time course changes in regional distribution of fat and lean tissue in unselected cancer patients on palliative care--correlations with food intake, metabolism, exercise capacity, and hormones. *Cancer*. May 15 2005;103(10):2189-98. doi:10.1002/cncr.21013

3. Shachar SS, Williams GR, Muss HB, Nishijima TF. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. *Eur J Cancer*. Apr 2016;57:58-67. doi:10.1016/j.ejca.2015.12.030

4. Lee K, Shin Y, Huh J, et al. Recent Issues on Body Composition Imaging for Sarcopenia Evaluation. *Korean J Radiol*. Feb 2019;20(2):205-217. doi:10.3348/kjr.2018.0479

5. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: Systematic review and meta-analysis. *Crit Rev Oncol Hematol*. Jan 2020;145:102839. doi:10.1016/j.critrevonc.2019.102839

6. Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N. Sarcopenia in patients with colorectal cancer: A comprehensive review. *World J Clin Cases*. Apr 6 2020;8(7):1188-1202. doi:10.12998/wjcc.v8.i7.1188

7. Petrelli F, Cortellini A, Indini A, et al. Association of Obesity With Survival Outcomes in Patients With Cancer: A Systematic Review and Meta-analysis. *JAMA Netw Open*. Mar 1 2021;4(3):e213520. doi:10.1001/jamanetworkopen.2021.3520

8. Lennon H, Sperrin M, Badrick E, Renehan AG. The Obesity Paradox in Cancer: a Review. *Curr Oncol Rep*. Sep 2016;18(9):56. doi:10.1007/s11912-016-0539-4

9. Shahjehan F, Merchea A, Cochuyt JJ, Li Z, Colibaseanu DT, Kasi PM. Body Mass Index and Long-Term Outcomes in Patients With Colorectal Cancer. *Front*

Oncol. 2018;8:620. doi:10.3389/fonc.2018.00620

10. Keller U. Nutritional Laboratory Markers in Malnutrition. *J Clin Med*. May 31 2019;8(6)doi:10.3390/jcm8060775

11. Stojkovic Lalosevic M, Pavlovic Markovic A, Stankovic S, et al. Combined Diagnostic Efficacy of Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), and Mean Platelet Volume (MPV) as Biomarkers of Systemic Inflammation in the Diagnosis of Colorectal Cancer. *Dis Markers*. 2019;2019:6036979. doi:10.1155/2019/6036979

12. Feliciano EMC, Kroenke CH, Meyerhardt JA, et al. Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer: Results From the C SCANS Study. *JAMA Oncol*. Dec 1 2017;3(12):e172319. doi:10.1001/jamaoncol.2017.2319

13. Park HJ, Shin Y, Park J, et al. Development and Validation of a Deep Learning System for Segmentation of Abdominal Muscle and Fat on Computed Tomography. *Korean J Radiol*. Jan 2020;21(1):88-100. doi:10.3348/kjr.2019.0470

14. Kim EH, Kim KW, Shin Y, et al. Reference Data and T-Scores of Lumbar Skeletal Muscle Area and Its Skeletal Muscle Indices Measured by CT Scan in a Healthy Korean Population. *J Gerontol A Biol Sci Med Sci*. Jan 18 2021;76(2):265-271. doi:10.1093/gerona/glaa065

15. Kim HK, Kim KW, Kim EH, et al. Age-related changes in muscle quality and development of diagnostic cutoff points for myosteatosis in lumbar skeletal muscles measured by CT scan. *Clin Nutr*. Jun 2021;40(6):4022-4028. doi:10.1016/j.clnu.2021.04.017

16. Examination Committee of Criteria for 'Obesity Disease' in J, Japan Society for the Study of O. New criteria for 'obesity disease' in Japan. *Circ J*. Nov 2002;66(11):987-92. doi:10.1253/circj.66.987

17. Ebadi M, Martin L, Ghosh S, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer*. Jun 27 2017;117(1):148-155.

doi:10.1038/bjc.2017.149

18. World Health Organization. Regional Office for the Western P. *The Asia-Pacific perspective : redefining obesity and its treatment*. Sydney : Health Communications Australia; 2000.

19. Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. *Anesth Analg*. May 2018;126(5):1763-1768. doi:10.1213/ANE.0000000000002864

20. Lee CM, Kang J. Prognostic impact of myosteatosis in patients with colorectal cancer: a systematic review and meta-analysis. *J Cachexia Sarcopenia Muscle*. Oct 2020;11(5):1270-1282. doi:10.1002/jcsm.12575

21. Silva AM, Shen W, Heo M, et al. Ethnicity-related skeletal muscle differences across the lifespan. *Am J Hum Biol*. Jan-Feb 2010;22(1):76-82. doi:10.1002/ajhb.20956

22. Lee CS, Murphy DJ, McMahon C, et al. Visceral Adiposity is a Risk Factor for Poor Prognosis in Colorectal Cancer Patients Receiving Adjuvant Chemotherapy. *J Gastrointest Cancer*. Sep 2015;46(3):243-50. doi:10.1007/s12029-015-9709-0

23. Clark W, Siegel EM, Chen YA, et al. Quantitative measures of visceral adiposity and body mass index in predicting rectal cancer outcomes after neoadjuvant chemoradiation. *J Am Coll Surg*. Jun 2013;216(6):1070-81. doi:10.1016/j.jamcollsurg.2013.01.007

24. Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. *Gut*. Jun 2013;62(6):933-47. doi:10.1136/gutjnl-2013-304701

25. Renfro LA, Loupakis F, Adams RA, et al. Body Mass Index Is Prognostic in Metastatic Colorectal Cancer: Pooled Analysis of Patients From First-Line Clinical Trials in the ARCAD Database. *J Clin Oncol*. Jan 10 2016;34(2):144-50. doi:10.1200/JCO.2015.61.6441

26. Granados A, Gebremariam A, Gidding SS, et al. Association of abdominal muscle composition with prediabetes and diabetes: The CARDIA study. *Diabetes*

Obes Metab. Feb 2019;21(2):267-275. doi:10.1111/dom.13513

27. Eastwood SV, Tillin T, Wright A, et al. Thigh fat and muscle each contribute to excess cardiometabolic risk in South Asians, independent of visceral adipose tissue. *Obesity (Silver Spring)*. Sep 2014;22(9):2071-9. doi:10.1002/oby.20796

28. Kim DW, Kim KW, Ko Y, et al. Assessment of Myosteatosis on Computed Tomography by Automatic Generation of a Muscle Quality Map Using a Web-Based Toolkit: Feasibility Study. *JMIR Med Inform*. Oct 19 2020;8(10):e23049. doi:10.2196/23049

29. Temel JS, Abernethy AP, Currow DC, et al. Anamorelin in patients with non-small-cell lung cancer and cachexia (ROMANA 1 and ROMANA 2): results from two randomised, double-blind, phase 3 trials. *Lancet Oncol*. Apr 2016;17(4):519-531. doi:10.1016/S1470-2045(15)00558-6

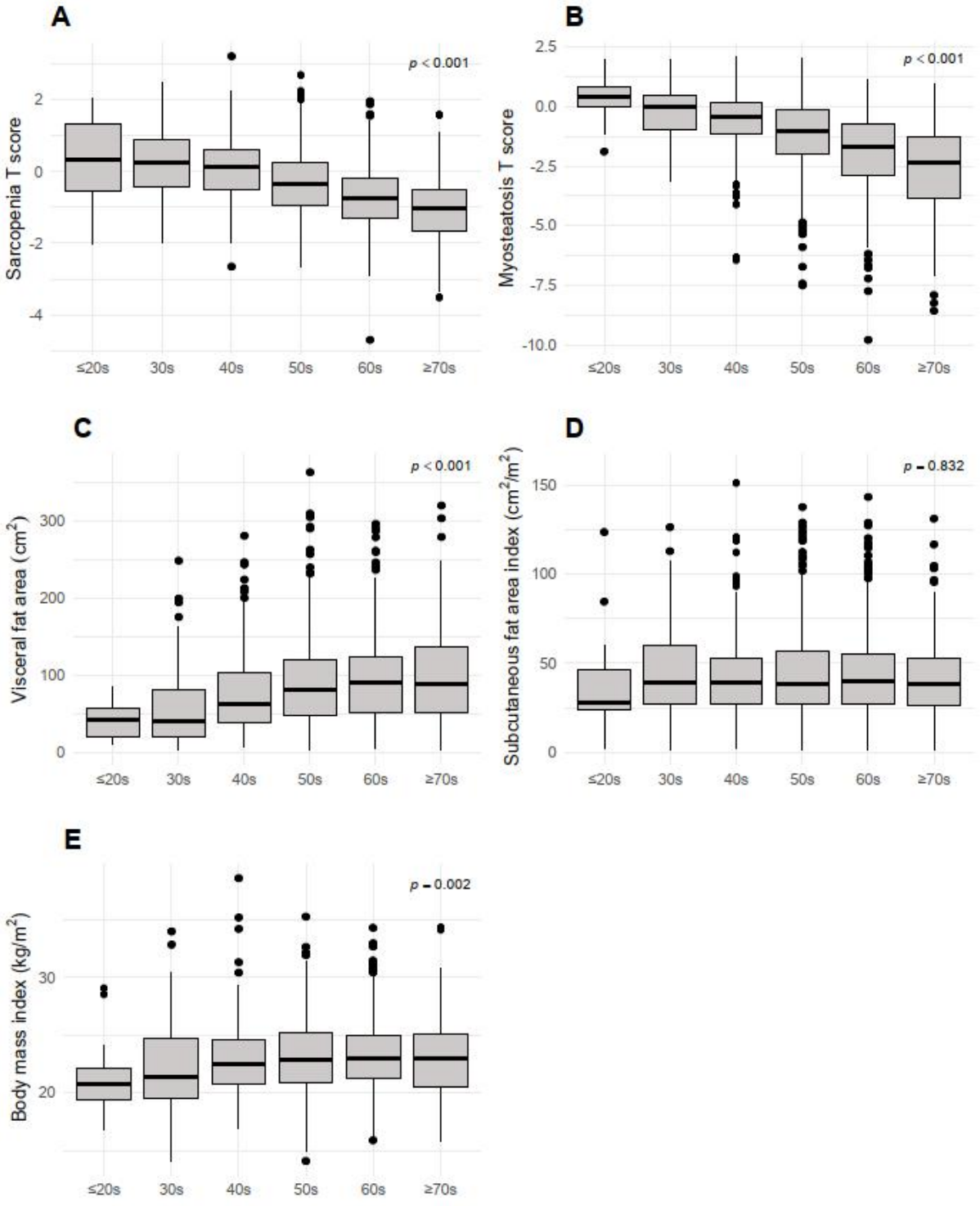
30. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*. Oct 1 2007;25(28):4396-404. doi:10.1200/JCO.2006.08.2024

31. Ryan AM, Reynolds JV, Healy L, et al. Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. *Ann Surg*. Mar 2009;249(3):355-63. doi:10.1097/SLA.0b013e31819a4789

Appendix

Appendix A1. Age at diagnosis and body composition.

(A) Sarcopenia T-score, (B) Myosteatosis T-score, (C) Visceral fat area, (D) Subcutaneous fat area index, (E) BMI.



Abstract

Background: In patients with metastatic colorectal cancer, body composition, including the quantity and quality of skeletal muscle, and body fat area and its distribution, may change during chemotherapy and have prognostic implications.

Methods: Patients with recurrent/metastatic colorectal cancer treated with palliative chemotherapy from 2008 to 2017 were retrospectively identified. Longitudinal computed tomography images were collected at multiple time points. Using a deep-learning software, the presence of sarcopenia, myosteatosis, and visceral and subcutaneous obesity was evaluated and their association with survival was assessed. Hazard ratios (HRs) for overall survival were assessed by time-dependent Cox regression and adjusted for clinical characteristics.

Results: A total of 1805 patients were included in the analysis. The median age at diagnosis was 57 years, with men comprising 62%. At baseline, 4.7%, 30.9%, 36.5%, and 37.1% of the patients had sarcopenia, myosteatosis, visceral obesity, and subcutaneous obesity, respectively. Approximately 54.5% of the patients experienced significant changes in their body composition during treatment, with 9.1% and 19.2% of them developing new sarcopenia and myosteatosis, respectively. In addition, 21.5% and 18.1% of the patients experienced either resolution of or newly developed visceral and subcutaneous obesity, respectively. These changes during treatment were associated with survival after stopping chemotherapy, irrespective of the baseline status. Throughout the treatment course, sarcopenia and myosteatosis were associated with poorer survival (HR for sarcopenia, 2.55 [95% confidence interval (CI), 2.06–3.16, $p < 0.001$; HR for myosteatosis, 2.37 [95% CI, 2.00–2.82], $p < 0.001$), whereas both visceral and subcutaneous obesity were associated with better survival (HR for visceral obesity, 0.69 [95% CI, 0.57–0.82], $p < 0.001$; HR for subcutaneous obesity, 0.78 [95% CI, 0.64–0.95], $p = 0.015$) without inverse trends at highest values for body fat area. The body composition markers showed weak associations with each other, body mass index, and laboratory

nutritional markers.

Conclusion: Abnormalities and changes in body composition were common during palliative chemotherapy in patients with advanced colorectal cancer, most notably, myosteatosis. Whereas sarcopenia and myosteatosis were poor prognostic factors, obesity, both visceral and subcutaneous, had a protective effect on survival. Computed tomography–based assessment of these body composition markers during systemic treatment can provide valuable prognostic information without requiring additional testing.