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Loss of muscle mass during preoperative chemotherapy as a prognosticator for poor survival in patients with colorectal liver metastases ☆

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ABSTRACT

Background: The survival impact of specific body composition changes during preoperative chemotherapy in patients with colorectal liver metastases undergoing curative-intent surgery remains unclear. This study aimed to determine the impact of changes in body weight and muscle mass during preoperative chemotherapy on survival after hepatectomy in patients with colorectal liver metastases.

Methods: Consecutive patients with colorectal liver metastases undergoing preoperative chemotherapy and curative hepatectomy during 2009–2013 were retrospectively analyzed. Recurrence-free and overall survival were examined according to body compositions, including muscle mass, as measured by skeletal muscle index (area of muscle [cm^2]/square of height [m^2]), and body weight before and after preoperative chemotherapy.

Results: The median follow-up duration in overall 169 patients was 47 months. Skeletal muscle index and body weight changed significantly during chemotherapy (skeletal muscle index: −0.52 cm^2/m^2, $P=.03$; body weight: +1.1 kg, $P=.002$). Patients with major muscle mass loss (≥7%) had significantly shorter median RFS than patients with no or minor muscle mass loss (<7%) (9.6 months vs 15.9 months; $P=.02$). Although major muscle mass loss was associated with poor outcome, skeletal muscle index before or after preoperative chemotherapy was not associated with recurrence-free or overall survival. On multivariate analysis, major muscle mass loss was independently associated with poorer recurrence-free survival (hazard ratio, 1.76; $P=.045$).

Conclusion: Major loss of muscle mass but not body weight loss during preoperative chemotherapy is significantly associated with poor recurrence-free survival after hepatectomy in patients with colorectal liver metastases. The mechanisms mediating this association may inform future trials on maintaining muscle mass with dedicated nutrition and exercise programs to improve outcomes.

Introduction

Hepatic resection is the standard approach for patients with resectable colorectal liver metastases (CRLM) and the only therapy that is potentially curative.[1,2] Neoadjuvant chemotherapy before such curative intent hepatectomy can help to identify responders, downsize metastases, exclude patients unfit for surgical resection, allow assessment of tumor response as to the effectiveness of the neoadjuvant regimen, and improve progression-free survival.[3–7]

Several body compositions, including body mass index (BMI), lean body mass, skeletal muscle mass, and muscle density, and their changes have been found to be associated with survival, falls, hospitalization, and institutionalization in noncancer patients.[8–14] Although sarcopenia (defined as progressive and generalized loss of skeletal muscle mass independent of fat mass) has been reported to be a risk factor for poor survival in patients with cancer, including CRLM,[13,15–19] the biologic mechanisms and

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implicated alterations in molecular pathways leading to poor cancer outcome remain ill defined. Several prior studies have found that chemotherapy significantly affects muscle mass and body weight in the palliative setting.[20–24] In these palliative patients with colorectal cancer, muscle mass loss during palliative chemotherapy has been reported to be common (approximately 5% of patients)[25] and a risk factor for poor survival.[26,27]

Although body composition changes have been studied in patients receiving palliative chemotherapy, the survival impact of specific body composition changes during preoperative chemotherapy in patients with resectable and potentially curative CRLM has not been investigated to date. Therefore the purpose of this study was to determine the survival impact of changes in body weight and muscle mass during preoperative chemotherapy in patients with resectable CRLM relative to the effect of chemotherapy on tumor biology.

Methods

The research protocol was approved by the Institutional Review Board of the University of Texas MD Anderson Cancer Center. Records of consecutive 736 patients with CRLM who underwent R0 hepatectomy (resection with negative margins) or R1 hepatectomy (resection with positive margins) at MD Anderson from January 2009 through December 2013 were retrieved from a prospectively maintained institutional database. Patients who were treated with preoperative chemotherapy for CRLM were eligible for this study. Exclusion criteria were as follows: (1) repeat hepatectomy ($n = 108$) or 2-stage hepatectomy ($n = 111$), (2) no preoperative chemotherapy for CRLM ($n = 84$), (3) lack of information regarding body weight before and after preoperative chemotherapy ($n = 118$), (4) lack of unenhanced computed tomography (CT) images from within 30 days before preoperative chemotherapy and during the period between preoperative chemotherapy and surgery ($n = 119$), (5) death within 90 days after hepatectomy ($n = 2$),[28] and (6) presence of extrahepatic metastases ($n = 25$).

Definitions

Pathologic response in the liver metastases to preoperative chemotherapy was defined as previously described: major response, 0% to 49% residual tumor cells; and minor response, ≥50% residual tumor cells.[29] Carcinoembryonic antigen (CEA) levels <5 ng/mL were considered normal.[30] Disease-free interval <12 months between resection of the colorectal primary and detection of liver metastases was considered as synchronous metastases.

Measurements of body composition

Skeletal muscle area was calculated using high-resolution diagnostic CT scans obtained before and after preoperative chemotherapy and analyzed using Synapse 3D image analysis software (Fujifilm Medical, Tokyo, Japan) for precise measurements. The cross-sectional skeletal muscle area (cm^2) was calculated within a Hounsfield unit range of −29 to 150 Hounsfield units at the level of the third lumber vertebra.[31] The skeletal muscle area (cm^2) was then divided by the square of the patient's height (m^2) to obtain a standardized measure of muscle mass, the skeletal muscle index (SMI).[13] Two trained researchers (M.O. and C.G.) who were blinded to the clinical outcomes at the time of calculation performed the radiologic assessment. Low SMI was defined as a SMI < 41 cm^2/m^2 in women, <43 cm^2/m^2 in men with a BMI <25, and <53 cm^2/m^2 in men with a BMI >25.[14] That definition has been widely used in studies in cancer patients.[27,32,33] Change in skeletal muscle area during preoperative chemotherapy was calculated (Fig. 1). Body weight measurements from before and after chemotherapy were obtained from the electronic medical record.

Fig. 1. Representative computed tomography images showing loss of muscle mass (green) during preoperative chemotherapy. (Color version of figure is available online.)

Statistical analysis

Data were analyzed using Student's t test or Wilcoxon signed-rank test for continuous variables and χ^2 test or Fisher exact test for categorical variables where appropriate. Continuous variables were expressed as mean (standard deviation [SD]) or median (range). The mean changes in SMI and body weight were analyzed with paired t tests. The correlations between the continuous valuables were analyzed using Spearman rank correlation test. Cutoff levels for changes in SMI and body weight were determined by optimal stratification, a statistical method similar to receiver operator analysis, to find the most significant P value by use of the log-rank χ^2 statistic as previously described.[13] These cutoffs were then used to dichotomize patients into groups with major muscle mass loss or no or minor muscle mass loss and major body weight loss or no or minor body weight loss during preoperative chemotherapy. Recurrence-free survival (RFS) and overall survival (OS) were calculated from the date of hepatectomy and estimated using the Kaplan-Meier method. The log-rank test was used to compare survival curves. A multivariate analysis based on the Cox regression model was used to identify risk factors for RFS and OS. All variables with $P < .20$ in univariate analysis were included in the Cox regression model for multivariate analysis. All tests were 2-tailed. All statistical computations were performed using JMP Pro 12.1 (SAS Institute, Inc, Cary, NC).

Results

A total of 169 patients were included in this study. The mean (SD) age at hepatectomy was 56.2 (11.7) years, and 97 patients (57.4%) were male. The median number of cycles of preoperative chemotherapy was 6 (range, 2–24). A total of 132 patients (78.1%) received bevacizumab but only 16 patients (9.5%) received cetuximab or panitumumab in addition to cytotoxic drugs (Table 1).

Changes in body composition during preoperative chemotherapy

Fifty-eight patients (34.3%) before preoperative chemotherapy and 61 patients (36.1%) after preoperative chemotherapy had low SMI. Mean SMI, mean largest tumor diameter, and mean CEA level decreased significantly during chemotherapy, and mean body weight increased significantly during chemotherapy (Table 2). Patients with high SMI before chemotherapy had significant muscle mass loss during chemotherapy (mean change, **−**0.87 cm^2/m^2; 95% confidence interval [CI], −1.53 to −0.21; $P = .01$), whereas patients with low SMI before chemotherapy had no significant muscle mass loss during chemotherapy (mean change, 0.13 cm^2/m^2; 95% CI, −0.48 to 0.75; $P = .66$).

Table 1
Patient characteristics at hepatectomy*.

Age, y	
Mean (SD)	56.2 (11.7)
Sex	
Male	97 (57.4)
Female	72 (42.6)
ASA-PS classification	
1–2	41 (24.3)
3–4	128 (75.7)
RAS mutation status	
Wild-type	89 (66.9)
Mutant	44 (33.1)
Untested	36
Primary tumor lymph node metastases	
Absent	61 (36.1)
Present	108 (63.9)
Primary tumor location	
Colon	138 (81.7)
Rectum	31 (18.3)
Timing of detection of liver metastases	
Metachronous	25 (14.8)
Synchronous	144 (85.2)
Multiple liver tumors	
No	63 (37.3)
Yes	106 (62.7)
Largest liver tumor diameter	
<5 cm	142 (84.0)
≥5 cm	27 (16.0)
CEA level	
<200 ng/mL	161 (95.3)
≥200 ng/mL	8 (4.7)
Prehepatectomy chemotherapy	
No. of cycles, median (range)	6 (2–24)
Oxaliplatin based	150 (88.8)
Irinotecan based	32 (18.9)
Multiple regimens	21 (12.4)
Use of bevacizumab	132 (78.1)
Use of cetuximab/panitumumab	16 (9.5)

ASA-PS, American Society of Anesthesiologists physical status.
* Values in table are number of patients (percentage) unless indicated otherwise.

Preoperative chemotherapy regimen (oxaliplatin based, irinotecan based, use of bevacizumab, and use of cetuximab/panitumumab) and number of cycles (>6 vs ≤6) of preoperative chemotherapy were not associated with muscle mass change. However, mean body weight loss was greater among patients treated with multiple regimens than among patients treated with a single regimen (2.0% vs. 0.4%, $P = .02$).

Correlations between changes in body composition and response to therapy

Correlation analysis revealed no moderate ($0.4 \leq |\rho| < 0.6$) or strong ($0.6 \leq |\rho|$) correlations between change in body weight, change in largest tumor diameter, change in CEA level, change in muscle mass, pathologic response, and number of cycles of chemotherapy (Table 3). Weak correlations were identified between body weight change and muscle mass change ($\rho = -0.23$, $P = .003$), between tumor diameter change and muscle mass change ($\rho = 0.17$, $P = .025$), between tumor diameter change and pathologic response ($\rho = 0.28$, $P = .0002$), and between body weight change and CEA change ($\rho = 0.15$, $P = .044$).

Survival

The median follow-up period for all patients was 47 months. Median RFS and OS were similar between the patients with low SMI ($n = 58$) and those with high SMI ($n = 111$) before preoperative chemotherapy (RFS: 10.9 months and 15.3 months, respectively; $P = .26$ [Fig. 2A]; OS: 68.4 months and 71.5 months, respectively; $P = .69$ [Fig. 2B]) and between the patients with low SMI ($n = 61$) and those with high SMI ($n = 108$) after preoperative chemotherapy (RFS: 12.5 months and 14.0 months, respectively; $P = .44$ [Fig. 2C]; OS: 76.6 months and 68.4 months, respectively; $P = .82$ [Fig. 2D]).

Optimal stratification determined 7% as a cutoff value in muscle mass loss and 3% as a cutoff value in body weight loss during chemotherapy (Supplemental Fig. A1). When patients were dichotomized, patients with major muscle mass loss (≥7%; $n = 22$) had significantly shorter median RFS than those with no or minor muscle mass loss (<7%; $n = 147$; 9.6 months vs 15.9 months; $P = .02$ [Fig. 3A]), but median OS was similar between the groups (71.5 months and 68.4 months, respectively; $P = .42$ [Fig. 3B]). Median RFS and OS were similar between patients with major body weight loss (≥3%; $n = 52$) and those with no or minor body weight loss (<3%; $n = 117$; RFS: 14.2 months and 13.9 months, respectively; $P = .17$ [Fig. 3C]; OS: 68.4 months and 71.7 months, respectively; $P = .83$ [Fig. 3D]).

On multivariate analysis, major muscle mass loss (hazard ratio [HR], 1.82; 95% CI, 1.04–3.01; $P = .036$), presence of primary tumor lymph node metastases (HR, 1.74; 95% CI, 1.15–2.70; $P = .009$), multiple liver tumors (HR, 1.53; 95% CI, 1.02–2.35; $P = .041$), and microscopically positive surgical margin (HR, 1.76; 95% CI, 1.00–2.90; $P = .049$) were independently associated with poorer RFS (Table 4).

Patient characteristics according to extent of muscle mass loss

Table 5 shows patient characteristics according to muscle mass loss during preoperative chemotherapy. Of the preoperative variables, CEA ≥ 200 ng/mL was associated with major muscle mass loss ($P = .06$). Regarding to the postoperative variables, the incidences of patients who were able to receive adjuvant chemotherapy ($P = .44$) and of patients who experienced postoperative complications ($P = .34$) were similar between the groups.

Discussion

In this study of patients with CRLM who had preoperative chemotherapy followed by curative hepatectomy, low muscle mass before or after preoperative chemotherapy was not associated with RFS or OS. However, we found that major loss of skeletal muscle mass (≥7%) but not body weight loss (≥3%) during preoperative chemotherapy predicted significantly worse RFS. Although extent of muscle mass loss was found to be an independent prognosticator, it was surprisingly unrelated to change in body weight or aggressive tumor biology (assessed by change in tumor size, tumor marker, and pathologic characteristics).

Table 2
Changes in body weight, muscle mass (skeletal muscle index), largest liver tumor diameter, and CEA level during preoperative chemotherapy.

Characteristic	*Prechemotherapy value, mean (SD)*	*Postchemotherapy value, mean (SD)*	*Change, mean (95% CI)*	P
Body weight, kg	81.1 (18.7)	82.2 (18.8)	1.1 (0.4–1.7)	.002
Skeletal muscle index, cm^2/m^2	51.2 (10.6)	50.6 (10.7)	−0.52 (−1.01 to −0.04)	.033
Largest tumor diameter, cm	3.6 (3.0)	2.5 (2.2)	−1.2 (−1.4 to −1.0)	<.0001
CEA level, ng/mL	219.0 (833.7)	53.7 (277.8)	−165.3 (−267.3 to −63.4)	.002

Table 3
Correlations among changes in body weight, muscle mass, CEA, largest liver tumor diameter, and number of cycles of chemotherapy.

	Change in body weight	*No. of cycles of chemotherapy*	*Change in largest liver tumor diameter*	*Change in CEA level*	*Pathologic response to chemotherapy*
No. of cycles of chemotherapy	$\rho = -0.10$, $P = .215$	–	–	–	–
Change in largest liver tumor diameter	$\rho = -0.04$, $P = .583$	$\rho = 0.02$, $P = .790$	–	–	–
Change in CEA level	$\rho = 0.15$, $P = .044$	$\rho = 0.004$, $P = .957$	$\rho = 0.10$, $P = .197$	–	–
Pathologic response to chemotherapy	$\rho = 0.001$, $P = .99$	$\rho = -0.12$, $P = .13$	$\rho = 0.28$, $P = .0002$	$\rho = -0.06$, $P = .41$	–
Change in muscle mass	$\rho = -0.23$, $P = .003$	$\rho = 0.11$, $P = .144$	$\rho = 0.17$, $P = .025$	$\rho = -0.01$, $P = .865$	$\rho = 0.09$, $P = .24$

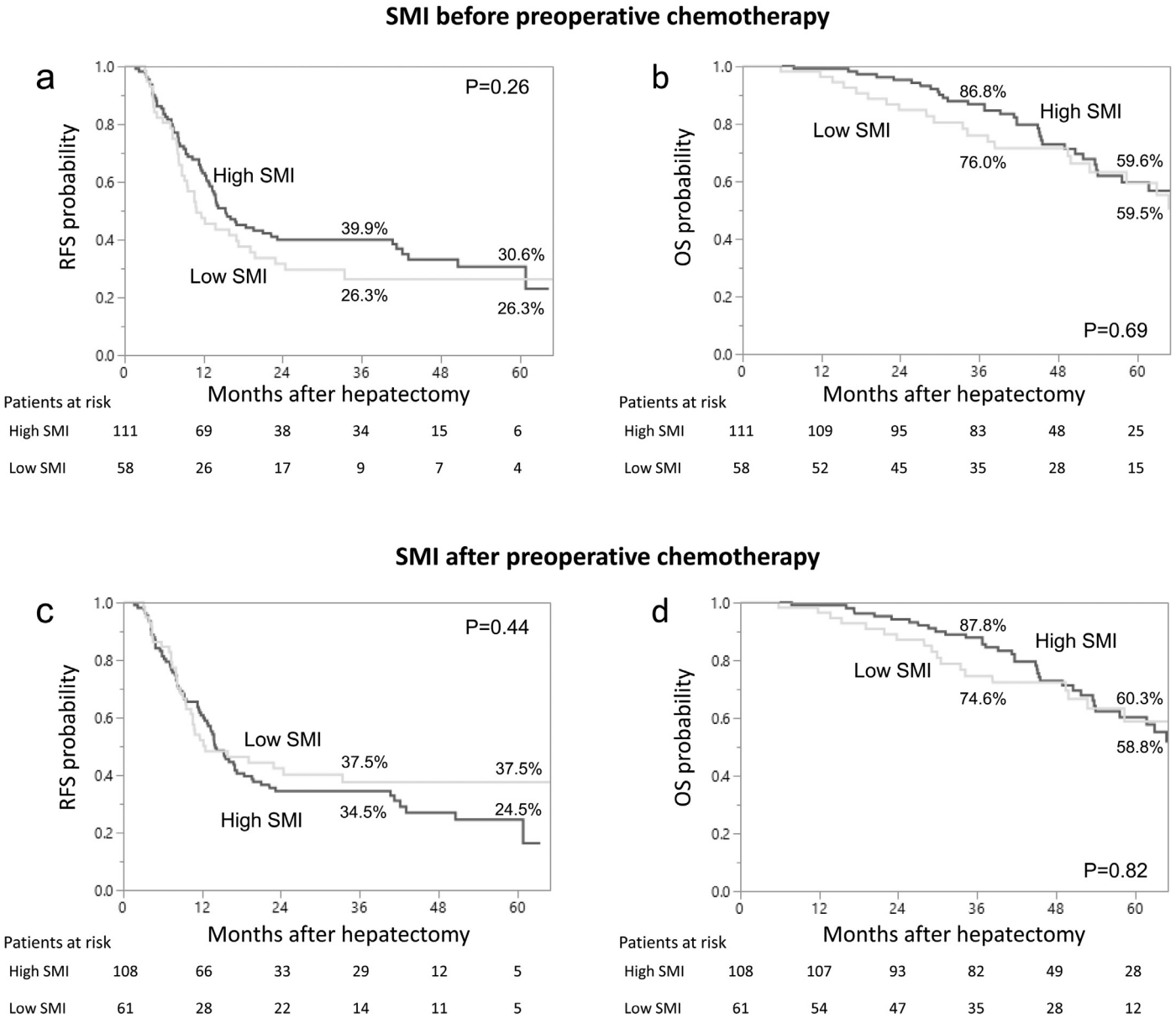

Fig. 2. (A, C) Recurrence-free survival (RFS) and (B, D) overall survival (OS) in patients with high and low skeletal muscle index (SMI; area of muscle [cm^2] / height [m^2]) before (A, B) and after (C, D) preoperative chemotherapy.

In the present analysis, low skeletal muscle mass calculated on the basis of CT images obtained before or after preoperative chemotherapy was not associated with survival. This finding contrasts with findings from previous reports on patients with CRLM.[16,25] This difference might be due to the differences in patient characteristics between this study and prior studies, which included patients who did not receive preoperative chemotherapy. In the additional analysis of patients who did not undergo preoperative chemotherapy, low skeletal muscle mass before hepatectomy was significantly associated with shorter RFS and OS (data not shown). In addition, a prior report finding no association between muscle mass loss during preoperative chemotherapy and survival is discrepant from the present study.[25] The finding was derived from a smaller study cohort and a different cutoff value of major muscle mass loss that may an explanation for the difference. Further, contrary to previous reports,[16,25] the degree of muscle mass

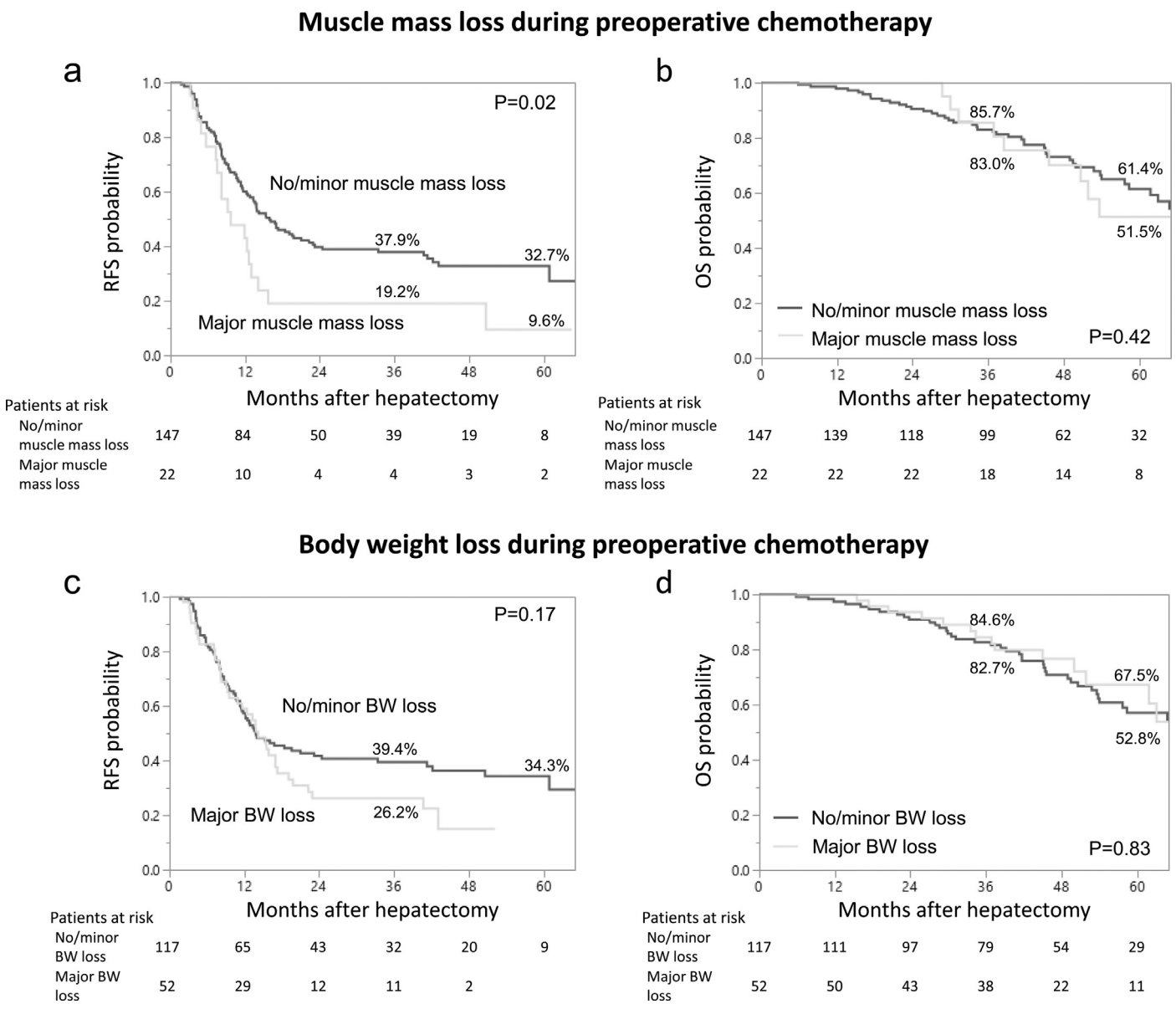

Fig. 3. (A) Recurrence-free survival (RFS) and (B) overall survival (OS) in patients with major muscle mass loss and no or minor muscle mass loss during preoperative chemotherapy; (C) RFS and (D) OS in patients with major body weight (BW) loss and no or minor BW loss during preoperative chemotherapy.

loss during chemotherapy over time should be considered as a prognostic factor in patients who receive preoperative chemotherapy rather than low skeletal muscle mass at a specific point.

Muscle mass loss among patients with cancer may be attributed to sarcopenia (impaired muscle synthesis signaling pathways) or cachexia (cytokine-mediated degradation of muscle).[8,34] Because cachexia is characterized by significant weight loss and is typically observed in progressive end-stage disease,[34] muscle mass loss during preoperative chemotherapy for resectable CRLM is considered to be related to sarcopenia. In our analysis, only a weak correlation was identified between muscle mass loss and body weight loss during chemotherapy ($\rho = -0.23$). In addition, only a very weak correlation was identified between muscle mass loss and radiographic response ($\rho = 0.17$), and no significant correlation was identified between muscle mass loss and CEA change, nor between muscle mass loss and pathologic response to chemotherapy. None of the patients had extrahepatic metastases, and all the patients had resectable CRLM. No significant difference of preoperative characteristics between major and no or minor muscle mass loss group was identified. These results indicate that muscle mass loss during chemotherapy is a truly independent prognosticator because it was found to be independent of cancer progression or chemoresistance assessed radiologically, biologically, and pathologically.

Several potential causes of sarcopenia during chemotherapy have been suggested, including increased inflammation and impaired nutritional intake as a result of the underlying cancer diagnosis.[34] Nevertheless, the precise mechanism by which muscle mass loss during chemotherapy negatively affects survival remains unclear. One possible explanation is that chemotoxicity that affects muscle mass impairs the completion of planned chemotherapy. However, in our analysis, regimen and number of cycles of preoperative chemotherapy were not associated with muscle mass loss. Another possible explanation for the association between muscle mass loss during preoperative chemotherapy and RFS is that the increased metabolic activity of aggressive tumors reduces muscle mass over time. However, as mentioned earlier, we identified no strong or even moderate correlation between muscle mass loss and

Table 4
Factors related to recurrence-free survival.

	Recurrence-free survival					
	Univariate analysis			*Multivariate analysis*		
Factor	*HR*	*95% CI*	P	*HR*	*95% CI*	P
Radiologic tumor response to preoperative chemotherapy						
Response (≥30%)						
Nonresponse (<30%)	1.25	0.85–1.83	.26			
Pathologic tumor response to preoperative chemotherapy						
Major response (viable cells ≥50%)						
Minor response (viable cells <50%)	1.37	0.87–2.10	.16	1.32	0.82–2.06	.24
Change in CEA level during preoperative chemotherapy						
Decrease/within normal limit						
Increase beyond normal limit	1.76	0.91–3.07	.088	1.76	0.88–3.25	.10
Muscle mass loss during preoperative chemotherapy						
No/minor loss (<7%)						
Major loss (≥7%)	1.79	1.04–2.90	.036	1.82	1.04–3.01	.036
Body weight loss during preoperative chemotherapy						
No or minor loss (<3%)						
Major loss (≥3%)	1.32	0.88–1.95	.18	1.47	0.97–2.70	.068
Age at hepatectomy						
<75 y						
≥75 y	1.29	0.58–2.48	.51			
Sex						
Male						
Female	1.09	0.75–1.60	.64			
ASA-PS classification						
1–2						
3–4	0.92	0.60–1.44	.70			
RAS mutation status						
Wild-type						
Mutant	1.04	0.67–1.58	.85			
Primary tumor lymph node metastases						
Absent						
Present	1.73	1.16–2.64	.007	1.74	1.15–2.70	.009
Primary tumor location						
Colon						
Rectum	0.98	0.59–1.56	.94			
Timing of detection of liver metastases						
Metachronous						
Synchronous	1.05	0.64–1.82	.86			
Multiple liver tumors						
No						
Yes	1.55	1.04–2.35	.030	1.53	1.02–2.35	.041
Largest liver tumor diameter at hepatectomy						
<5 cm						
≥5 cm	1.33	0.78–2.16	.28			
CEA level						
<200 ng/mL						
≥200 ng/mL	1.20	0.37–2.86	.73			
Microscopic surgical margin						
Negative						
Positive	1.59	0.93–2.57	.09	1.76	1.00–2.90	.049

ASA-PS, American Society of Anesthesiologists physical status.

chemoresistance. Therefore we hypothesize that muscle mass loss might be reflective of an aspect of tumor biology that is not a traditional measures of tumor aggressiveness such as increased tumor size, tumor marker, or decreased pathologic response. Nevertheless, loss in muscle mass specifically does increase recurrence risk after curative hepatectomy. Consequently, muscle mass loss during preoperative chemotherapy in patients with resectable CRLM may be a novel prognostic factor for RFS after hepatectomy.

This study found an impact of muscle mass loss on RFS but not OS. Although it is conceivable that this discrepancy was due to a lower rate of adjuvant chemotherapy between the major and minor muscle mass loss groups, there was no difference in the rate of administration of adjuvant chemotherapy between the groups.

Today there is no universally accepted therapy for improving and maintaining muscle mass in patients with cancer, and its importance may be underestimated. Several interventions for sarcopenia in cancer patients have been investigated, and guidelines recommend nutrition interventions for cancer patients to prevent muscle mass loss.[35] Pilot studies reported the feasibility and potential effectiveness of a physical exercise training program during preoperative chemoradiotherapy in rectal[36] and pancreatic cancer patients.[37] Another clinical study investigating the efficacy of nutrition counseling for colorectal cancer patients is ongoing.[38] These interventions may have the potential to reverse or prevent sarcopenia during preoperative chemotherapy; however, further study is needed to determine whether these interventions contribute to better prognosis in patients with CRLM.

Limitations of this study include the retrospective nature of this analysis. However, to our knowledge, this study is the first to report an association between muscle mass loss during preoperative chemotherapy and RFS in patients with resectable CRLM. In this context the proposed cutoff value of muscle mass loss during preoperative chemotherapy in patients with resectable cancer varies by articles,[26,27,39,40] and therefore the optimal cutoff value

Table 5
Patient characteristics according to muscle mass loss during preoperative chemotherapy.

Factor	*Total* (N = *169*)	*No/minor muscle mass loss* (*<7%*) (n = *147*)	*Major muscle mass loss* (*≥7%*) (n = *22*)	P
Characteristic of preoperative chemotherapy				
Oxaliplatin based				
Yes	150 (88.8)	129 (87.8)	21 (95.5)	.47
No	19 (11.2)	18 (12.2)	1 (4.5)	
Irinotecan based				
Yes	32 (18.9)	29 (19.7)	3 (13.6)	.77
No	137 (81.1)	118 (80.3)	19 (86.4)	
Multiple regimens				
Yes	21 (12.4)	17 (11.6)	4 (18.2)	.48
No	148 (87.6)	130 (88.4)	18 (81.8)	
Use of bevacizumab				
Yes	132 (78.1)	115 (78.2)	17 (77.3)	1.00
No	37 (21.9)	32 (21.8)	5 (22.7)	
Use of cetuximab/panitumumab				
Yes	16 (9.5)	14 (9.5)	2 (9.1)	1.00
No	153 (90.5)	133 (90.5)	20 (90.9)	
No. of cycles				
>6	51 (30.2)	43 (29.3)	8 (36.4)	.62
≤6	118 (69.8)	104 (70.7)	14 (63.6)	
Preoperative factors				
Age at hepatectomy				
<75 y	158 (93.5)	136 (92.5)	22 (100)	.36
≥75 y	11 (6.5)	11 (7.5)	0 (0)	
BMI, kg/m^2				
<30	118 (69.8)	102 (69.4)	16 (72.7)	1.00
≥30	51 (30.2)	45 (30.6)	6 (27.3)	
Sex				
Male	97 (57.4)	86 (58.5)	11 (50.0)	.49
Female	72 (42.6)	61 (41.5)	11 (50.0)	
ASA-PS classification				
1–2	41 (24.3)	36 (24.5)	5 (22.7)	1.00
3–4	128 (75.7)	111 (75.5)	17 (77.3)	
RAS mutation status				
Wild-type	89 (66.9)	76 (67.3)	13 (65.0)	1.00
Mutant	44 (33.1)	37 (32.7)	7 (35.0)	
Untested	36	34	2	
Primary tumor lymph node metastases				
Absent	61 (36.1)	55 (37.4)	6 (27.3)	.48
Present	108 (63.9)	92 (62.6)	16 (72.7)	
Primary tumor location				
Colon	138 (81.7)	121 (82.3)	17 (77.3)	.56
Rectum	31 (18.3)	26 (17.7)	5 (22.7)	
Timing of liver metastases				
Metachronous	25 (14.8)	22 (15.0)	3 (13.6)	1.00
Synchronous	144 (85.2)	125 (85.0)	19 (86.4)	
Multiple tumor				
No	63 (37.3)	55 (37.4)	8 (13.4)	1.00
Yes	106 (62.7)	92 (62.6)	14 (63.6)	
Largest tumor diameter before chemotherapy				
<5 cm	133 (78.7)	115 (78.2)	18 (81.8)	1.00
≥5 cm	36 (21.3)	32 (21.8)	4 (18.2)	
CEA level before chemotherapy				
<200 ng/mL	151 (89.4)	134 (91.2)	17 (77.3)	.06
≥200 ng/mL	18 (10.6)	13 (8.8)	5 (22.7)	
Postoperative factors				
Adjuvant chemotherapy				
No	42	35 (24.1)	7 (31.8)	.44
Yes	125	110 (75.9)	15 (68.2)	
Unknown	2	2	0	
Postoperative complication				
Absent	111 (65.7)	94 (63.9)	17 (77.3)	.34
Present	58 (34.3)	53 (36.1)	5 (22.7)	
Major postprocedure complication*				
Absent	151 (89.4)	129 (18.8)	22 (100)	.13
Present	18 (10.6)	18 (12.2)	0 (0)	

ASA-PS, American Society of Anesthesiologists physical status.
* Clavien-Dindo classification ≥3.

in patients with resectable CRLM remained unclear.[25] In contrast to prior reports, cutoff values of muscle mass change and body weight loss were determined by optimal stratification. A limitation of this is a potential for selection bias: patients who experienced severe muscle mass loss or body weight loss during preoperative chemotherapy might not have been considered candidates for hepatectomy. However, because at our institutions potentially resectable patients with CRLM are discussed at a multidisciplinary tumor board before initiation of preoperative chemotherapy, a nonreferral bias is unlikely.

Major muscle mass loss (≥7%) during preoperative chemotherapy in patients with resectable CRLM is significantly associated with poor RFS after curative hepatectomy and may be a novel prognosticator. This result was independent of commonly assumed important body compositional changes such as body weight loss or even radiographic, biologic, or pathologic signs of chemoresistance to preoperative chemotherapy. Future investigations should aim at the role of nutrition support or exercise during preoperative chemotherapy to potentially improve survival in patients with resectable CRLM.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.surg.2018.07.031.

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