의학석사 학위논문

Deep Neural Network for Automated Volumetric Segmentation of Abdominal Muscle Volume Predicts Short- and Long-term Outcomes of Colorectal Cancer Patients

딥러닝에 기반한 자동화된 체성분 분석을 이용한 대장암 환자의 근육량과 장단기 결과의 연관성 분석

2022년 02월

서울대학교 의과대학원

의학과 외과학전공

Bimurzayeva Aiya

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Master of Science in Medicine

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Department of Surgery

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지도교수 정 승 용

이 논문을 의학석사 학위논문으로 제출함

2021년 10월

서울대학교 의과대학원

의학과 외과학 전공

Bimurzayeva Aiya

Bimurzayeva Aiya의 의학석사 학위논문을 인준함

2022년 01월

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Deep Neural Network for Automated Volumetric Segmentation of Abdominal Muscle Volume Predicts Short- and Long-term Outcomes of Colorectal Cancer Patients

by

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A thesis submitted to the Department of Surgery in partial fulfillment of the requirements for the Master's Degree in Medicine at Graduate School of Seoul National University College of Medicine

January 2022

Approved by Thesis Committee:

Professor_____ Chairman

Professor _____Vice chairman

Professor _____

ABSTRACT

Introduction: Inadvertant weight loss has been recognized as a hallmark of advanced malignancy, but weight loss could be variable in their composition. In the previous literature, the areas of abdominal compositions were predictive of prognosis for colorectal cancer patients. However, the optimal measurement of the body composition parameters and the cut-off values were not clearly defined. In the most of existing studies, authors have used parameters in the cross-sectional area of the third lumbar (L3) vertebra and the tissues of the upper and lower extremities, but there has been no investigation about whole abdominal waist muscle and fat volume and mass. Therefore, this study aimed to assess the abdominal waist parameters and their impact on oncologic outcomes in colorectal cancer (CRC) patients, and to compare different body composition parameters to determine better predictive factors for oncologic outcomes.

Methods: In Seoul National University Hospital, patients who underwent surgery for stage II/III CRC between January 2010 and December 2016 were assessed for body weight, height, postoperative complications, survival, and body compositional data by abdomen and pelvis computed tomography (CT). The body compositional data were skeletal muscle, subcutaneous fat (SF), abdominal visceral fat (AVF) and intramuscular adipose tissue (IMAT) that were measured at both the third lumbar (L3) vertebra (control) and abdominal waist (AW). Skeletal muscle index (SMI), skeletal muscle density (SMD), and skeletal muscle gauge (SMG) at the L3 level were calculated using previous references. Cut-off values for abdominal volume and mass were newly determined using X-tile plots of the preoperative patients' group with respect to each sex. Patients were divided into two groups in all categories according to whether the value was higher or lower than the cutoff point and treatment outcomes were compared.

Results: Kaplan-Meier survival analysis revealed a significantly worse 5-year survival in the low muscle mass and low muscle volume groups than in the high muscle mass and volume groups (5-year overall survival rate (5-OS): 70.2% vs. 86.9%, $p<0.001$; 5-year disease free survival rate (5-DFS): 61.7% vs. 81.0%, $p<0.001$ for muscle mass; 5-OS: 62.5% vs. 86.0%, $p<0.001$; 5-DFS: 54.2% vs. 78.7%, $p<0.001$ for muscle volume). For SF parameters, the groups with high SF mass and volume had significantly better survival rates than groups with low SF mass and volume (5-OS: 87.9% vs. 70.8%, $p<0.001$; 5-DFS: 81.0% vs. 61.7%, $p<0.001$ for SF mass; 5-OS: 86.1% vs. 63.5%, $p<0.001$; 5-DFS: 78.5% vs. 57.7% $p<0.001$ for SF volume groups). Low SMD, SMG and IMAT showed the worse 5-OS and 5-DFS compared to high levels (5-OS: 78.1% vs. 86.1%, $p=0.041$; 5-DFS: 705% vs. 78.8%, $p=0.041$ for SMD; 5-OS: 73.0% vs. 86.9%, $p<0.001$; 5-DFS: 66.7% vs. 79.1%, $p=0.004$ for SMG; 5-OS: 73.6% vs. 85.0%, $p=0.025$; 5-DFS: 64.2% vs. 77.8%, $p=0.020$ for IMAT). The incidence of

postoperative complications was significantly higher in the high AVF volume and mass groups compared to low AVF volume and mass groups (27.4% and 27.1% vs. 18.7% and 19.0%, p=0.021 and p=0.028, respectively).

Multivariate analysis adjusted by age, tumor location and cancer stage identified low muscle mass and volume (HR 2.423, 95% CI 1.504 – 3.905, p<0.001; HR 2.662, 95% CI 1.501 – 4.720, p<0.001, respectively), low SF mass and volume (HR 2.041, 95% CI 1.300 – 3.204, p=0.002; HR 2.195, 95% CI 1.288 – 3.741, p=0.004, respectively), low SMG and IMAT (HR 2.083, 95% CI 1.294 – 3.354, p=0.003; HR 2.125, 95% CI 1.186 – 3.808, p=0.011, respectively) as independent prognostic factors for worse OS. For DFS adjusted by tumor location and cancer stage, low muscle mass and volume (HR 2.347, 95% CI 1.504 – 3.664, p<0.001; HR 3.136, 95% CI 1.894 – 5.139, p<0.001, respectively), low SF mass and volume (HR 1.739, 95% CI 1.132 – 2.672, p<0.012; HR 2.062, 95% CI 1.224 – 3.475, p=0.007, respectively), low SMD and SMG (HR 1.710, 95% CI

1.124 – 2.601, p=0.012; HR 1.938, 95% CI 1.253 – 2.996, p=0.003, respectively) were determined as independent prognostic factors for negative cancer outcomes.

For comparison of all body composition parameters using gradient boosting model, muscle volume and mass in the abdominal waist showed the best relative correlation for OS.

Conclusions: Body composition parameters in the abdominal waist can be a more clinically useful survival predictor than parameters in the L3 level. Body composition can be analyzed accurately in a short time using AI automatic segmentation, and the program can provide predictive information for prognosis in a simple and understandable form.

Keywords: body composition, muscle mass, muscle volume, abdominal waist, colorectal cancer, artificial intelligence

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LIST OF ABBREVIATIONS

CRC	Colorectal Cancer
DFS	Disease-free Survival
OS	Overall Survival
5-DFS	5 year Disease-free Survival
5-OS	5 year Overall Survival
AJCC	American Joint Committee on Cancer
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BC	Body Composition
AI	Artificial Intelligence
WHO	World Health Organization
HU	Hounsfield Units
AVF	Abdominal Visceral Fat
SF	Subcutaneous Fat
SMI	Skeletal Muscle Index
SMD	Skeletal Muscle Density
SMG	Skeletal Muscle Gauge
IMAT	Inter- and intramuscular Adipose Tissues
LAMA	Low Attenuation Muscle Area
NAMA	Normal Attenuation Muscle Area
DICOM	Digital Imaging and Communications in Medicine
CT	Computed Tomography
MRI	Magnetic Resonance Imaging
SMA	Skeletal muscle cross-sectional area

1. INTRODUCTION

For decades, cancer has been a major problem and one of the main causes of death worldwide [1, 2, 3]. The clinical implication of the good distribution of body components for favorable disease outcomes has already been proven. More than half of cancer patients at the time of treatment initiation have abnormal body composition, which is explained by a combination of nutritional deficiency and restructuring of the patient's metabolism because of the pro-inflammatory cytokines from tumor cells [4]. Greater muscle mass was associated with a decreased hematological toxic effects, whereas visceral obesity and muscle loss are associated with an increased frequency of low relative dose intensity and a 30% increased risk of death [5].

Weight loss is one of the main presentations of patients with advanced cancer and these patients often suffer from cancer cachexia. However, cancer cachexia can manifest without any weight loss; around 40-60 % of cancer patients have overweight, only about 10 % of cancer patients are underweight.

And around 40–50 % of people with newly diagnosed cancer had muscle loss [6. 7]. Body surface area (BSA) or body mass index (BMI) has been used as an index of metabolic mass to scale chemotherapy doses. Nevertheless, BMI does not discern the body composition, which is defined as the proportions and distribution of bone, muscle and fat tissues. The body composition of cancer patients is highly variable with respect to the features of muscle and fat mass as well as the distribution of visceral and subcutaneous fat. Patients with any given BMI can present abnormal body composition. Several studies demonstrated that abnormal body composition was associated with treatment toxicity, shorter survival and higher incidence of postoperative complications [2. 8, 9].

Obesity is considered as one of risk factors for the development of cancer. However, obesity with a normal body composition has a paradoxical protective factor for the survival of cancer patients [10, 11]. Low muscle and low fat mass has been associated with an increased risk of death in cancer patients [9, 12].

The development of computers and software, the advent of computed tomography (CT) and magnetic resonance imaging (MRI) have made it possible to investigate body composition fast and accurately. Recent studies showed that artificial intelligence (AI) had high accuracy in a pathological diagnosis, determining the exact composition of the body and tumor boundaries when analyzing images [13, 14].

Many studies have shown the association between body composition and treatment outcomes. However, most of these studies have used muscle and adipose tissue parameters in the cross-sectional area of the third lumbar (L3) vertebra and the tissues of the upper and lower extremities. A question arises about using a wider body surface than a single L3 level to determine treatment outcomes. Considering the high prevalence of tumors of the digestive tract and the unfavorable prognosis for the life of patients, it seems relevant to a search for prognostic and predictive factors that are convenient for use in clinical practice. In the present study, we are the first who analyze skeletal muscle, abdominal visceral fat (AVF) and subcutaneous fat (SF) volume (cm3) and mass (g/height (m2))

at the abdominal waist level for colorectal cancer. Muscle and adipose tissue areas at the L3 level as a control group were also analyzed to compare the efficacy of volumetric parameters. The essence of the study was to analyze computed tomography data of patients with colorectal cancer using a deep learning program to determine the number of patients with normal and abnormal body composition. Then all parameters of body composition were compared to define more accurate predictors of oncologic outcomes.

2. MATERIALS AND METHODS

2.1 Study population

The baseline, CT, clinical, pathological and oncologic outcomes were retrieved from the prospectively collected cancer databases in Seoul National University Hospital. Between January 2010 and December 2016, primary colorectal cancer cases who underwent curative surgery were analyzed. Patients with available CT data of preoperative, 6 and 12 months after surgery were included for the analysis. Patients with hereditary colorectal cancer syndromes, metastatic diseases, synchronous cancer, only one anatomy field CT (abdominal or pelvis), CT without contrast, follow-up period less than 5 years were excluded. Patients who received preoperative neoadjuvant chemotherapy or chemoradiotherapy were also excluded (Fig. 1).

This study was approved by Seoul National University Hospital Institutional Review Board (IRB no 2108-166-1248).

2.2 Outcome parameters.

Patient demographics and clinical data were recorded, including age, gender, BMI, American Society of Anesthesiologists (ASA) grade, comorbidities, postoperative chemotherapy and The American Joint Committee on Cancer (AJCC) stage. CT data of preoperative, postoperative 6 and 12 months were collected. Surgical and pathological data included the date of the operation, tumor location, the operation time, postoperative complications, 30-day postoperative mortality, length of hospital stay, and pathologic outcomes. Survival and recurrence data were also analyzed by normal and abnormal body composition. Overall survival (OS) was defined as the time from the date of surgery to death and disease-free survival (DFS) was defined as the time from the date of surgery to recurrence or death. We collected data until the death of patients or until the end of June 2021, when 5-year follow-up data was collected for all patients. Local recurrence was defined as clinical, pathological, or radiological evidence of local recurrence of colorectal cancer. To assess the impact of abnormal body composition on oncologic outcomes, volume and L3 area of skeletal muscle, AVF, and SF of preoperative CT were measured by automated

volumetric segmentation using DeepCatch program (MEDICALIP Co. Ltd., Seoul, Korea).

2.3 Segmentation of body composition using DeepCatch program

Abdomen and pelvis CT with contrast was used to assess body composition. DeepCatch program was used [15], and CT images were uploaded as a DICOM file. The program segmented CT images into 7 areas in different colors, which improved the perception of the picture (skin, bone, muscle, abdominal visceral fat, subcutaneous fat, internal organs, and central nervous system).

DeepCatch program automatically analyzes body compositions using a deep learning algorithm to confirm accurate numerical and 3D visualization information. This product uses a Convolutional Neural Network (CNN), a type of deep learning model, to learn metadata from CT images. It automatically segments the body composition, and provides accurate segmentation of body composition [16]. After measuring the linear attenuation coefficient of the Hounsfield unit (HU) and

pixels from the CT image, the body composition is divided using the standardized value based on water and air. The volume and area of body compositions are calculated using the number of pixels in the boundary line of the body area, and then generated in a report. After completing analysis, all data is grouped into a Microsoft Excel file indicating the mass, area, volume and attenuation of body compositions in the L3 vertebra level, abdominal waist, and entire abdomen.

2.4 Definition of body composition parameters

For our study, 3 parameters were selected: skeletal muscle, AVF, and SF. The area (cm2) at the L3 level, volume cm3) and mass (g/height(m2)) in the abdominal waist were used in this study. Skeletal muscle mass in gram was estimated by multiplying the muscle volume by a density of 1.06 g/cm3 for skeletal muscle mass [20], and fat mass in gram was estimated by multiplying the volume with the adipose tissue density – 0.92 g/cm3 [17]

Definition of muscle quality (density) was mean radiation attenuation in HU on CT imaging. Pure fat density was defined

as ≤ −30 HU and pure muscle density was defined between 30 and 190 HU [18, 19].

2.5 Determination of the cut−off point according to body composition data

Since the body composition of men and women is very different, we determined the cut−off points separately according to sex. There was not validated cutoff points for parameters at the abdominal waist level, we used X−tile software (Rimm laboratory, Yale medical school, USA) to determine survival outcomes [20].

For parameters in the L3 level, we used cutoffs that was validated in the previous literatures. For skeletal muscle index (SMI) (cm2/m2), cross−sectional area of muscle (cm2) at the L3 level was normalized by the square of the height (m2). Martin L et al. defined cutoff point for SMI as: ≤ 53.0 cm2/m2 if BMI ≥25kg/m2 and 43.0 cm2/m2 if BMI <25kg/m2 for male, ≤41.0 cm2/m2 for female. For skeletal muscle density at the level L3, 41 HU for patients with a BMI <25 kg / m2 and 33 HU for a BMI ≥25 kg / m2 was used as cut−off points [7]. The

skeletal muscle gauge was calculated by multiplying SMI by SMD (SMI × SMD).

Three subgroups according to the severity of fatty infiltration on the muscle were also analysed. The 3 groups were intramuscular adipose tissue area (IMAT) (-190HU ~ -30HU), low-attenuation muscle area (LAMA), that was sum of abnormal muscle 1 (-29HU ~ 0HU) and abnormal muscle 2 (+1HU ~ +29HU), and normal-attenuation muscle area (NAMA) (+30HU ~ +150HU). The cut-off points for these parameters were determined by X-tile plots with respect to each sex. Cut-offs were listed in Table1.

2.6 Statistical analysis

Demographic data were presented as the number, percentages, or mean, with the standard deviation or range, as appropriate. The Chi-square test or Student's t-test was used to compare categorical or continuous variables according to body composition groups. Muscle and fat volume, and muscle and fat mass in the abdominal waist were grouped as dichotomous variables using the X-tile software by cutoff points.

The OS and DFS were analyzed by the Kaplan–Meier method. The log–rank test and the univariate Cox regression model were used to evaluate prognostic factors for survival. Significant factors selected through univariate regression were included in the multivariate Cox regression model using a backward stepwise process. For comparison of preoperative parameters, gradient boosting model (GBM) was used by R software.

Statistical significance was defined as $p<0.05$ and the confidence interval (CI) was set at 95%. Analysis was conducted in SPSS software, version 25 (SPSS, Chicago, IL) and R (R Core Team, 2021).

3. RESULTS

3.1 Demographic, clinical characteristics, surgical and pathology data

A total of 499 patients were included in this study (Fig. 1). Baseline characteristics of all patients are illustrated in Table 3. 57.7% of patients were male and 81.6% had a colon cancer. 64.7% of patients had AJCC stage III cancers, and 89.4% of patients received adjuvant chemotherapy.

3.2 Preoperative body composition analysis.

Patients' preoperative body composition according to sex were shown in Table 4. Area, volume, and mass of muscle and AVF were higher in men, while those of SF were higher in women (all $p<0.001$). Muscle attenuation was lower in female, and the ratio of adipose tissue and abnormal muscle 1 and 2 was higher in the female group (all $p<0.001$).

3.3 Survival analysis

Kaplan-Meier survival analysis revealed a significantly worse 5-year survival in the low muscle mass group than in the high muscle mass group (5-OS: 70.2% vs. 86.9%, $p<0.001$; 5-DFS:

61.7% vs. 81.0%, p<0.001; Fig. 2, A and B). Similarly, low muscle volume group showed a significantly worse 5-year survival than high muscle volume group (5-OS: 62.5% vs. 86.0%, p<0.001; 5-DFS: 54.2% vs. 78.7%, p<0.001; Fig. 2, C and D).

There is no significant difference between low and high AVF mass groups (5-OS: 83.4% vs. 84.1%, p=0.539; 5-DFS: 76.7% vs. 76.0%, p=0.905; Fig. 3, A and B). Low AVF volume group compared to high AVF volume group also showed no statistical significant difference (5-OS: 83.3% vs. 84.3%, p=0.510; 5-DFS: 77.3% vs. 75.4%, p=0.871; Fig. 3, C and D).

Low SF mass group showed the worse 5-year survival than high SF mass group (5-OS: 70.8% vs. 87.9%, p<0.001; 5-DFS: 61.7% vs. 81.0%, p<0.001; Fig. 4, A and B). Low SF volume group also showed significantly worse 5-year survivals than high SF volume group (5-OS: 63.5% vs. 86.1%, p<0.001; 5-DFS: 57.7% vs. 78.5%, p<0.001; Fig. 4, C and D).

There is no significant difference between low SMI and high SMI groups (5-OS: 82.5% vs. 85.1%, p=0.721; 5-DFS: 75.7% vs. 77.0%, p=0.882; Fig. 5, A and B). Low SMD group showed

the worse 5-OS and 5-DFS compared to high SMD group, (5-OS: 78.1% vs. 86.1%, p=0.041; 5-DFS: 70.5% vs. 78.8%, p=0.041; Fig. 5, C and D). Low SMG group showed low OS and DFS compared with high SMG group (5-OS: 73.0% vs. 86.9%, p<0.001; 5-DFS: 66.7% vs. 79.1%, p=0.004; Fig. 5, E and F).

Low IMAT group showed the worse 5-OS and 5-DFS compared to high IMAT group, (5-OS: 73.6% vs. 85.0%, p=0.025; 5-DFS: 64.2% vs. 77.8%, p=0.020; Fig. 6, A and B).

Low LAMA group showed higher OS and DFS compared with high LAMA group (5-OS: 86.9% vs. 80.1%, p=0.030; 5-DFS: 80.6% vs. 71.2%, p=0.011; Fig. 6, C and D).

High NAMA group had better OS and DFS than low NAMA group (5-OS: 85.1% vs. 69.0%, p=0.003; 5-DFS: 77.9% vs. 59.5%, p=0.003; Fig. 6, E and F).

3.4 Postoperative complications and body compositions

The incidence of postoperative complications was significantly higher in the high AVF volume and mass groups compared with low AVF volume and mass groups (27.4% and 27.1% vs. 18.7%

and 19.0%, p=0.021 and p=0.028, respectively). Other groups showed no significant differences (Table 5).

3.5 Cox regression for multivariate analysis

Multivariate analysis adjusted by age, tumor location and cancer stage identified low muscle mass and volume (HR 2.423, 95CI 1.504−3.905, p<0.001; HR 2.662, 95CI 1.501−4.720, p<0.001, respectively), low SF mass and volume (HR 2.041, 95CI 1.300−3.204, p=0.002; HR 2.195, 95CI 1.288−3.741, p=0.004, respectively), low SMG and IMAT (HR 2.083, 95CI 1.294−3.354, p=0.003; HR 2.125, 95CI 1.186−3.808, p=0.011, respectively) as independent prognostic factors for worse OS (Table 6). For DFS, adjusted by tumor location and cancer stage, low muscle mass and volume (HR 2.347, 95CI 1.504−3.664, p<0.001; HR 3.136, 95CI 1.894−5.139, p<0.001, respectively), low SF mass and volume (HR 1.739, 95CI 1.132−2.672, p<0.012; HR 2.062, 95CI 1.224−3.475, p=0.007, respectively), low SMD and SMG (HR 1.710, 95CI 1.124−2.601, p=0.012; HR 1.938, 95CI 1.253−2.996, p=0.003, respectively) were determined as independent prognostic factors for worse DFS (Table 7).

3.6 Correlation analysis for complications, death and relapses

Correlations between body composition parameters and outcomes were described in Table 8. Muscle mass and volume in the abdominal waist level showed good correlation with mortality and relapse ($r = -.177$, $p<0.001$; $r\ (497) = -.135$, $p=0.003$ for muscle mass and $r\ (497) = -.188$, $p<0.001$; $r\ (497) = -.190$, $p<0.001$ for muscle volume, respectively). There is a significant correlation between SF mas and volume in the abdominal waist level with death and relapse ($r\ (497) = -.197$, $p<0.001$; $r\ (497) = -.137$, $p=0.002$ for SF mass and $r\ (497) = -.188$, $p<0.001$; $r\ (497) = -.154$, $p=0.001$ for SF volume, respectively). In the L3 level good correlation was between SMD and death ($r\ (497) = -.0.99$, $p=0.027$) and SMG with death and relapse ($r\ (497) = -.157$, $p<0.001$; $r\ (497) = -.112$, $p=0.012$, respectively). All muscle and fat attenuation parameters, IMAT, LAMA, NAMA, illustrated good correlation with death ($r\ (497) = -.095$, $p=0.034$; $r\ (497) = -.091$, $p=0.043$; $r\ (497) = -.121$, $p=0.007$, respectively). LAMA

and NAMA with relapse showed (r (497) = .097, p=0.03; r (497) = −.131, p=0.003, respectively).

3.7 Combined parameters

Body composition components are often combined, e.g., muscle mass loss and decreased muscle density. In this connection, we united patients into different groups to determine which groups were at high risk (Table 9). We combined muscle mass, muscle volume in the abdominal waist and SMI in the L3 level with low−muscle attenuation. SMD and SMG did not use, because these are similar parameters.

In the muscle mass group combination high muscle mass / low LAMA showed better 5−year OS than low muscle volume / high LAMA (88.6% vs. 67.2%, p<0.001; Fig. 7A). Similarly, combination high muscle mass / high LAMA showed better 5−year OS than low muscle volume / high LAMA (84.5% vs. 67.2%, p=0.010; Fig. 7A). For DFS a significant better result showed combination high muscle mass / low LAMA than low muscle mass / high LAMA (82.7% vs. 58.6%, p<0.001; Fig. 7B), and combination high muscle mass / high LAMA showed better

5-DFS than low muscle mass / high LAMA (75.6% vs. 58.6%, p=0.010; Fig. 7B)

In the muscle volume group combination high muscle volume / low LAMA showed better 5-year OS than low muscle volume / high LAMA (88.1% vs. 63.9%, p=0.001; Fig. 7C). Similarly, combination high muscle volume / low LAMA showed better 5-year OS than low muscle volume / low LAMA (88.1% vs. 58.3%, p=0.029; Fig. 7C). High muscle volume / high LAMA 5-OS was better than low muscle volume / high LAMA (83.2% vs. 63.9%, p=0.019; Fig. 7C). For DFS a significant better result showed combination high muscle volume / low LAMA than low muscle volume / high LAMA (82.0% vs. 55.6%, p=0.001; Fig. 7D). Similarly, combination high muscle volume / low LAMA showed better 5-year OS than low muscle volume / high LAMA (82.0% vs. 50.0%, p=0.029; Fig. 7D). Combination high muscle volume / high LAMA had better 5-DFS than low muscle volume / high LAMA (74.2% vs. 55.6%, p=0.019; Fig. 7D). For SMI group result of analyzing OS and DFS without significant differences (Fig 7E and F).

3.8 Gradient Boosting Model for parameters comparison

The Gradient Boosting Model demonstrates that the parameters in the abdominal waist, muscle mass and muscle volume, had the highest predictive ability. Muscle mass and volume preop relative correlation with OS 26.7% and 23.6%, respectively. The sum of all values is 100% (Figure 8).

Table 1. Definitions of cut-off points for body composition parameters

Mass and Volume of Abdominal waist							
Author	Reference	Year	Method	Variable	Unit	Cutoff	
						Male	Female
Present study			X-tile software	Muscle mass	g/height(m2)	316.8	283.5
				AVF mass		132.6	516.1
				SF mass		200.2	309.7
				Muscle volume	cm3	665.9	607.7
				AVF volume		381.9	1235.4
				SF volume		393.2	723.2
Area of L3 level							
Martin et al.	J Clin Oncol	2013	The cross-sectional area of muscle (cm^2) at the L3 normalized by the square of the height (m^2)	Skeletal Muscle Index (SMI)	cm^2/m^2	43.0 for BMI <25 53.0 for BMI ≥25	41.0
Martin et al.	J Clin Oncol	2013	CT-defined cross-sectional skeletal muscle measurements at the L3	Skeletal Muscle Density (SMD)	Hounsfield unit (HU)	<41 for BMI <25 <33 for BMI ≥25	
Present study			X-tile software	Skeletal Muscle Gauge (SMG)	(cm^2 tissue × average HU) / (m^2 height)	1666.5	1433.3

Table 2. Groups' definition according to the cutoff point

Variables		Male (n = 288)	Female (n=211)	Total (n = 499)
Groups definition according to the mass in AW (g/height (m^2))				
High muscle mass (g/height (m2))		237 (82.3%)	168 (79.6%)	405 (81.2%)
Low muscle mass (g/height (m2))		51 (17.7%)	43 (20.4%)	94 (18.8%)
High AVF (g/height (m2))		237 (82.3%)	9 (4.3%)	246 (49.3%)
Low AVF (g/height (m2))		51 (17.7%)	202 (95.7%)	253 (50.7%)
High SF (g/height (m2))		205 (71.2%)	174 (84.5%)	379 (76%)
Low SF (g/height (m2))		90 (18.8%)	37 (15.5%)	120 (24%)
Groups definition according to the volume in AW (cm^3)				
High muscle volume(cm3)		274 (95.1%)	177 (83.9%)	451 (90.4%)
Low muscle volume (cm3)		14 (4.9%)	34 (16.1%)	48 (9.6%)
High AVF (cm3)		237 (82.3%)	11 (5.2%)	248 (49.7%)
Low AVF (cm3)		51 (17.7%)	200 (94.8%)	251 (50.3%)
High SF (cm3)		264 (91.7%)	183 (86.7%)	447 (89.6%)
Low SF (cm3)		24 (8.3%)	28 (13.3%)	52 (10.4%)
Groups definition according to the muscle area in the L3 level				
Skeletal Muscle Index (cm^2/m^2)	High SMI	110 (38.2%)	138 (65.4%)	248 (49.7%)
	Low SMI	178 (61.8%)	73 (34.6%)	251 (50.3%)
Skeletal Muscle Density (HU)	High SMD	233 (80.9%)	120 (56.9%)	353 (69.7%)
	Low SMD	55 (19.1%)	91 (43.1%)	146 (29.3%)
Skeletal Muscle Gauge	High SMG	250 (86.8%)	138 (65.4%)	388 (77.8%)
	Low SMG	38 (13.2%)	73 (34.6%)	111 (22.2%)

Table 3. Patients' demographic, clinical and surgical characteristics

Variables	n=499(%)
Age (years)	
<65	265 (53.1%)
≥65	234 (46.9%)
Sex	
male	288 (57.7%)
female	211 (42.3%)
BMI (kg/m2)	
<25	320 (64.1%)
≥25	179 (35.9%)
ASA class (%)	
1	178 (35.7%)
2	305 (61.1%)
3	15 (3.0%)
4	1 (0.2%)
CRC location (%)	
Colon	407 (81.6%)
Rectum	92 (18.4%)
Hospital stay (days)	
min	3
max	37
Reop within 30 days (%)	
yes	10 (2.0%)
no	489 (98%)
Postop mortality (%)	
yes	0
no	499 (100%)
AJCC stage (%)	
2	176 (35.3%)
3	323 (64.7%)
T stage	
1	5 (1.0%)
2	27 (5.4%)

3	398 (79.8%)
4	69 (13.8 %)
N stage	
0	176 (35.3%)
1	232 (46.5%)
2	91 (18.2%)
Postoperative chemotherapy	
Yes	446 (89.4%)
No	53 (10.6%)

Table 4. Volume, mass and index of skeletal muscle, abdominal visceral fat, and subcutaneous fat according to sex

Variables		Male (n=288) Mean (±SD)	Female (n = 211) Mean (±SD)	P
Age	<65	148 (51.4%)	117 (55.5%)	0.004
	>65	140 (48.6%)	94 (44.5%)	
Height		166.6 (±6.4)	154.8 (±6.0)	<0.001
Weight		66.8 (±10.1)	57.1 (±9.2)	<0.001
BMI		24.0 (±3.3)	23.8 (±3.4)	0.481
Abdominal waist				
Muscle volume (cm^3)		1048.9 (±259.6)	776.3 (±178.0)	<0.001
AVF volume (cm^3)		968.4 (±578.5)	621.2 (±421.6)	<0.001
SF volume (cm^3)		848.5 (±402.2)	1250.9 (±498.4)	<0.001
Muscle mass (g/height (m2))		398.9 (±88.2)	341.6 (±67.2)	<0.001
AVF mass (g/height (m2))		321.6 (±192.0)	239.3 (±162.9)	<0.001
SF mass (g/height (m2))		280.8 (±131.8)	478.7 (±183.8)	<0.001
L3 level				
Muscle area (cm^2)		137.6 (±22.5)	99.3 (±15.7)	<0.001
AVF area (cm^2)		125.2 (±70.6)	78.0 (±49.1)	<0.001
SF area (cm^2)		108.5 (±48.5)	153.7 (±60.1)	<0.001
Muscle attenuation (HU)		44.7 (±7.7)	39.0 (±9.9)	<0.001
AVF attenuation (HU)		−84.6 (±12.1)	−84.3 (±8.3)	0.707

SF attenuation (HU)	−87.8 (±11.5)	−94.9 (±8.5)	<0.001
Adipose tissue(%)	0.6 (±0.1)	0.7 (±0.2)	<0.001
Abnormal muscle 1 (%)	5.8 (±3.4)	10.2 (±5.1)	<0.001
Abnormal muscle 2 (%)	16.2 (±6.1)	20.1 (±6.7)	<0.001
Normal muscle (%)	77.3 (±9.8)	67.7 (±12.8)	<0.001
Skeletal muscle Index (SMI) (cm^2/m^2)	49.6 (±8.0)	41.4 (±5.9)	<0.001
Skeletal muscle density (SMD) (HU)	44.7 (±7.7)	39.0 (±(10.0)	<0.001
Skeletal muscle Gauge (SMG) (cm^2 tissue × average HU) / (m^2 height)	2223.6 (±541.1)	1606.5 (±447.6)	<0.001

Table 5. Tretment outcomes according to body compositions

Operative outcomes according to muscle, AVF, SF volume in AW (cm^3)

Variables	High muscle volume (n = 451)	Low muscle volume (n = 48)	P	High AVF volume (n = 248)	Low AVF volume (n = 251)	P	High SF volume (n = 447)	Low SF volume (n = 52)	P
Complications	9 (18.8%)	106 (23.5%)		68 (27.4%)	47 (18.7%)		14 (26.9%)	101 (22.6%)	
Wound infection	2	33		23	12		4	31	
Postoperative ileus	3	33	0.458	26	10	0.021	2	34	0.484
Respiratory	2	33		20	15		4	31	
Urinary	4	22		15	11		6	20	
Chyle	3	12		6	9		3	12	
Bleeding	0	4		3	1		0	4	
Anastomosis leak	0	1		1	0		0	1	
Other	4	8		6	1		1	7	
Reop within 30 days	1 (2%)	9 (2%)	0.9667	8 (3.2%)	2 (0.8%)	0.053	2 (3.8%)	8 (1.8%)	0.3118

Treatment outcomes according to muscle, AVF, SF mass in AW (g/height(m^2))

Variables	Low muscle mass (n = 94)	High muscle mass (n = 405)	P	High AVF mass (n = 246)	Low AVF mass (n = 253)	P	High SF mass (n = 379)	Low SF mass (n = 120)	P
Complications	19 (20.2%)	96 (23.7%)		67 (27.1%)	48 (19.0%)		86 (22.6%)	29 (24.2%)	
Wound infection	4	31		22	13		28	7	
Postoperative ileus	5	31	0.470	26	10	0.028	29	7	0.739
Respiratory	7	28		20	15		29	6	
Urinary	6	20		15	11		15	11	
Chyle	4	11		7	8		9	6	
Bleeding	0	4		3	1		4	0	
Anastomosis leakage	0	1		1	0		1	0	
Other	2	6		6	2		7	1	
Reop within 30 days	1 (1.1%)	9 (2.2%)	0.	8 (3.2%)	2 (0.8%)	0.	6 (1.6%)	4 (3.3%)	0.

			4 7 1			0 5 0			2 3 4

Treatment outcomes according to the muscle area in the L3 level

Variables	Low SMI (n = 251)	High SMI (n = 248)	P	Low SMD (n = 146)	High SMD (n = 353)	P	Low SMG (n = 111)	High SMG (n = 388)	P
Complications	56 (23.5%)	56 (22.6%)		33 (22.6%)	82 (23.2%)		28 (25.2%)	87 (22.4%)	
Wound infection	17	18		10	25		9	26	
Postoperative ileus	17	19	0.807	7	29	0.805	5	31	0.537
Respiratory	13	22		14	21		12	23	
Urinary	19	7		9	17		4	22	
Chyle	5	10		3	12		3	12	
Bleeding	1	3		2	2		2	2	
Anastomosis leakage	0	1		0	1		0	1	
Other	4	4		5	3		2	6	
Reop within 30 days	7 (2.8%)	3 (1.2%)	0.209	3 (2.1%)	7 (2.0%)	0.959	3 (2.7%)	7 (1.8%)	0.552

Treatment outcomes according to the severity of fatty infiltration on the muscle

Variables	High IMAT (n = 446)	Low IMAT (n = 52)	P	High LAMA (n = 226)	Low LAMA (n = 273)	P	High NAMA (n = 457)	Low NAMA (n = 42)	P
Complications	101 (22.6%)	7 (13.5%)		53 (23.5%)	55 (20.1%)		99 (21.7%)	9 (21.4%)	
Wound infection	20	9		13	16		26	4	
Postoperative ileus	28	4	0.539	19	13	0.534	31	1	0.795
Respiratory	23	7		14	16		26	4	
Urinary	20	0		11	9		20	0	
Chyle	11	1		9	3		12	0	
Bleeding	4	0		1	3		4	0	
Anastomosis leakage	1	0		1	0		1	0	
Other	5	2		2	5		7	0	
Reop within 30 days	8 (1.8%)	2 (3.8%)	0.332	5 (2.2%)	5 (1.8%)	0.763	9 (2.0%)	1 (2.4%)	0.856

Table 6. Univariate and multivariate analysis for overall survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Sex						
Male	1.0					
Female	1.152	0.733–1.808	0.540			
Age						
<65	1.0			1.0		
>65	2.013	1.286–3.153	0.002	2.266	1.441–3.562	<0.001
BMI						
≤25	1.0					
>25	0.865	0.542–1.380	0.542			
Comorbidities						
No	1.0					
Yes	1.168	0.742–1.838	0.501			
Tumor location						
Colon	1.0			1.0		
Rectum	3.543	2.269–5.532	<0.001	3.643	2.318–5.726	<0.001
Histology						
Well/Moderate	1.0					
Poor	0.767	0.333–1.769	0.534			
Mucinous / SRC	1.439	0.481–4.306	0.515			
ASA class						
1 & 2	1.0					
3 & 4	2.305	0.931–5.706	0.071			
AJCC						
2	1.0			1.0		
3	2.500	1.427–4.379	0.001	2.122	1.207–3.730	0.009
Postoperative chemotherapy						
No	1.0					
Yes	1.245	0.621–2.495	0.537			

Body composition according to muscle, AVF, SF volume (cm3) and mass (g/height(m2)) in AW						
High muscle mass	1.0			1.0		
Low muscle mass	2.675	1.685–4.247	<0.001	2.423	1.504–3.905	<0.001
High muscle volume	1.0			1.0		
Low muscle volume	3.833	2.250–6.532	<0.001	2.662	1.501–4.720	0.001
High AVF mass	1.0					
Low AVF mass	1.146	0.741–1.773	0.540			
High AVF volume	1.0					
Low AVF volume	1.157	0.748–1.790	0.512			
High SF mass	1.0			1.0		
Low SF mass	2.589	1.668–4.021	<0.001	2.041	1.300–3.204	0.002
High SF volume	1.0			1.0		
Low SF volume	3.189	1.901–5.350	<0.001	2.195	1.288–3.741	0.004
Body composition according to muscle area in L3 level (cm2)						
High SMI	1.0					
Low SMI	1.084	0.697–1.687	0.721			
High SMD	1.0			1.0		
Low SMD	1.586	1.013–2.484	0.044	1.440	0.901–2.301	0.127
High SMG	1.0			1.0		
Low SMG	2.238	1.422–3.523	<0.001	2.083	1.294–3.354	0.003
Body composition according to the to the severity of fatty infiltration on the muscle in the L3 level (%)						
High IMAT	1.0			1.0		
Low IMAT	1.908	1.072–3.395	0.028	2.125	1.186–3.808	0.011
High LAMA	1.0			1.0		
Low LAMA	0.620	0.400–0.961	0.033	0.677	0.428–1.072	0.096
High NAMA	1.0			1.0		
Low NAMA	2.383	1.314–4.139	0.004	2.582	1.355–4.922	0.004

Table 7. Univariate and multivariate analysis for diseases free survival

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	P	HR	95%CI	P
Sex						
Male	1.0					
Female	1.017	0.675-1.533	0.937			
Age						
<65	1.0					
>65	1.418	0.945-2.128	0.092			
BMI						
≤25	1.0					
>25	0.887	0.559-1.408	0.610			
Comorbidities						
No	1.0					
Yes	1.375	0.891-1.781	2.122			
Tumor location						
Colon	1.0			1.0		
Rectum	2.930	1.922-4.467	<0.001	2.691	1.763-4.108	<0.001
Histology						
Well/Moderate	1.0					
Poor	1.075	0.436-2.653	0.875			
			0.184			
Mucinous / SRC	2.133	0.698-6.521				
ASA class						
1 & 2	1.0					
3 & 4	1.015	0.321-3.205	0.980			
AJCC						
2	1.0			1.0		
3	3.172	1.826-5.511	<0.001	2.936	1.687-5.108	<0.001
Postoperative chemotherapy	1.0					
No	0.802	0.388 -1.654	0.550			
Yes						

Body composition according to muscle, AVF, SF volume (cm3) and mass (g/height(m2)) in AW				
High muscle mass	1.0		1.0	
Low muscle mass	2.075	1.333- 3.230 0.001	2.347	1.504- 3.664 <0.001
High muscle volume	1.0		1.0	
Low muscle volume	3.210	1.955- 5.270 <0.001	3.136	1.894- 5.139 <0.001
High AVF mass	1.0			
Low AVF mass	1.047	0.699- 1.569 0.823		
High AVF volume	1.0			
Low AVF volume	1.022	0.682- 1.532 0.914		
High SF mass	1.0		1.0	
Low SF mass	1.986	1.304- 3.026 0.001	1.739	1.132- 2.672 0.012
High SF volume	1.0		1.0	
Low SF volume	2.524	1.525- 4.180 <0.001	2.062	1.224- 3.475 0.007
Body composition according to muscle area in L3 level (cm2)				
High SMI	1.0			
Low SMI	0.910	0.607- 1.364 0.910		
High SMD	1.0		1.0	
Low SMD	1.537	1.011- 2.335 0.044	1.710	1.124- 2.601 0.012
High SMG	1.0		1.0	
Low SMG	1.792	1.161- 2.765 0.008	1.938	1.253- 2.996 0.003
Body composition according to the to the severity of fatty infiltration on the muscle in the L3 level (%)				
High IMAT	1.0			
Low IMAT	1.712	0.986- 2.974 0.056		
High LAMA	1.0		1.0	
Low LAMA	0.625	0.416- 0.939 0.024	0.582	0.387- 0.875 0.009
High NAMA	1.0		1.0	
Low NAMA	2.314	1.331- 4.021 0.003	3.324	1.881- 5.874 <0.001

Table 8. Correlation between body composition parameters and outcomes

Variables	Death		Relapse		Complications	
	Correlation coefficient	P	Correlation coefficient	P	Correlation coefficient	P
Body composition according to muscle, AVF, SF volume (cm^3) and mass (g/height(m^2)) in AW						
Muscle mass	−0.177	<0.001	−0.135	0.003	0.032	0.470
Muscle volume	−0.188	<0.001	−0.190	<0.001	0.033	0.458
AVF mass	−0.010	0.821	−0.003	0.938	0.098	0.028
AVF volume	−0.014	0.761	0.003	0.949	0.103	0.021
SF mass	−0.197	<0.001	−0.137	0.002	−0.015	0.739
SF volume	−0.188	<0.001	−0.154	0.001	−0.031	0.484
Body composition according to muscle area in L3 level						
SMI)	−0.035	0.430	0.023	0.602	−0.011	0.807
SMD	−0.099	0.027	−0.084	0.059	0.007	0.880
SMG	−0.157	<0.001	−0.112	0.012	−0.028	0.537
Body composition according to the to the severity of fatty infiltration on the muscle in the L3 level (%)						
IMAT	−0.095	0.034	−0.083	0.063	−0.028	0.539
LAMA	0.091	0.043	0.097	0.030	0.028	0.534
NAMA	−0.121	0.007	−0.131	0.003	0.012	0.795

Table 9. Groups' definition according to amount of muscle mass and volume and severity of fatty infiltration on the muscle (muscle quality)

Group definition	No = 499
High Muscle Volume / High LAMA[$]	190 (38.1%)
High Muscle Volume / Low LAMA[$$]	261 (52.3%)
Low Muscle Volume / High LAMA	36 (7.2%)
Low Muscle Volume / Low LAMA	12 (2.4%)
High Muscle Mass / High LAMA	168 (33.7%)
High Muscle Mass / Low LAMA	237 (47.5%)
Low Muscle Mass / High LAMA	58 (11.6%)
Low Muscle Mass / Low LAMA	36 (7.2%)
High SMI* / High LAMA	120 (24.0%)
High SMI / Low LAMA	128 (25.7%)
Low SMI** / High LAMA	106 (21.2%)
Low SMI / Low LAMA	145 (29.1%)

* High SMI or Sarcopenic
** Low SMI or non-sarcopenic
[$] Higher degree of myosteatosis
[$$] Lower degree of myosteatosis

Figure 1. Flowchart

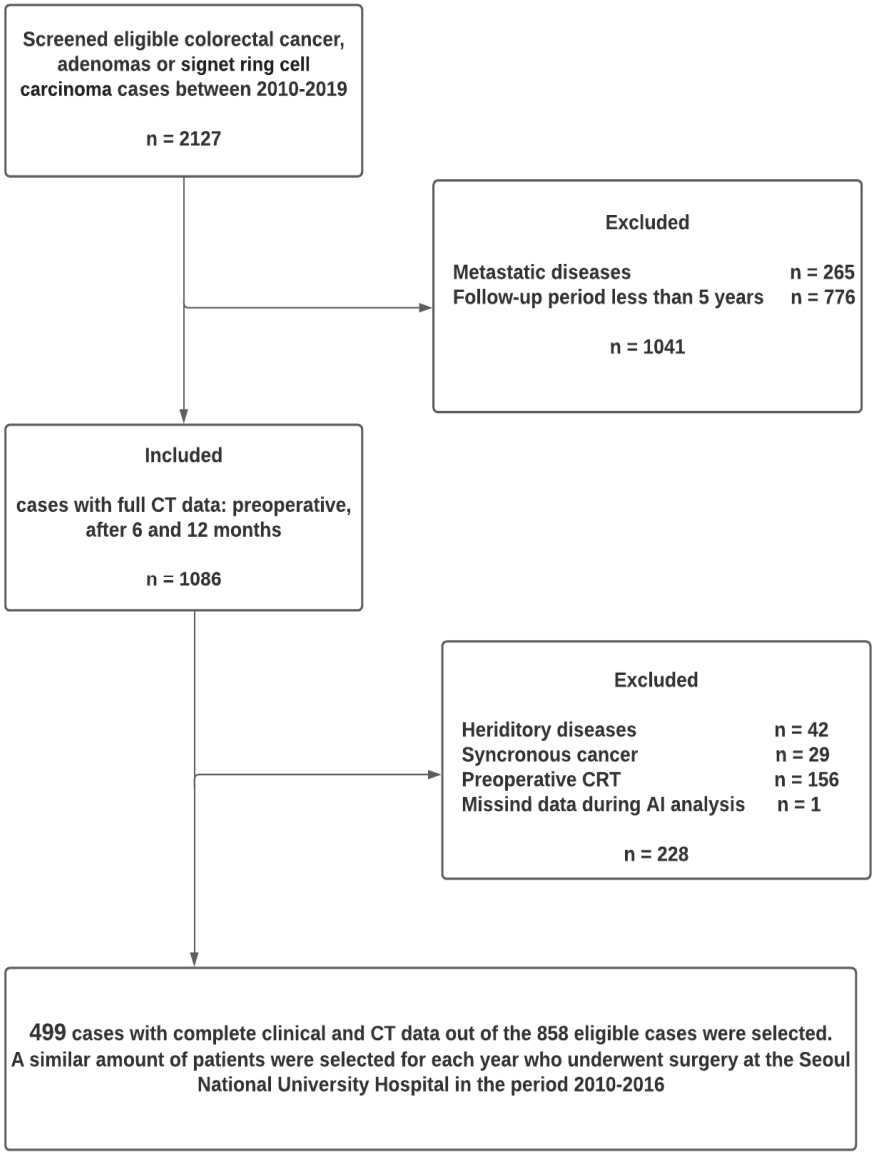
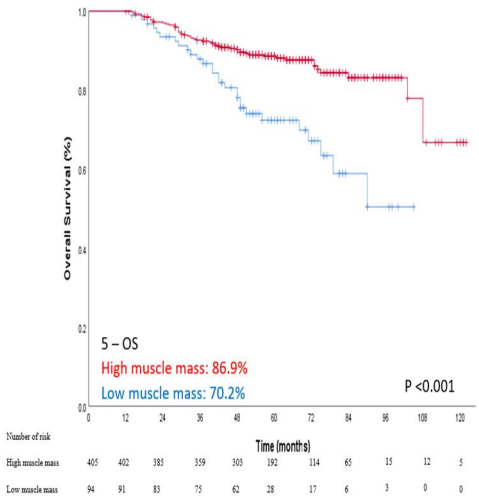
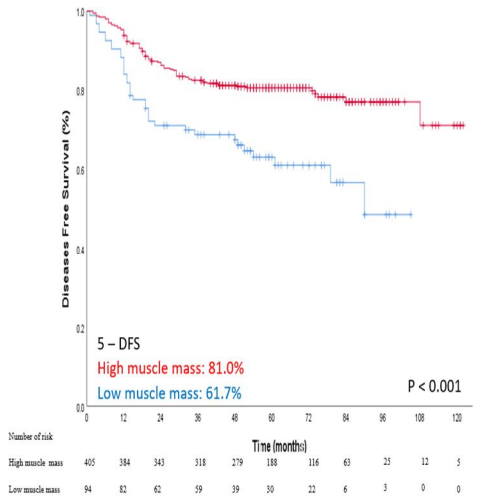


Figure 2. Kaplan-Meier curves for muscle mass and volume in the abdominal waist

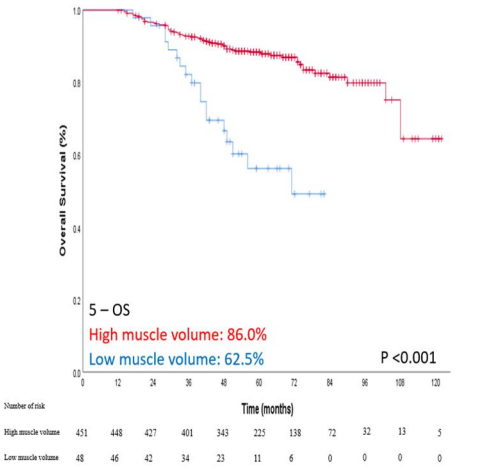
(A) Overall survival



(B) Diseases-free survival



(C) Overall survival



(D) Diseases-free survival

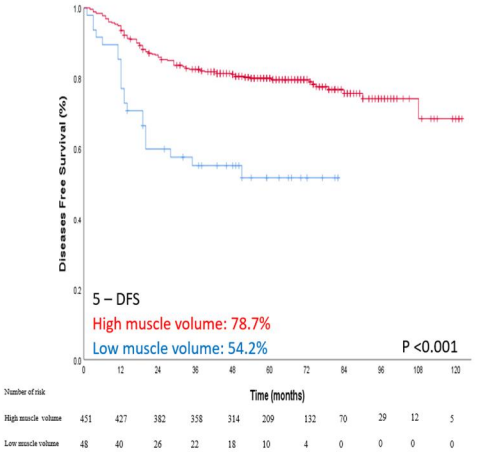
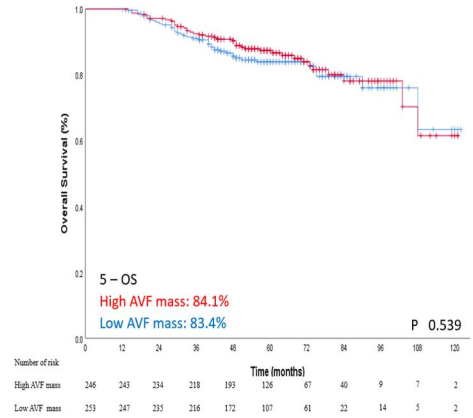
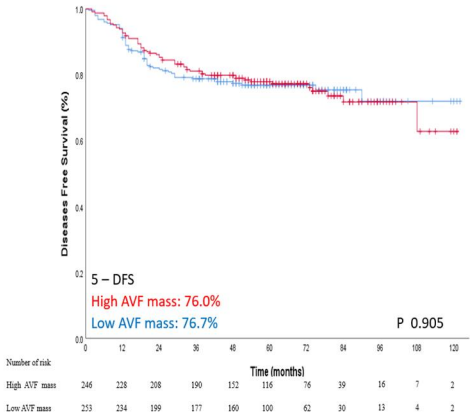


Figure 3. Kaplan-Meier curves for abdominal visceral fat mass and volume in the abdominal waist

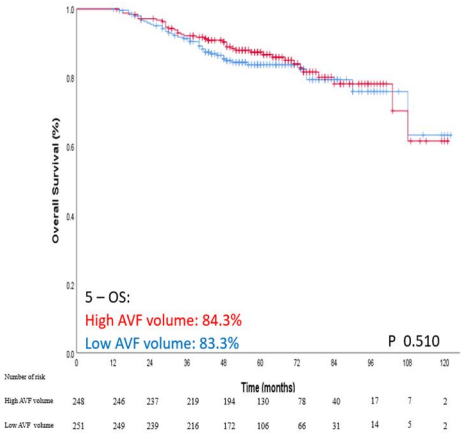
(A) Overall survival



(B) Diseases-free survival



(C) Overall survival



(D) Diseases-free survival

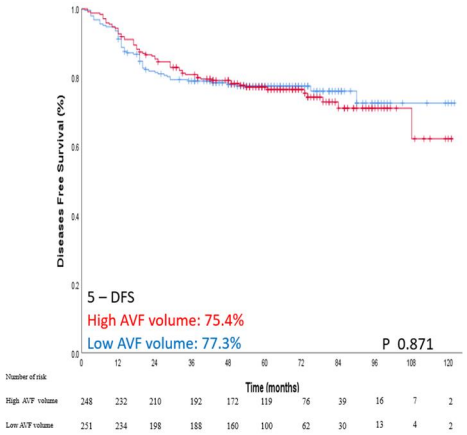
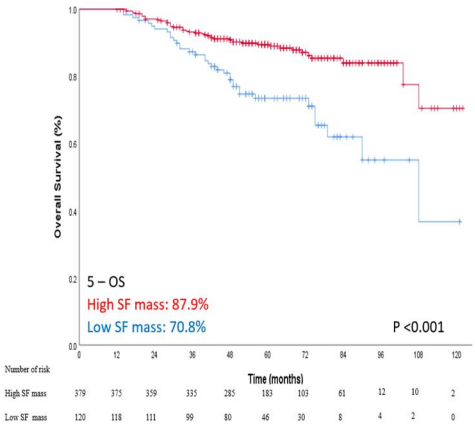
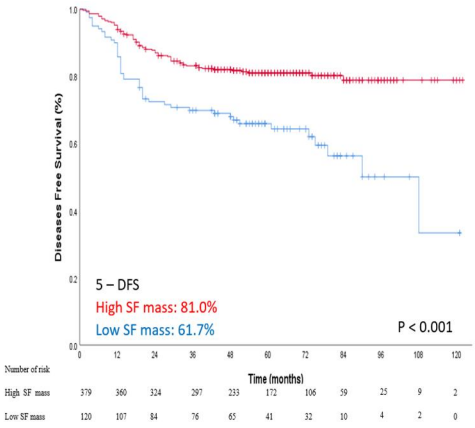


Figure 4. Kaplan–Meier curves for subcutaneous fat (SF) mass and volume in the abdominal waist

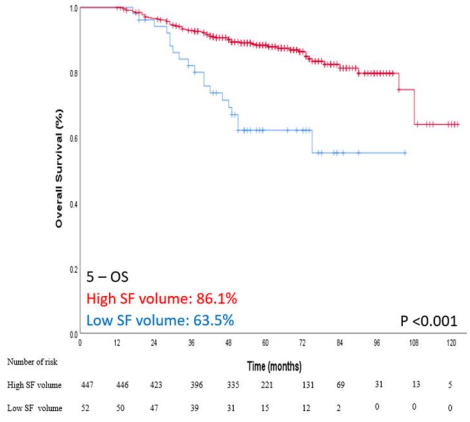
(A) Overall survival



(B) Diseases–free survival



(C) Overall survival



(D) Diseases–free survival

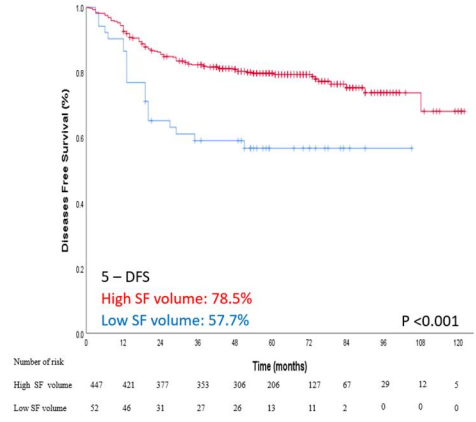
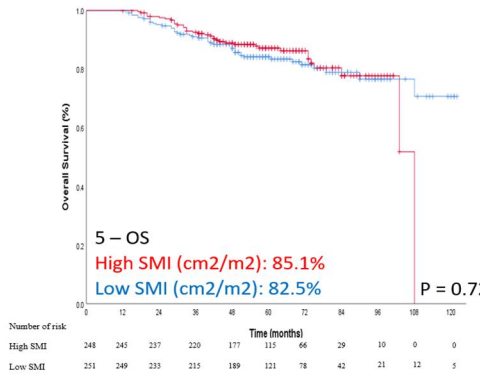
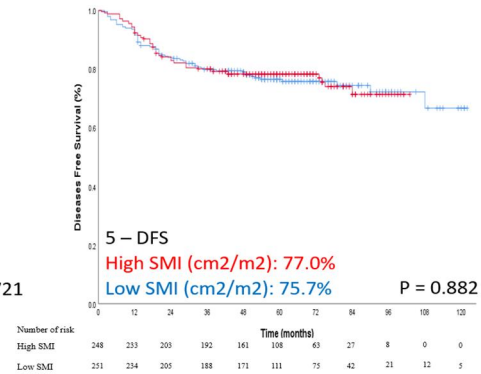


Figure 5. Kaplan-Meier curves for skeletal muscle index (SMI), skeletal muscle density (SMD), and skeletal muscle gauge (SMG)

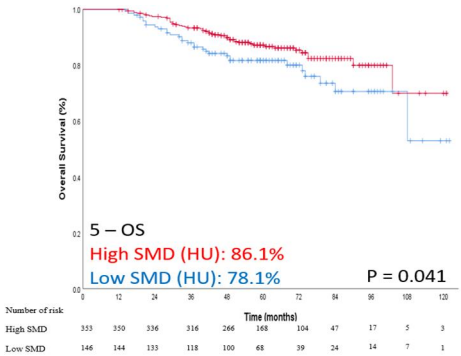
(A) Overall survival



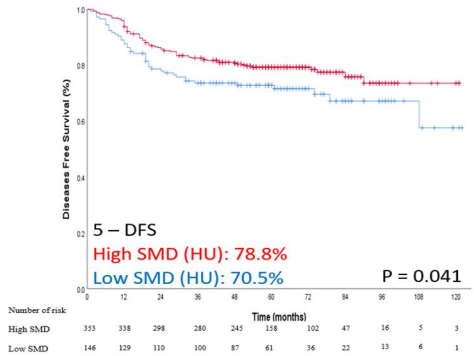
(B) Diseases-free survival



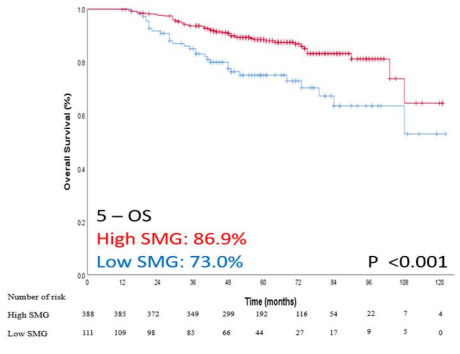
(C) Overall survival



(D) Diseases-free survival



(E) Overall survival



(F) Diseases-free survival

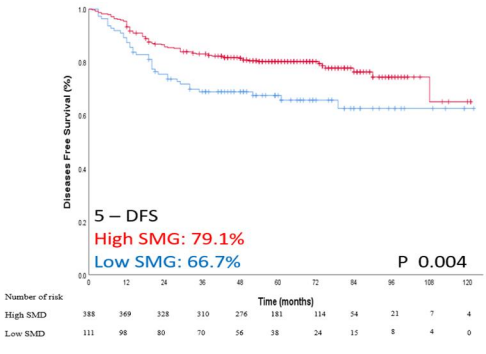
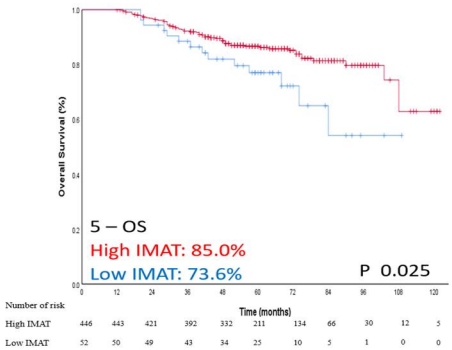
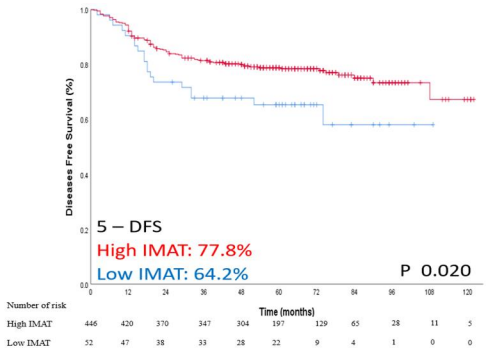


Figure 6. Kaplan–Meier curves for intramascular adipose tissue, low attenuation muscle ares, and normal attenuation muscle area

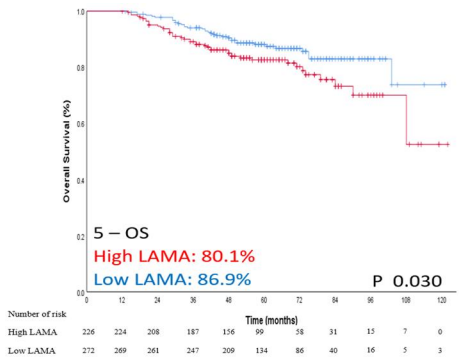
(A) Overall survival



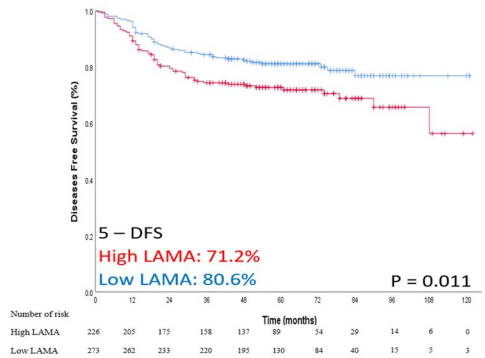
(B) Diseases–free survival



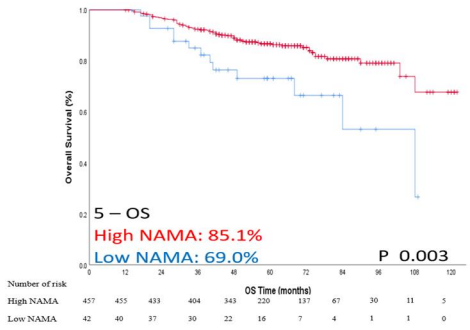
(C) Overall survival



(D) Diseases–free survival



(E) Overall survival



(F) Diseases–free survival

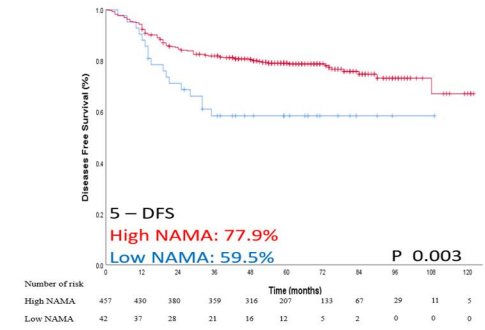
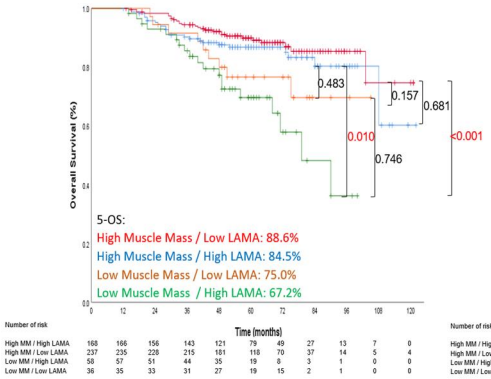
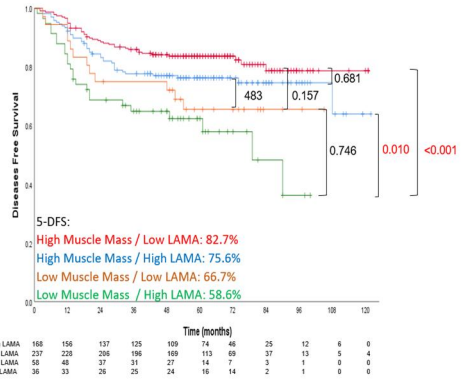


Figure 7. Kaplan-Meier curves for groups combination according to amount of muscle mass and volume and severity of fatty infiltration on the muscle (muscle quality)

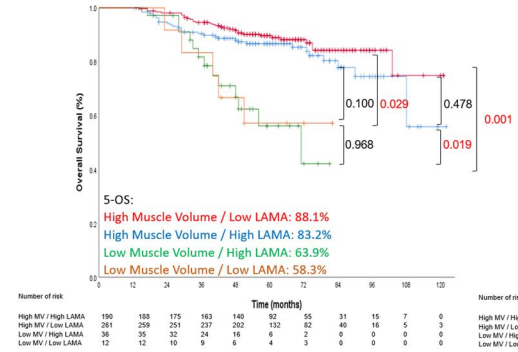
(A) - Overall survival



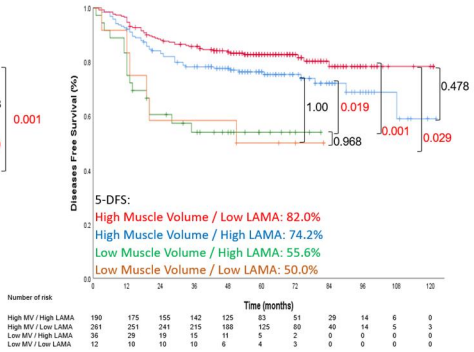
(B) - Diseases-free survival



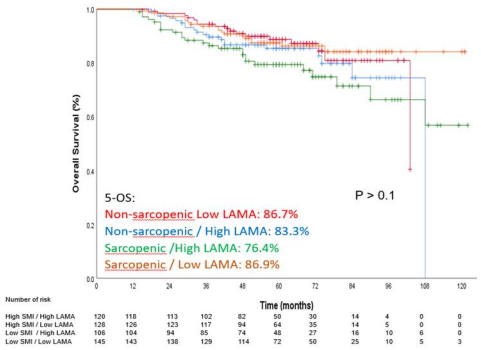
(C) - Overall survival



(D) - Diseases-free survival



(E) - Overall survival



(F) - Diseases-free survival

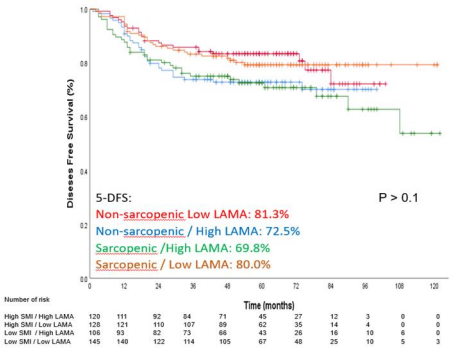
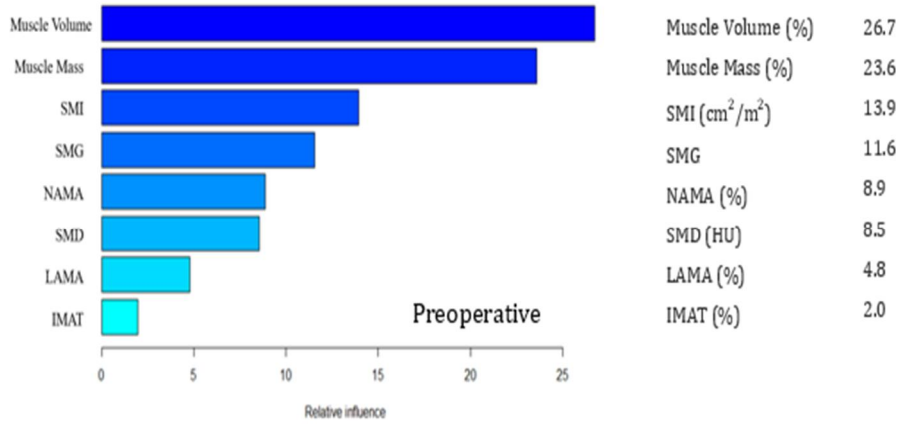


Figure 8. Gradient boosting model for comparison of parameters



4. DISCUSSIONS AND CONCLUSSIONS

4.1 Discussion.

In recent years, with wide use of CT scans, body composition of cancer patients had a great attention of researchers, and it led to an increase in the number of studies in this field. A large number of representative studies confirm the negative impact of abnormal body composition on the patients' survival. In addition, there is more and more evidence of a correlation between changes in body composition and the adverse outcomes of surgical (complications and mortality) and drug (toxicity) treatments [4, 5, 6, 9, 21]. At the same time, the lack of generally accepted diagnostic criteria leads to heterogeneity of studies.

In our study, we used CT scans to obtain information of potential clinical relevance. Using high technology, we determined the body composition for each patient in a short time with high accuracy [16]. In addition, from the obtained body composition data, we extracted addition data about muscle and fat tissue attenuation. Patients in our study had similar

body weights, but had differences in muscle and fat mass, volume, and area, and these characteristics predicted survival. In particular, BMI did not play an important role (there was no significant difference in BMI in both groups).

According to the conventional wisdom about cancer cachexia, patients who appear thin or emaciated often have a history of weight loss, wasting skeletal muscle mass, and a poor prognosis [7, 8]. Patients in our cohort were more likely to be normal or slightly overweight but some had latent muscle wasting. Evaluation of CT scans provides additional important information, especially for patients who are not thin or emaciated and may be of normal weight, overweight, or obese.

Gonzales et al. reported that the obesity paradox is present in cancer patients only if patient does not have abnormal body composition. Cancer patients with high mortality risk can be identified by a body-composition assessment [11].

Hopkins et al. (2019) reported that low SMI is a predictor of poor survival, and their combined effect allows highly predictive predictions of decreased overall, disease-free and cancer-specific survival for colorectal cancer patients [22]. Jeroen et

al. (2018) reported that low SMI and muscle density are associated with the impaired postoperative recovery and increased postoperative complication rate after colorectal surgery. No association was found with overall, cancer-specific, and disease-free survival [23]. Malietzis et al. (2016) proved that the abnormal body composition is related the systemic inflammatory response in colorectal cancer patients [24]. Most studies on the association of body composition with cancer outcomes report a poor prognosis for patients [4, 5, 6, 12, 25, 26].

The association between general emaciation of the human body and chemotherapy has been proven for a long time. Recent studies have shown that abnormal body composition is associated with more severe chemotherapy toxicity, resulting in dose reduction, delay or permanent discontinuation of therapy [27, 28, 29]. In addition, low muscle mass can lead to infection. Both premature discontinuation of treatment and infection, which often develops on the background of general emaciation of the body, can reduce survival [30, 31]. However, these previous studies were based on the parameters of the cross-

sectional area of the third lumbar (L3) vertebra. The parameters of the abdominal waist are still insufficiently studied. In particular, there are no studies of the relationship between the parameters of the abdominal waist and colorectal cancer outcomes. Both the etiology and the prognostic value of low muscle mass and volume in abdominal waist for cancer patients remain the subject of further research.

The results presented here using survival analysis can further refine these diagnostic criteria to include weight loss, muscle loss and specific criteria for body composition. We believe that the label "cachexia" can be applied to all patients suffering from all factors: weight loss, muscle and fat mass and volume loss, sarcopenia and myosteatosis, because these patients share an equally high risk of poor prognosis.

This study emphasizes the potential ability of computed tomography and subsequent analysis of CT scans in determining the exact body composition of patients.

Muscle mass can be increased in several ways: an individually selected meal plan depending on the patient's parameters (most patients experience loss of appetite and severe anorexia, in

other cases, the appetite persists, and muscle loss may develop on the background of systemic inflammation), medication (hormones, insulin-like growth factor, glucocorticoid therapy, etc.), the selected rehabilitation plan is aimed at restoring muscle mass, volume and strength. The emerging opportunity to assess and modify muscle and fat tissue before and after cancer treatment will stimulate the development of new treatment protocols. It is a well-known fact that treating patients with chronic diseases, including cancer, is very costly for the patient himself and the government [32]. Therefore, it is clear that preoperative body composition analysis offers a new opportunity not only for identifying high-risk patients before surgery but also for identifying those who have the potential to incur high costs. This study showed that abnormal body composition is associated with a higher risk of adverse treatment outcomes. The development of the concept and application of preliminary rehabilitation for each patient individually, the principle of personalized medicine, has a clinically significant perspective. Early detection of muscle mass and strength, replacement of muscles with adipose tissue

will allow for adequate preoperative therapeutic rehabilitation of such patients before and after surgery to optimize the patient's reserve and achieve positive treatment outcomes.

In our study: comparing measurements of all body composition parameters, the significantly better results showed muscle volume and mass in the abdominal waist for survival prognosis with highly significant $p \leq 0.001$, which is most likely due to a broader surface and a large volume of analyzed muscle and fat tissues. Multivariate analysis adjusted by age, tumor location and cancer stage demonstrated that body composition parameters in the abdominal waist could be significant predictors and correlate with OS and DFS.

We performed additional analyzes to assess the association between body composition and the risk of recurrence development. All parameters in the abdominal waist and L3 were analyzed. No one parameter in the AW and L3 level could not achieve a significant difference between two groups in our patients cohort. Based on the analysis results, we can say that the body composition might be related to OS and DFS or non-cancer-specific death, but not to cancer-specific death.

(Kaplan–Meier curves were not inserted in the manuscript).

In addition, for postoperative complications, only one parameter showed good predictive ability among all parameters: AVF on abdominal waist level. High AVF mass and volume were not associated with survivals but with postoperative complications. Ding et al. (Colorectal Dis., 2015) reported that patients with visceral obesity had a longer operation time, greater blood loss, a greater length of the resected bowel, and higher intraoperative and postoperative complications rates than patients without visceral obesity. This may be due to an abnormal profile of systemic metabolism since adipose tissue is an active endocrine organ, is involved in the development of the metabolic syndrome and affects the regulation of inflammation [33].

The strength of our study is that to minimize external influences on body composition, we included only patients who had not received chemotherapy before surgery. Also, a sufficient number of patients and CT scans at different periods of the patient's treatment made it possible to obtain reliable

results. Another one is that the program can analyze body composition in a short time and with great accuracy; the program provides extensive information in a simple form, understandable and quickly processed by any specialist with any work experience.

The limitations of the present study were that data on patients' social level (incomes), sports activities, habits and diet, which can also affect body composition, did not include. Also, we did not analyze the interaction between changes in body composition, immunologic responses, chemotherapy and correlation with cancer outcomes. This field also needs further research into the relationship between environmental factors, body composition and cancer outcomes. We did not analyze the reasons for the poor prognosis in patients with low muscle mass and volume in terms of disease-free survival. One potential explanation is that these patients were less likely to receive chemotherapy in a complete course because of an adverse reaction, malnutrition and general weakening of the body. A further prospective study is needed in order to analyze the association between body composition, chemotherapy and

risk of relapses. After discussion with AI specialists to obtain more accurate data, we decided to use one type of CT, CT abdomen& pelvis with contras. Also, we decided to utilize only the venous or portal phase. We did not analyze the pre-contrast phase; therefore, further study is needed in order to analyze the association between body composition and cancer outcomes using non-contrast CT.

4.2 Conclusion. Body composition parameters in the abdominal waist can be a more clinically useful survival predictor than parameters in the L3 level. CT with subsequent AI-based body composition analysis will allow choosing the optimal treatment algorithm to achieve positive results. Body composition can be analyzed accurately in a short time using AI automatic segmentation; the program provides massive information in a simple form, understandable and quickly processed by any specialist with any work experience.

5. REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer Journal for Clinicians 2018; 68 (6): 394-424. Epub 2020/08/06.
2. Rawla P., Sunkara T., Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Gastroenterology Rev 2019; 14 (2): 89-103. Epub 2019/01/06
3. Sung H., Ferlay J., L. Siegel R., Laversanne M., Soerjomataram I., Jemal A., Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer Journal for Clinicians. 2021 May;71(3):209-249. Epub 2021/02/04
4. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a

population-based study. The Lancet Oncology 2008; 9 (7): 629-35.

5. Cespedes Feliciano EM, Chen WY, Lee V, et al. Body Composition, Adherence to Anthracycline and Taxane-Based Chemotherapy, and Survival After Nonmetastatic Breast Cancer. JAMA Oncology 2020; 6 (2): 264-70.
6. Prado C.M., Baracos V.E., McCargar L.J, Mourtzakis M., Mulder K.E., Reiman T., Butts C.A., Scarfe A.G., Sawyer M.B. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clinical Cancer Reserch. 2007 Jun 1;13(11):3264-8.
7. Lisa Martin L., Birdsell L., Macdonald N., Reiman T., Clandinin M.T., McCargar L.J., Murphy R., Ghosh S., Sawyer M.B., Baracos V.E. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. Journal of Clinical Oncology (American Cancer Soiciety). 2013 Apr 20;31(12):1539-47. Epub 2013/03/25.
8. Prado C. M. , Cushen S. J. , Orsso C. E. , Ryan A. M. Sarcopenia and cachexia in the era of obesity: clinical and

nutritional impact. Published online by Cambridge University Press: 2016/01/08

9. Baracos V.E., Arribas L., Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. Annals of Oncology, 2018/02/01. E-pub: 2019/12/04

10. Lee D.H., Giovannucci E.L. The Obesity Paradox in Cancer: Epidemiologic Insights and Perspectives. Current Nutrition Report. 2019 Sep;8 (3):175-181.

11. Gonzalez M.C., Pastore C.A., Orlandi S.P., Heymsfield S.B. Obesity paradox in cancer: new insights provided by body composition. The American Journal of Clinical Nutrition, Volume 99, Issue 5, May 2014, Pages 999-1005. Epub 2014/02/26.

12. Malietzis G., Currie A.C., Athanasiou T., Johns N., Anyamene N., Glynne-Jones R., Kennedy R.H., Fearon K.C.H., Jenkins J.T. Influence of body composition profile on outcomes following colorectal cancer surgery. British Journal of Surgery, Volume 103, Issue 5, April 2016, Pages 572-580. Epub: 16/03/16

13. Elisabeth J. M. Baltussen, Esther N. D. Kok, Susan G. Brouwer de Koning, Joyce Sanders, Arend G. J. Aalbers, Niels F. M. Kok, Geerard L. Beets, Claudie C. Flohil, Sjoerd C. Bruin, Koert F. D. Kuhlmann, Henricus J. C. M. Sterenborg, Theo J. M. Ruersa. Hyperspectral imaging for tissue classification, a way toward smart laparoscopic colorectal surgery. Journal of Biomedical Optics. 2019 Jan; 24(1): 016002. Epub 2019/01/30

14. Ferrari R., Mancini-Terracciano C., Voena C., Rengo M., Zerunian M., Ciardiello A., Grasso S., Mare V., Paramatti R., Russomando A., Santacesaria R., Satta A., Solfaroli Camillocci E., Faccini R., Laghi A. MR-based artificial intelligence model to assess response to therapy in locally advanced rectal cancer. European Journal of Radiology, volume 118, September 2019, Pages 1-9. Epub 2019/06/22.

15. "Medical IP" company website https://medicalip.com/

16. Yoon Seong Lee Y.S., Hong N, Witanto J.N., Choi Y.R., Park J.B., Decazes P., Eude F., Kim C.O., Kim H.C., Goo J.M., Rhee Y., Yoon S.H. Deep neural network for automatic volumetric segmentation of whole-body CT images for body

composition assessment. Clinical Nutricology. 2021 Aug;40(8):5038-5046. Epub 2021 Jul 15.

17. Lönn L, Kvist H, Ernest I, Sjöström L. Changes in body composition and adipose tissue distribution after treatment of women with Cushing's syndrome. Metabolism 1994 Dec;43(12):1517-22.

18. Engelke K., Museyko O., Wang L., Laredo JD. Quantitative analysis of skeletal muscle by computed tomography imaging-State of the art. Journal of Orthopaedic Translation 2018 Oct 28;15:91-103.

19. Poltronieri T.S., Silva de Paula N., Chaves GV. Assessing skeletal muscle radiodensity by computed tomography: An integrative review of the applied methodologies. Clinical Physiology and Functional Imaging 2020;40:207-223.

20. Camp R.L., Dolled-Filhart M., Rimm D.L. X-Tile. A New Bio-Informatics Tool for Biomarker Assessment and Outcome-Based Cut-Point Optimization. Clinical Cancer Research, 2004

21. Weinberg MS., Shachar S.S., Hyman B Muss, Allison M

Deal, Karteek Popuri, Hyeon Yu, Kirsten A Nyrop, Shani M Alston, Grant R Williams. Beyond sarcopenia: Characterization and integration of skeletal muscle quantity and radiodensity in a curable breast cancer population. The Breast Journal 2018 May;24(3):278-284.

22. Hopkins JJ, Reif RL, Bigam DL, et al. The Impact of Muscle and Adipose Tissue on Long-term Survival in Patients With Stage I to III Colorectal Cancer. Diseases of the Colon & Rectum 2019; 62 (5): 549-60.

23. Jeroen L.A van Vugt, Robert R.J. Coebergh van den Braak, Zarina S.Lalmahomed, Wietske W.Vrijlandb, Jan W.T.Dekker, David D.E.Zimmerman, Wouter J.Vles, Peter-Paul L.O.Coene, Jan N.M.IJzermans. Impact of low skeletal muscle mass and density on short and long-term outcome after resection of stage I-III colorectal cancer. European Journal of Surgical Oncology. Volume 44, Issue 9, September 2018, Pages 1354-1360

24. Malietzis G, Johns N, Al-Hassi HO, et al. Low muscularity and myosteatosis is related to the host systemic inflammatory response in patients undergoing surgery for

colorectal cancer. Annals of Surgery 2016; 263 (2): 320-5.

25. Sueda T, Takahasi H, Nishimura J, et al. Impact of Low Muscularity and Myosteatosis on Long-term Outcome After Curative Colorectal Cancer Surgery: A Propensity Score-Matched Analysis. Diseases of the Colon & Rectum 2018; 61 (3): v364-74.

26. Aro R, Mäkäräinen-Uhlbäck E, Ämmälä N, et al. The impact of sarcopenia and myosteatosis on postoperative outcomes and 5-year survival in curatively operated colorectal cancer patients-A retrospective register study. European Journal of Surgical Oncology 2020; 46(9):1656-62.

27. Rosenthal MA, Oratz R. Phase II clinical trial of recombinant alpha 2b interferon and 13 cis retinoic acid in patients with metastatic melanoma. American Journal of Clinical Oncology 1998/08/21:352-354.

28. Visovsky C, Schneider SM. Cancer-related fatigue. Online Journal of Issues in Nursing 2003; 8:8.

29. Fabrizio Pin, Marion E. Couch, Bonettoa A. Preservation of muscle mass as a strategy to reduce the toxic effects of cancer chemotherapy on body composition. Current Opinion

in Supportive and Palliative Care. 2018 Dec; 12(4): 420-426. Epub: 2018/8/21.

30. Richards CH, Roxburgh CS, MacMillan MT, Isswiasi S, Robertson EG, Guthrie GK et al. The relationships between body composition and the systemic inflammatory response in patients with primary operable colorectal cancer. PloS One 2012; 7: e41883. E-Pub: 2012/08/03

31. Malietzis G, Johns N, Al-Hassi HO, Knight SC, Kennedy RH, Fearon KC et al. Low muscularity and myosteatosis is related to the host systemic inflammatory response in patients undergoing surgery for colorectal cancer. Annals of Surgery 2016 Feb;263(2):320-5.

32. Sheetz KH, Waits SA, Terjimanian MN, Sullivan J, Campbell DA, Wang SC. Cost of major surgery in the sarcopenic patient. Journal of the American College of Surgeons 2013; 217: 813-818.

33. Ding Z., Wu X.-R., Remer E. M., Lian L., Stocchi L., Li Y., McCullough A., Remzi F. H., Shen B. Association between high visceral fat area and postoperative complications in patients with Crohn's disease following primary surgery.

Colorectal Diseases 2016 Feb;18(2):163-72.

국문 초록

서론: 체중 감소는 악성 종양의 주요 증상 중 하나이나, 감소한 몸의 구성 성분에 따라 임상적 의미가 다를 수 있으며, 이전 연구에서 골격근 고갈은 암 환자의 낮은 생존율과 연관이 있는 것으로 보고되었다. 그러나 아직까지 대장암 환자에서 골격근을 측정하는 최적의 방법과 그 기준값에 대한 연구가 부족한 실정이다. 따라서 본 연구는 대장암 환자의 종양학적 성적에 대한 체성분의 영향을 평가하고, 기존의 L3 에서 측정한 체성분 변수와 본 연구에서 새로이 분석한 복부 체성분의 부피와 양에 대한 변수를 비교하여 더 나은 예후 예측 인자를 밝히고자 한다.

방법: 2010 년 1 월부터 2016 년 12 월까지 서울대병원에서 2 기 및 3 기 대장암에 대해 근치적 수술을 받았던 환자를 대상으로 한 후향적 연구이다. 수술 전, 수술 후 6 개월 및 12 개월 CT 영상이 모두 가용한 환자를 대상으로 하였고, 전이가 있거나 유전성 대장암 환자, 외부에서 CT 를 시행한 환자, 임상 데이터가 부족한 환자 등은 제외하였다. 신체 구성 데이터는 골격근, 피하지방, 내장지방, 근육 내 지방조직으로 제 3 허리뼈와 복부 허리에서 모두 측정되었다. 골격근 지수, 골격근 밀도, 골격근 게이지는 L3 의 골격근 영역을 사용하여 계산되었다. 환자 그룹에 대한 기준치는 각

성별에 대해 X-tile 프로그램에 이용하여 결정되었다. 각 체성분에 대한 기준치보다 높고 낮음에 따라 환자를 두 그룹으로 나누고 치료 결과를 비교하였다.

결과: 생존 분석 결과 근육량과 근육 부피가 작은 군 에서 큰 군에 비해 생존율이 유의미하게 낮았다 (근육량 5-OS: 70.2% vs. 86.9%, p<0.001; 5-DFS: 61.7% vs. 81.0%, p<0.001; 근육 부피 5-OS: 62.5% vs. 86.0%, p<0.001; 5-DFS: 54.2% vs. 78.7%, p<0.001). 피하지방량과 부피가 큰 그룹은 작은 그룹에 비해 생존율이 현저히 높았다 (피하지방량 5-OS: 87.9% vs. 70.8%, p<0.001; 5-DFS: 81.0% vs. 61.7%, p<0.001; 피하지방 부피 5-OS: 86.1% vs. 63.5%, p <0.001; 5-DFS: 78.5% vs. 57.7%, p<0.001).

골격근 밀도가 낮은 그룹은 높은 그룹에 비해 더 나쁜 전체생존율 및 무병생존율을 보였다 (5-OS: 78.1% vs. 86.1%, p=0.041; 5-DFS: 70.5% vs. 78.8%, p=0.041). 골격근 게이지가 낮은 그룹은 높은 그룹에 비해 낮은 생존율 보였다 (5-OS: 73.0% vs. 86.9%, p<0.001; 5-DFS: 66.7% vs. 79.1%, p=0.004). 근육내 지방량이 작은 그룹은 많은 그룹에 비해 더 나쁜 생존율을 보였다 (5-OS: 73.6% vs. 85.0%, p=0.025; 5-DFS: 64.2% vs. 77.8%, p=0.020).

수술 후 합병증의 위험은 복부내장지방량과 부피가 작은 그룹(각각 27.4% 및 27.1% vs. 18.7% vs. 19.0%, p=0.021 및 p=0.028)에 비해 복부내장지방량과 부피가 큰 0 그룹에서 유의하게 높았다.

연령, 종양의 위치 및 병기를 보정한 다변량 분석 결과, 골격근양과 부피 (각각 HR 2.423, 1.504 – 3.905, p<0.001; HR 2.662, 1.501 – 4.720, p=0.001), 피하지방량과 부피 (각각 HR 2.041, 1.300 – 3.204, p=0.002; HR 2.195, 1.288 – 3.741, p=0.004), 골격근 게이지와 근육내 지방 (각각 HR 2.083, 1.294 – 3.354, p=0.003; HR 2.125, 1.186 – 3.808, p=0.011)이 전체 생존률을 위한 독립적인 예후 요인으로 확인되었다. 또한, 종양의 위치와 병기를 보정한 다변량 분석 결과, 무병생존율에 있어서 골격근량와 부피(각각 HR 2.347, 1.504 – 3.664, p<0.001; HR 3.136, 1.894 – 5.139, p<0.001), 피하지방량과 부피 (각각 HR 1.739, 1.132 – 2.672, p=0.012; HR 2.062, 1.224 – 3.475, p=0.007), 골격근 밀도와 게이지 (각각 HR 1.710, 1.124 – 2.601, p=0.012; HR 1.938, 1.253 – 2.996, p=0.003)는 독립적인 예후 요인으로 나타났다.

연관성 분석 및 gradient boosting model 에서 모든 신체 구성 변수를 비교하였고, 생존 예후에서 골격근량과 부피가 대장암 환자의 전체생존율과 관련성이 가장 높은 것으로 나타났다.

결론: 복부의 골격근량 및 부피 변수는 L3 레벨의 골격근 면적보다 임상적으로 더 유용한 생존 예측 변수로 확인되었다. . 대장암 환자의 골격근 및 피하지방, 복부내장지방에 대한 부피 및 양에 대한 분석은 AI 자동 분할을 사용하여 짧은 시간 안에 정확하게 분석할 수 있으며, 예후를 예측하는데 유용하게 사용될 수 있다.

주요어: 체성분, 골격근 량, 골격근 부피, 대장암, 인공지능, 예후

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