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Sarcopenia diagnosis in patients with colorectal cancer: a review of computed tomography-based assessments and emerging ways to enhance practicality

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Traditionally, cancer treatment has focused on the stages of the disease; however, recent studies have highlighted the importance of considering the overall health status of patients in the prognosis of cancer. Loss of skeletal muscle, known as sarcopenia, has been found to significantly affect outcomes in many different types of cancers, including colorectal cancer. In this review, we discuss the guidelines for diagnosing sarcopenia, with a specific focus on CT-based assessments. Many groups worldwide, including those in Europe and Asia, have introduced their own diagnostic guidelines for sarcopenia. Seemingly similar yet subtle discrepancies, particularly in the cutoff values used, limit the use of these guidelines in the general population, warranting a more universal guideline. Although CT-based measurements, such as skeletal muscle index and radiodensity, have shown promise in predicting outcomes, the lack of standardized values in these measurements hinders their universal adoption. To overcome these limitations, innovative approaches are being developed to assess changes in muscle mass trajectories and introduce new indices, such as skeletal and appendicular muscle gauges. Additionally, machine learning models have shown superior performance in predicting sarcopenic status, providing an alternative to CT-based diagnosis, particularly after surgery. CT has tremendous benefits and a significant role in visually as well as quantitatively retrieving information on patient body composition. In order to compensate for the limitation of standard cutoff value, 3-dimensional analysis of the CT, artificial intelligence-based body composition analysis, as well as machine learning algorithms for data interpretation and analysis have been proposed and are being utilized. In conclusion, despite the varying definitions of sarcopenia, CT-based measurements coupled with machine-learning models are promising for evaluating patients with cancer. Standardization efforts can improve diagnostic accuracy, reduce the reliance on CT examinations, and make sarcopenia assessments more accessible in clinical settings.
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Key Words: Colorectal neoplasms, Computed tomography, Diagnosis, Myosteatosis, Sarcopenia

INTRODUCTION

Treatment of patients with cancer is mainly based on the stage of the cancer. Despite such stage-based treatments, many studies have revealed that a patient's general status also influences their outcomes. Many studies are now focusing on modifiable factors, such as lifestyle changes and preoperative prehabilitation, that could impact the patient's prognosis [1,2]. Recently, the role of sarcopenia and the prognosis of patients have been emphasized in many oncological diseases, and

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colorectal cancer (CRC) is not an exception. Shachar et al. [3] have shown that a low skeletal muscle index (SMI) is associated with poor overall survival (OS), worse cancer-specific survival (CSS), and worse disease-free survival (DFS) not only in CRC but also in many different tumor types. A study by Oh et al. [4] revealed sarcopenia as a risk factor for postoperative complications in patients who underwent laparoscopic colon cancer surgery. Lee et al. [5] showed significantly lower 3-year DFS in both preoperative and postoperative sarcopenic patients.

As the 3rd most common cancer in Korea, the prevalence of CRC is increasing [6]. There are many different types of methods for diagnosing sarcopenia from simple questionnaires to performance tests to CT scans as well as machine-learning algorithms. In this review, we aim to outline the general diagnostic guidelines for sarcopenia and discuss the diagnostic methods for CT-based sarcopenia assessment in patients with CRC. We began by reviewing major definitions and guidelines on sarcopenia. Given the limitations of these guidelines, we searched for recent trends in diagnosing sarcopenia using CT and machine-learning algorithms.

Furthermore, we plan to investigate the variability and limitations of the currently used clinical diagnostic criteria for sarcopenia and ways to overcome such constraints.

MAIN BODY

Definition of sarcopenia in the European Working Group on Sarcopenia in Older People

Sarcopenia is characterized by the loss of skeletal muscle mass, strength, and function that occurs with aging. It is associated with various negative outcomes, including reduced physical performance, increased risk of falls, impaired mobility, and decreased quality of life [7]. In order to address the challenges associated with sarcopenia, understanding how the term came into use is important.

The European Working Group on Sarcopenia in Older People (EWGSOP) first reported its guidelines on sarcopenia in 2010 with a practical clinical definition and consensus criteria for age-related sarcopenia [8]. In its diagnostic criteria, 3 factors were relevant: muscle mass, muscle strength, and physical performance. After a decade of research investigating sarcopenia, a revised definition emerged in which muscle strength and physical performance remained unchanged, and muscle mass was amended to muscle quantity and quality (EWGSOP2) [9]. The summary of these 2 guidelines is presented in Fig. 1.

Several diagnostic tools have been developed to measure these values. Initial screening for sarcopenia relied on the SARC-F questionnaire. Muscle strength can be measured using grip strength or the chair-stand test. Numerous imaging studies can be used to measure muscle mass in terms of size and quality, such as appendicular skeletal muscle mass (ASM) using dual-energy X-ray absorptiometry (DXA), whole-body skeletal muscle mass or ASM predicted using bioelectrical impedance analysis (BIA), and lumbar muscle cross-sectional area using CT or MRI. Additionally, muscle biopsy, CT, MRI, or magnetic resonance spectroscopy can be used to evaluate muscle quality in research settings. Finally, physical performance can be measured using gait speed, short physical performance battery (SPPB), timed up-and-go test (TUG), or 400-m walk or long-distance corridor walk test [9].

After these tests had been performed, the cutoff points for both males and females were given. Low strength was measured using grip strength (male, <27 kg; female, <16 kg) and chair stand (>15 seconds for 5 rises). Low muscle quantity cutoff points for ASM and ASM/height^2 were <20 kg and <7.0 kg/m^2 for males and <16 kg and <5.5 kg/m^2 for females, respectively. Low performance was diagnosed with gait speeds ≤0.8 m/sec, SPPB ≤8 points, TUG ≥20 seconds, or 400-m walk test of non-completion or ≥6 minutes for completion.

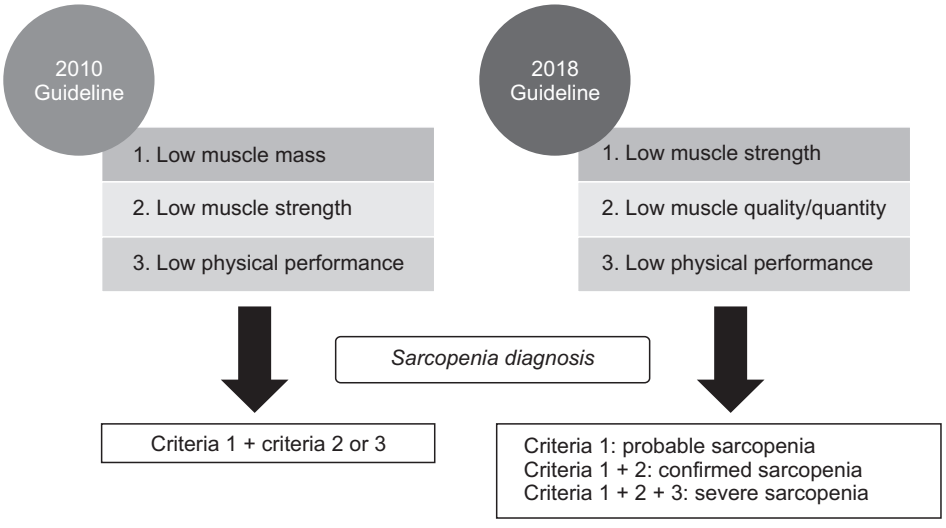

Fig. 1. European Working Group on Sarcopenia in Older People (EWGSOP) 2010 and 2018 Guidelines.

The guidelines summarize the consensus by using a practical algorithm that can be used in a clinical setting. Abbreviated to 'F-A-C-S,' we need to first *Find cases* through SARC-F questionnaires or through clinical suspicion, after which we need to *Assess* muscle strength. If sarcopenia is likely, we need to *Confirm* sarcopenia by measuring muscle quantity or quality. Once confirmed, the *Severity* of sarcopenia should be assessed through physical performance evaluation.

Definition of sarcopenia in the Asian Working Group for Sarcopenia

Due to ethnic differences between Asian and Western body compositions and cultural and lifestyle-related differences, the Asian Working Group for Sarcopenia (AWGS) announced its 2019 consensus update on sarcopenia diagnosis and treatment, focusing on the Asian population [10]. The algorithm is subdivided into 2 categories based on the setting: the primary healthcare or community preventive services settings *vs.* the acute to chronic healthcare or clinical research settings. Both settings begin with case findings using calf circumference (male, <34 cm; female, <33 cm) or SARC-F (≥4) or SARC-CalF (≥11), but the health care settings also include those with clinical suspicion (i.e., functional decline or limitations, unintentional weight loss, depressive mood, cognitive impairment, repeated falls, malnutrition, and chronic conditions). Muscle strength and physical performance were assessed. In the primary health care or community setting, either muscle strength, measured by handgrip strength (male, <28 kg; female, <18 kg), or physical performance, measured by the 5-time chair stand test (≥12 seconds), is sufficient to diagnose possible sarcopenia. However, in an acute-to-chronic healthcare setting, muscle strength, physical performance, and ASM are all required for a proper diagnosis. Physical performance measurement tools are expanded using the 6-m walk (<1.0 m/sec) or SPPB (≤9). DXA (male, <7.0 kg/m^2; female, <5.4 kg/m^2) or BIA (male, <7.0 kg/m^2; female, <5.7 kg/m^2) is used for ASM. If all 3 criteria were met, the patient was diagnosed with severe sarcopenia.

The Korean Working Group on Sarcopenia also introduced its own new guideline in 2023 [11]. Their screening tests resemble the aforementioned guidelines and are comprised of 7 different tools: (1) SARC-F (≥4), (2) calf circumference (male, <34 cm; female, <33 cm), (3) the finger-ring test, (4) the chair stand test (5 times; >10 seconds in the standing position, >11 seconds in the sitting position; male, ≤17 seconds; female, ≤15 seconds), (5) the handgrip strength (male, <28 kg; female, <18 kg), (6) gait speed (4-m or 6-m, <1.0 m/sec), and (7) TUG (≥12 seconds). With at least 1 of the screening criteria met, possible sarcopenia is diagnosed, after which physical performance, muscle mass, and muscle strength are measured. DXA (male, <7.0 kg/m^2; female, <5.4 kg/m^2) or BIA (male, <7.0 kg/m^2; female, <5.7 kg/m^2) is used for the measurement of muscle mass. Muscle strength was measured using a conventional handgrip strength of <28 kg for males and <18 kg for females. Evaluation of physical performance encompasses 5 different tools: (1) gait speed (4-m or 6-m) <1.0 m/sec, (2) TUG (≥12 seconds), 3) chair stand test (5-time; >10 seconds in standing position and >11 seconds in sitting position), (4) chair stand (30 seconds; male, ≤17 seconds; female, ≤15 seconds), and (5) 400-m walk test (non-completion or ≥6 minutes). The degree of sarcopenia was diagnosed according to different combinations of these 3 measurements, as shown in Fig. 2.

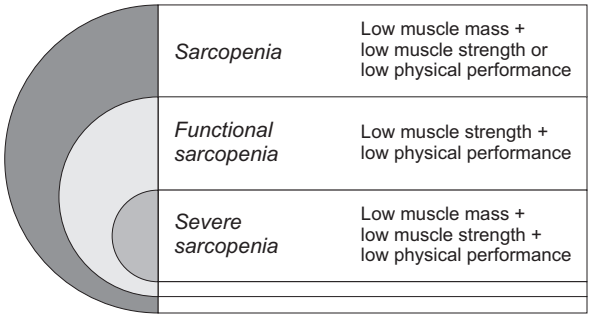

Fig. 2. Korean Working Group on Sarcopenia (KWGS) Guideline.

Definition of sarcopenia in different guidelines

The Sarcopenia Definitions and Outcomes Consortium (SDOC) is another group that focuses on identifying different cutoff points for grip strength and gait speed. The SDOC offered a much higher cutoff for grip strength (<35.5 kg for males and <20 kg for females) compared to the previous 2 guidelines. Moreover, the measurement of <0.8 m/sec of gait speed was deemed as low.

As one can concur, the 3 aforementioned criteria are different in their diagnosis of sarcopenia. Meza-Valderrama et al. [12] exquisitely summarized the comparison of the 3 recommendations (EWGSOP2, SDOC, and AWGS). In summary, the EWGSOP2 identifies sarcopenia through the presence of low muscle strength and low muscle mass, whether in terms of quality or quantity and uses physical performance to gauge its severity. The SDOC sets its diagnostic criteria based on muscle strength and gait speed. The AWGS, while akin to EWGSOP2 regarding the emphasis on muscle mass, allows for the diagnosis of sarcopenia through either low muscle strength or impaired physical performance. The 3 main core factors are muscle strength, muscle mass (quantity/quality, and physical performance), and the diagnostic examinations for each criterion are shown in Fig. 3.

Different diagnostic criteria among several guidelines

We have to wonder why we have these different cutoff values for the same diagnosis. Most apparent is the hand-grip strength

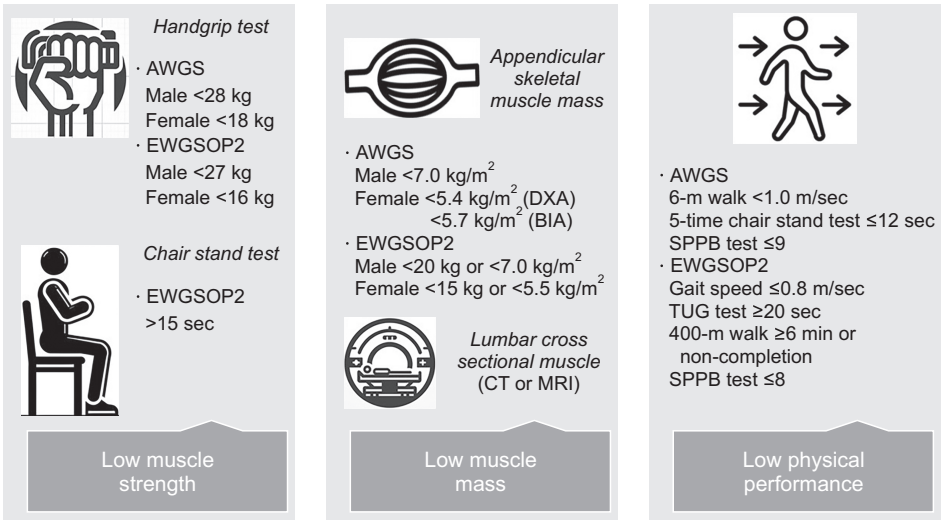

Fig. 3. Diagnostic tests performed for each criteria. AWGS, Asian Working Group for Sarcopenia; EWGSOP, European Working Group on Sarcopenia in Older People; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; SPPB, short physical performance battery; TUG, timed up-and-go.

used to measure muscle strength, showing a wide range of cutoffs: <27 kg for male and <16 kg for female in EWGSOP2; <35.5 kg for male and <20 kg for female in SDOC; <28 kg for male and<18 kg for female in AWGS. The experts reviewed the EWSGOP2 and found that its definition was derived from a normal population from which cutoff points were based on a T-score <–2.5 standard deviations for males and females, resulting in 27 kg for males and 16 kg for females [13]. In contrast, the SDOC used the CART (classification and regression tree) analyses to identify the best cutoff that statistically defined a higher incidence of falls, mortality, mobility, and hip fractures, resulting in 35.5 kg for males and 20 kg for females [14].

Another point of discussion is the inclusion of DXA among these criteria. While the EWSGOP2 and AWGS recommend the use of DXA, the SDOC does not, arguing that no difference in adverse events according to the cutoff value of DXA was observed in its analysis. This claim is supported by the International Clinical Practice Guidelines for Sarcopenia, which state that the level of evidence for DXA imaging is low owing to a lack of studies in low-middle income countries, limitations of DXA in measuring lean body mass, and no additional benefit of DXA in predicting poor outcomes [15]. Due to these reasons, clinicians are experimenting with different measurement tools, as was the case in Lim et al. [16], where the upper high SMI was used for the diagnosis of sarcopenia in patients with liver transplants.

CT-defined sarcopenia and myosteatosis

In nearly all of the guidelines, DXA and BIA scans are used as diagnostic tools. However, these scans are not routinely performed in cancer patients, and utilization of these scans on every cancer patient solely for the diagnosis of sarcopenia is time-consuming and costly. As an alternative, CT-based

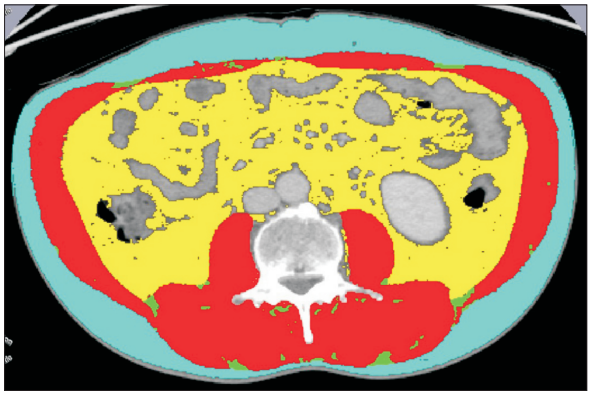

Fig. 4. Extraction of skeletal muscle index (SMI) and skeletal muscle density (SMD) using SliceOmatic image analysis software (version 5.0, TomoVision). Red, muscle; blue, subcutaneous fat; green, intramuscular fat; yellow, visceral fat. After delineation of each component, data for SMI and SMD can be retrieved.

measurements of skeletal muscles have been rigorously used in the field of oncology [17,18]. Likewise, CT-defined myosteatosis using skeletal muscle radiodensity has been studied [19-22]. Sarcopenia is often measured using the SMI via CT at the L3 level by dividing the area of skeletal muscle by the patient's height squared (cm^2/m^2). Myosteatosis, measured by skeletal muscle density (SMD), is also calculated using CT at the L3 level but by evaluating fat attenuation according to Hounsfield units (HU) (Fig. 4).

CT-defined sarcopenia in patients with cancer has been extensively researched, and a crucial meta-analysis evaluating the association between SMI and clinical outcomes was published by Shachar et al. [3] in 2016. In a review of 37 studies, sarcopenia measured as the SMI had a significant prognostic value in predicting poor OS in all cancer types (hazard ratio [HR], 1.437; 95% confidence interval [CI], 1.32–1.56; $P < 0.001$). When

stratified by cancer stage, this relationship was also apparent in both metastatic and nonmetastatic settings. Low SMI was also associated with worse CSS (HR, 1.93; 95% CI, 1.38–2.70; P < 0.001), and similar findings were apparent for DFS (HR, 1.16; 95% CI, 1.03–1.30; P = 0.014). Likewise, according to the study carried out by our group, a systematic review and meta-analysis on CT-defined myosteatosis in patients with CRC also revealed a significant increase in overall mortality in patients with myosteatosis in both univariate (HR, 1.38; 95% CI, 1.21–1.58; P < 0.00001) and multivariate (HR, 1.55; 95% CI, 1.23–1.96; P < 0.00001) analyses [21].

Cutoff values of CT-defined sarcopenia and myosteatosis

The prognostic significance of sarcopenia and myosteatosis has been corroborated in numerous studies. However, an issue similar to the conventional sarcopenia criteria applies, namely the cutoff values. Among the various cutoff values, the value suggested by Martin et al. [23], in which patients were divided according to body mass index (BMI) and sex for both SMI and SMD, was selected. Patients with BMIs <25 kg/m^2 and SMIs <43 cm^2/m^2 for males and <41 cm^2/m^2 for females were defined as sarcopenic. For SMD, a value of <41 HU for both males and females was defined as myosteatosis. Similarly, in patients with BMIs >25 kg/m^2, the cutoffs for sarcopenia were <53 cm^2/m^2 for males and <41 cm^2/m^2 for females, and <33 HU for both sexes in the myosteatosis group [23]. Prado et al. [24] focused on the SMI and introduced a different cutoff of 52.4 cm^2/m^2 for males and 38.5 cm^2/m^2 for females.

Discrepancies of CT-defined sarcopenia and myosteatosis

While previous studies by Shachar et al. [3] provided significant prognostic values for SMIs in many different cancer types, He et al. [25] focused on CRC. Reviewing 20 studies, sarcopenia measured using SMIs was present in 34% of patients with CRC, and the presence of sarcopenia led to poor OS, DFS, and CSS. However, opposing studies have reported no significant differences in patients with CRC [4,26-30]. The results of these studies are summarized in Table 1.

The discrepancy in CT-defined sarcopenia among the studies may be attributed to 2 main reasons. The first is the difference in body composition according to patient ethnicity. Second, as previously mentioned, sarcopenia has various definitions. A study conducted by Nishigori et al. [31] showed the prevalence of sarcopenia according to 5 different SMI cutoff values, and the percentage varied from 6% to 64%.

Several different thresholds for defining low SMIs and SMDs in patients with different types of cancer have been investigated [32]. The SMI range varied greatly from <25.66 cm^2/m^2 to <55.4 cm^2/m^2 in males and <21.73 cm^2/m^2 to <46.4 cm^2/m^2 in females. Similar results were found for the SMD in a systematic summary of 73 studies that found 32 different cut-off values [33]. Therefore, to make decisions in a clinical setting, the choice of cutoff values may rely heavily on the characteristics of each patient. These obstacles may hinder the generation of international criteria for CT-defined sarcopenia or myosteatosis, and further research is required to compensate for these limitations.

Several attempts to address the constraints associated with CT-defined sarcopenia and myosteatosis

Our group investigated ways to compensate for the limitations of CT-defined sarcopenia and myosteatosis. The first approach we considered was the trajectory change in the skeletal muscle. Ninety-three patients diagnosed with rectal cancer who underwent preoperative chemoradiation therapy (CRT) at a single tertiary center were reviewed. CT was performed before CRT initiation and 4–6 weeks after CRT cessation [18]. The study analyzed the change in muscle mass/100 days after allocating patient stratification by sarcopenia and non-sarcopenia using Prado et al.'s cutoff [24]. Severe muscle loss was defined as the change in muscle mass <−4.2%/100 days, and the distribution of these patients was similar in both groups (25% *vs.* 24.4%). Although no significant difference was noted in the OS or DFS between the pre-sarcopenia and pre-non-sarcopenia patient groups, the 5-year

Table 1. Summary of studies showing no significance of CT-defined sarcopenia in prognosis of CRC patients

Study	Year	Country	No. of enrolled	Included patients	Outcomes[a)]
Miyamoto et al. [29]	2015	Japan	215	Unresectable CRC	P = 0.740 (overall survival) (Q1–Q4 of SMI in pretreatment)
van Vugt et al. [30]	2018	Netherlands	797	CRC stage I–III	HR, 1.06 (95% CI, 0.80–1.42); P = 0.680
Looijaard et al. [28]	2020	Australia	378	CRC stage I–III	HR, 0.998 (95% CI, 0.840–1.187); no significance
Cárcamo et al. [26]	2021	Chile	359	CRC stage I–III	HR, 0.94 (95% CI, 0.54–1.62); no significance
Oh et al. [4]	2020	Korea	423	CRC stage I–III	HR, 1.38 (95% CI, 0.79–2.41); P = 0.115
Han et al. [27]	2020	Korea	1,384	Rectal cancer	HR, 0.947 (95% CI, 0.728–1.233); P = 0.688

CRC, colorectal cancer; SMI, skeletal muscle index; HR, hazard ratio; CI, confidence interval.
[a)]Sarcopenia *vs.* non-sarcopenia.

OS was significantly lower in the post-sarcopenia group (72.5% *vs.* 83.3%, P = 0.043). Multivariate analysis revealed that post-sarcopenia and severe changes in muscle mass were significant prognostic factors for OS.

Secondly, many researchers have explored a new marker known as skeletal muscle gauge (SMG), which is defined as a combination of SMI and SMD [34-38]. With only studies focusing on breast, endometrial, and ovarian cancers having been published, implementing a similar design solely in patients with CRC revealed a significant impact of SMG in these patients [22]. A total of 727 and 268 patients with CRC at 2 tertiary centers were included in the training and test sets, respectively. Using X-tile software (version 3.6.1, Yale University School of Medicine), cutoff values for SMG were retrieved at 1,642.1 arbitrary unit (AU) for males and 1,523.4 AU for females [39]. The Kaplan-Meier curves for OS according to low and high SMGs were significant in both the training and test sets (both P < 0.0001). While SMI, SMD, and SMG were all significant in univariate analysis, multivariate analysis showed that SMG was the sole significant prognostic factor in predicting OS.

Finally, a new composite index, albumin-myosteatosis gauge (AMG, albumin × SMD), was investigated for better stratification. After analyzing 906 patients diagnosed with stage I–III CRC, patients were stratified into 4 groups by quartile classification of AMG [20]. The survival curve showed a significant trend of decreasing OS with lower AMG levels. Univariate and multivariate analyses showed a significant association between AMG and OS, and the iAUC of 0.681 (95% CI, 0.638–0.723) for AMG was much higher than that of SMD (0.610; 95% CI, 0.566–0.654), albumin (0.627; 95% CI, 0.586–0.668), and SMI (0.551; 95% CI, 0.511–0.594) confirming the reliability of AMG as a prognostic factor in patient with CRC.

Defining skeletal muscle gauge without CT

The use of CT-defined sarcopenia and myosteatosis is possible owing to the routine nature of imaging studies during cancer evaluation. However, CT is not accessible to the general population, and postoperatively, exposure to radiation is a concern, and accurate measurement is difficult.

Machine learning is a form of artificial intelligence that involves the application of models and algorithms to analyze data. Patients who underwent surgical resections with curative intent for CRC at a single tertiary center were retrospectively reviewed [40]. Patients were allocated to the training (n = 656) and validation (n = 438) sets. The least absolute shrinkage and selection operator (LASSO) model for dimension reduction, feature selection, and signature building was used in the training set. Generation of the LASSO-based linear predictor (LP-SMG) for low SMG in the training set yielded 10 factors, including sex, age, height, BMI, smoking status, tumor location, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, hemoglobin, and albumin-bilirubin score. After a formula for LP-SMG was retrieved using the training set, we applied the data from validation set to LP-SMG. Using the newly formulated linear predictor (LP-SMG), multivariate analysis showed a significant association with low SMG in the test set (P < 0.001). The area under the receiver operating characteristic curve of the LP-SMG was 0.846 (95% CI, 0.811–0.881) in the training set and 0.869 (95% CI, 0.824–0.913) in the test set. In this study, we confirmed that the LP-SMG model for predicting sarcopenic

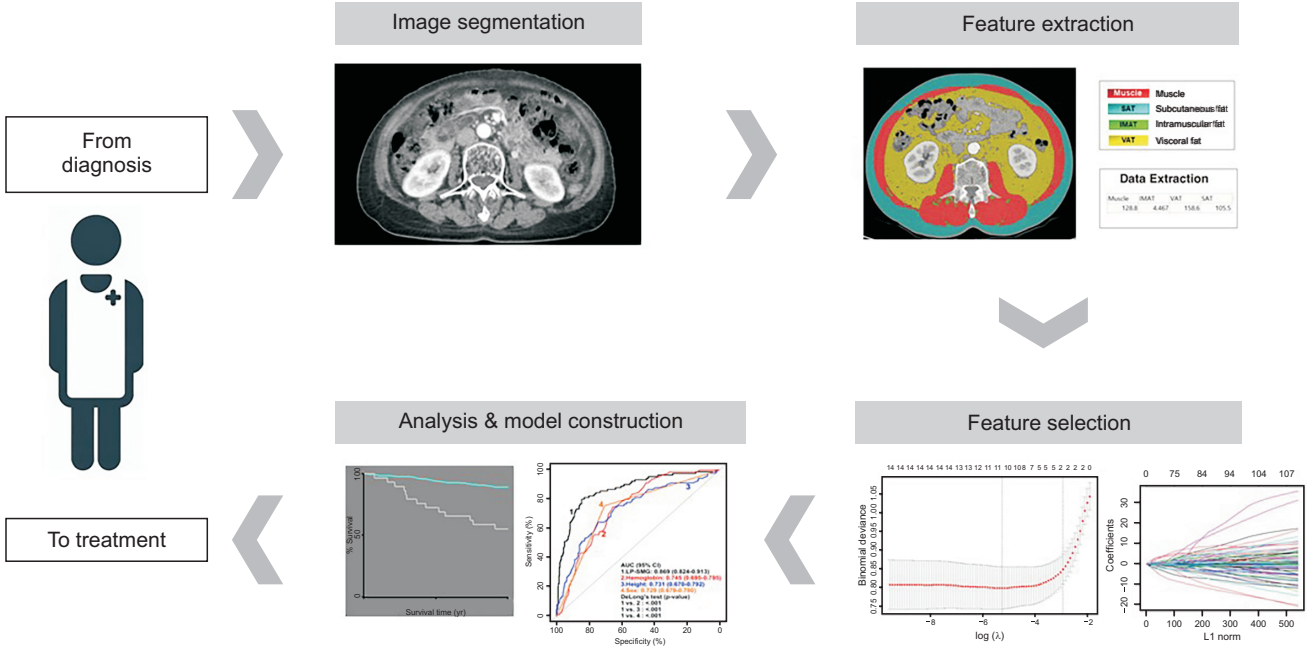

Fig. 5. Schematic process of extracting machine-learning–based algorithm for sarcopenia diagnosis.

status showed superior performance compared to other single clinical variables. Our model can potentially be adopted as a screening tool to detect sarcopenia, and applying a machine learning model may be beneficial in reducing the effort, cost, and radiation exposure associated with conventional CT-based diagnosis. A schematic process of machine-learning based model prediction can be seen in Fig. 5.

In conclusion, the methods used to define sarcopenia vary and require better organization and standardization. The use of CT-based measurements to define sarcopenia is promising, particularly in patients with cancer. In order to compensate for these limitations, future studies on machine-learning algorithms can be employed to define sarcopenia in these patients, omitting CT examinations.

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Conflicts of Interest

Jeonghyun Kang, serving as an Associate Editor of *Annals of Surgical Treatment and Research*, did not participate in the review process of this article. No other potential conflicts of interest pertinent to this article were reported.

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Formal Analysis, Investigation: HJC
Writing – Original Draft: HJC, JK
Writing – Review & Editing: JK

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