Impact of low skeletal muscle mass and density on short and long-term outcome after resection of stage I-III colorectal cancer

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A R T I C L E I N F O

A B S T R A C T

Background: Preoperative low skeletal muscle mass and density are associated with increased postoperative morbidity in patients undergoing curative colorectal cancer (CRC) surgery. However, the long-term effects of low skeletal muscle mass and density remain uncertain.
Methods: Patients with stage I-III CRC undergoing surgery, enrolled in a prospective observational cohort study, were included. Skeletal muscle mass and density were measured on CT. Patients with high and low skeletal muscle mass and density were compared regarding postoperative complications, disease-free survival (DFS), overall survival (OS), and cancer-specific survival (CSS).
Results: In total, 816 patients (53.9% males, median age 70) were included; 50.4% had low skeletal muscle mass and 64.1% low density. The severe postoperative complication rate was significantly higher in patients with low versus high skeletal muscle and density (20.9% versus 13.6%, p = 0.006; 20.0% versus 11.8%, p = 0.003). Low skeletal muscle mass (OR 1.91, p = 0.018) and density (OR 1.87, p = 0.045) were independently associated with severe postoperative complications. Ninety-day mortality was higher in patients with low skeletal muscle mass and density compared with patients with high skeletal muscle mass and density (3.6% versus 1.7%, p = 0.091; 3.4% versus 1.0%, p = 0.038). No differences in DFS were observed. After adjustment for covariates such as age and comorbidity, univariate differences in OS and CSS diminished.
Conclusions: Low skeletal muscle mass and density are associated with short-term, but not long-term, outcome in patients undergoing CRC surgery. These findings recommend putting more emphasis on preoperative management of patients at risk for surgical complications, but do not support benefit for long-term outcome.

Introduction

Colorectal cancer is one of the leading causes of cancer-related death with an estimated total cancer burden of 7% and a great impact on disability-adjusted life years worldwide [1,2]. Recently, there has been a rising interest in the impact of low skeletal muscle mass and density on short and long term outcome in cancer patients [3]. Skeletal muscle depletion may result from cancer, as part of the cancer-cachexia syndrome, and ageing (i.e. sarcopenia, the involuntary age-related loss of skeletal muscle mass and strength) [4].

The impact of low skeletal muscle mass and density on post-operative outcome (i.e. postoperative complications and mortality) [2,5–8] and chemotherapy toxicity [9–11] has frequently been

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described in colorectal cancer patients. Furthermore, low skeletal muscle mass and density are prognostic factors in patients undergoing surgery for colorectal metastases [12,13] or chemotherapy for metastatic colorectal cancer [9,14]. However, its effect on long-term outcome in patients with stage I-III colorectal cancer has been reported in only a few studies [15–17].

Therefore, the aim of the present study was to investigate the association between low skeletal muscle mass and density on both short and long-term outcome in patients undergoing colorectal cancer surgery with curative intent in a multi-center prospective study.

Methods

Study design and patient selection

Patients were selected from the MATCH-study, an ongoing prospective observational cohort study enrolling patients undergoing curative resection for primary colorectal cancer in seven centers in the region of Rotterdam, the Netherlands [18,19]. The study was approved by the IRB and all patients provided written informed consent (MEC-2007-088). All aspects listed in the STROBE guidelines were followed, and the paper was written accordingly [20].

All patients with stage I-III colorectal cancer, according to the 5th edition of the AJCC staging manual, included in the first 6 years of the MATCH-study (July 1st, 2007–July 1st, 2013) were included in the current study. Exclusion criteria were unavailability of preoperative computed tomography (CT) or unknown body mass index (BMI). Demographics, and tumor (e.g. tumor location and grade), surgical, and additional treatment characteristics were collected. Comorbidity was graded according to the American Society of Anesthesiologists (ASA)-classification and the Charlson Comorbidity Index (CCI) [21]. BMI was categorized in groups <20, 20–24.9, and $\geq$25 kg/m^2.

Outcome parameters

All postoperative complications occurring within 30 days after surgery, during hospital admission or during readmission within 30 days after discharge, were recorded. Severity was graded according to the Clavien-Dindo (CD) classification [22]. Severe complications were defined as CD grade$\geq$3a. The comprehensive complications index, integrating all complications including their severity in a scale from 0 (no complication) to 100 (death) [23], was calculated for each patient. Postoperative mortality was defined as mortality within 90 days postoperatively. Length of hospital stay (LOS) was calculated from the date of surgery to the date of discharge. Discharge status (home or other; rehabilitation, nursing home) was recorded.

Disease-free (DFS) and overall survival (OS) were calculated from the date of surgery until recurrence or death, respectively. Survival status and cause of death were obtained from the Dutch Central Bureau of Statistics, which were used to investigate differences in colorectal cancer-specific survival (CSS). Patients who were still alive on December 31, 2016 were censored. Patients who underwent a non-radical resection were excluded from the disease-free survival analysis. DFS was defined as the time elapsed between the data of surgery and either the date of recurrence or the last date of follow-up. Recurrence was defined as the date of pathologically confirmed recurrence or the date of imaging on which a highly suspicious lesion was detected.

Skeletal muscle mass and density measurements

Skeletal muscle mass and density were measured on contrast-enhanced CT examinations [24], which were routinely performed as part of preoperative diagnosis and work-up. In rectal cancer patients, only CT examinations performed after neoadjuvant therapy were included.

As previously described [13], the total cross-sectional muscle area (cm^2) at the level of the third lumbar vertebra (L3) was selected and adjusted for patients' height using validated software [24]. This resulted in the skeletal muscle index (SMI; cm^2/m^2). The mean muscle attenuation (Hounsfield Units [HU]) of the cross-sectional area (CSMA) was noted as a measure of skeletal muscle density. CSMA is considered superior over psoas only measurements [25].

The cut-off values to define low skeletal muscle mass were 41 cm^2/m^2 for women, 43 cm^2/m^2 for men with BMI<25 kg/m^2 and 53 cm^2/m^2 for men with BMI$\geq$25 kg/m^2 [26]. Low skeletal muscle density was defined as HU < 41 for patients with BMI<25 kg/m^2 and HU < 33 for patients with a BMI$\geq$25 kg/m^2 [26].

Statistical analysis

Frequencies are presented in absolute numbers and percentages. Continuous data are presented as median with the interquartile range (IQR). Differences between groups were tested using the Chi-squared and Mann-Whitney-U tests where appropriate. Kaplan-Meier estimates and Cox regression analysis were used for the survival analysis. Factors with a significance level of p < 0.1 in univariate analysis were selected for a multivariable analysis with the factor of interest (low skeletal muscle mass/density). Univariate and multivariable logistic regression analyses were performed to investigate the association between low skeletal muscle mass and density and severe complications. Collinearity between variables was assessed using the variance inflation factor (VIF). All analyses were performed using SPSS for Windows version 22 (IBM Corp., Armonk, NY, USA). Two-sided p-values<0.05 were considered statistically significant.

Results

Patient characteristics

A total of 981 patients with stage I-III colorectal cancer were included in the MATCH-study in the given period. CT examinations were not available in 157 patients and BMI could not be retrieved from 8 patient charts, leaving a total cohort of 816 patients. The

Table 1
Postoperative complications and recovery.

	High skeletal muscle mass	Low skeletal muscle mass	p-value	High skeletal muscle density	Low skeletal muscle density	p-value
Complications (overall)	187 (46.3)	197 (47.8)	0.662	111 (38.5)	271 (51.7)	<0.001
Severe complications (CD $\geq$ 3)	55 (13.6)	86 (20.9)	0.006	34 (11.8)	105 (20.0)	0.003
Comprehensive complication index	0 (0–21)	0 (0–21)	0.135	0 (0–21)	9 (0–21)	<0.001
LOS (days)	7 (5–11)	8 (6–13)	0.022	7 (5–10)	8 (6–14)	<0.001
Discharge to home	359 (95.7)	364 (91.5)	0.035	268 (98.2)	435 (91.0)	0.001

Abbreviations: CD, Clavien Dindo classification; LOS, Length of Stay.