Agreement between PG-SGA category and fat-free mass in colorectal cancer patients

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Abstract

Background and aims: Low fat-free mass (FFM) is associated with adverse outcomes in colorectal cancer (CRC) patients. Patient-Generated Subjective Global Assessment (PG-SGA) is a widely used tool developed to detect patients at risk of malnutrition. The aim of this study was to investigate the concordance between PG-SGA category and FFM in patients with non-metastatic CRC.

Methods: Ninety-seven patients were included and categorized as well nourished (PG-SGA:A, n=67) or malnourished (PG-SGA:B, n=30). No patients were severely malnourished (PG-SGA: C). Bioelectrical impedance analysis (BIA) was used to assess FFM. Low FFM was defined as low fat-free mass index (FFMI) according to cut-off values recently proposed by The European Society for Clinical Nutrition and Metabolism (ESPEN).

Results: Twenty-nine percent of the patients were identified with low FFMI. The proportion with low FFMI was significantly higher among patients classified as malnourished by PG-SGA compared to well nourished (p=0.015). The sensitivity was however low, as the PG-SGA categorization classified only 50.0 % of the patients with low FFMI as malnourished (PG-SGA B). Using the PG-SGA scores (cut-off point > 4), the sensitivity increased to 60.7 %. Physical examination in the PG-SGA identified only 64.3 % of the patients with low FFMI as muscle depleted.

Conclusion: our results indicate a low concordance between PG-SGA category and low FFMI among patients with non-metastatic CRC. In clinical practice, PG-SGA should be supplemented by muscle mass assessments by BIA or other methods in order to detect low FFM in this patient group.

Introduction

Malnutrition and weight loss in cancer occurs due to a negative energy-and protein balance caused by a reduced food intake in combination with metabolic alterations induced by the tumor, such as elevated resting metabolic rate, lipolysis, and proteolysis driven by systemic inflammation and catabolic factors[1]. Appetite and food intake may also be affected by chemotherapy and radiotherapy induced side effects such as nausea, vomiting and diarrhea, constipation and changes in taste and smell.

It is now recognized that in particular the loss of fat-free mass (FFM) is linked to adverse outcomes in cancer patients. Progressive loss of skeletal muscle, the major constituent of FFM, is shown to be an independent predictor of chemotherapy toxicity[2], post-operative complications[3] and mortality[4, 5] in cancer patients. Depletion of FFM may occur with or without loss of fat mass, and may therefore be masked by a stable body weight[6]. Furthermore, weight gain during recovery may be characterized by an increase in fat mass rather than FFM[7].

Loss of skeletal muscle mass may subsequently lead to sarcopenia, defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as "a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength, which is associated with adverse outcomes such as physical disability, poorer quality of life and death"[8].

We have recently demonstrated that low FFM is common in patients with non-metastatic CRC[9]. Low FFM is shown to be associated with reduced survival in patients with non-metastatic primary CRC[10]. For CRC patients, identification of low FFM and sarcopenia is therefore of clinical importance since appropriate interventions may improve prognosis. Interventions focusing on optimizing food intake and reducing nutritional impact symptoms (i.e. symptoms affecting food intake) may decrease weight loss or facilitate weight gain in cancer patients[11, 12]. Ravasco and coworkers demonstrated that early individualized nutritional counselling reduced radiotherapy

toxicity and improved nutritional status, quality of life and survival in colorectal cancer (CRC) patients receiving radiotherapy[13]. According to the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients, nutritional therapy should be combined with physical therapy, i.e. counseling regarding physical activities of daily life, resistance and aerobic exercise training, to maintain or increase muscle mass[1].

ESPEN recently defined low FFM as FFM index (FFMI) below 15 kg/m^2 and 17 kg/m^2, in females and males, respectively[14]. FFMI can be estimated by the use of different modalities, including air displacement plethysmography, labeled water-isotope dilution techniques, dual energy x-ray absorptiometry (DXA), computed tomography (CT) scans at third lumbar level, and bioelectrical impedance analysis (BIA)[15]. In clinical practice, access to these methods is limited. The Scored Patient-Generated Subjective Global Assessment (PG-SGA)[16, 17] is one of few comprehensive nutritional assessment tools that covers all domains of the definition of malnutrition[18]. The PG-SGA includes four patient-generated components (weight history, food intake, nutritional impact symptoms and activities and function) and three professional components (age and diagnosis, metabolic stress and physical examination). The examination consists of visual inspection and palpation of muscles, subcutaneous fat and edema. Based on an evaluation of the patient-generated components and the physical examination, the patients are categorized as well-nourished (PG-SGA A), moderate/suspected malnutrition (PG-SGA B) or severely malnourished (PG-SGA C). The scored version also includes numerical scores for each of the components as well as a total numerical score. PG-SGA is recommended by the Academy of Nutrition and Dietetics as one of the nutritional assessment tools to use in clinical oncology practice[19]. However, although PG-SGA includes an evaluation of muscle and fat depletion, it is not known whether PG-SGA is suitable to detect low FFM in cancer patients. The aim of this study was therefore to investigate the concordance between PG-SGA category and FFM in patients with non-metastatic CRC.

Subjects and methods

Patients

Patients were enrolled between August 2013 and March 2015. Eligible patients were women and men aged 50 to 80 years with a confirmed primary CRC (ICD-10 18-20), and staged I-III according to the tumor node staging (TNM) system[20]. Patients with distant metastases were not included. All patients had undergone surgery at Oslo University Hospital or Akershus University Hospital in Norway.

The patients included in this cross-sectional study were recruited from the ongoing randomized clinical trial (RCT), The Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study[21]. All measurements were performed prior to the diet intervention. The CRC-NORDIET study was carried out in accordance to the Helsinki Declaration and informed consent was obtained from all participants. The study was approved by the Regional Committees for Medical and Health Research Ethics (REC Protocol Approval 2011/836) and by the data protection officials in Oslo University Hospital and Akershus University Hospital, and registered on the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010).

Measurements

All measurements were conducted at start of the clinical trial (2-9 months post-surgery) and were performed by trained personnel. The patients were instructed to fast overnight and until all measurements were completed. They were also asked to void their bladders prior to measurements.

Nutritional assessment by the scored PG-SGA

A Norwegian version of the scored PG-SGA (15-004 v10.13.16) was used in the present study, and permission for use was given by the copyright holder of the instrument. The assessment was carried

out by trained registered clinical dietitians, and the scoring was controlled by one researcher (H.R). Patients were classified as well-nourished (PG-SGA A), moderate/suspected malnutrition (PG-SGA B) or severely malnourished (PG-SGA C). Patients classified as PG-SGA B is hereafter called "malnourished" for simplicity. Each section of the PG-SGA was scored according to the guidelines and a total PG-SGA score was calculated for each patient [22].

Total PG-SGA score in the range of 4-8 indicates need of an intervention supervised by a dietitian targeting the reported symptoms, and total PG-SGA score ≥ 9 indicates a critical need of a nutritional intervention[16]. The number of patients with scores below and above 4 and 9 was therefore identified. The PG-SGA includes registration of current body weight as well as body weight one month and six months prior to assessment. According to the guidelines [22], scoring of weight loss should preferably be based on weight history in the last month instead of the last six months. Weight loss was therefore calculated by subtracting the current weight from the one-month weight.

Muscle wasting was investigated by visual inspection and palpation of muscles with loss of bulk and tone in temporal areas, deltoids and quadriceps indicating muscle depletion. The triceps and midaxillary line at the level of the lower ribs were investigated with regard to depletion of subcutaneous fat. Ankles were examined for the presence of edema. The degree of muscle and fat depletion was evaluated and rated as 0 (normal) to 3 (severe deficit) [22]. All dietitians underwent training in the PG-SGA procedure, as traning has been shown to increase comprehensibility [23]

Body weight, height and body mass index (BMI)

Body weight was measured by the use of a non-slip Marsden M-420 Digital Portable Floor Scale (Marshden, Rotherham, South Yorkshire, United Kingdom) or a digital wireless measuring station for height and weight, Seca 285 (Seca, Birmingham, United Kingdom). Measurements were

performed with patients wearing light clothes and no shoes. Body weight was subtracted by 0.5 kg to adjust for clothing. Height (cm) was measured post-surgery by the use of either a mechanical height rod (Kern MSF- 200) or a digital wireless stadiometer (Seca 285). BMI was calculated based on recorded weight and height.

BIA

To obtain FFM estimates, a single frequency whole-body BIA, BIA 101 (SMT Medical, Würzburg, Germany) was used. BIA measures body composition indirectly by measuring the impedance (i.e the resistance and reactance) of a low-voltage current passing through the body. FFM is then calculated by the BIA software, which utilizes the impedance data in empiric regression equations incorporated in the software. We have previously validated BIA against DXA in a subgroup of CRC patients included in the CRC-NORDIET study[9].

BIA was performed under standardized conditions according to the manufacturer`s protocol. Measurements were performed by placing two skin electrodes on the right hand and two electrodes on the right foot of the patient when lying in supine position. The device applies current of 400 µA at a constant frequency of 50 kHz.

Determination of low FFMI and sarcopenia

FFM values from BIA were used to calculate FFMI (FFM (kg)/height (m^2). FFMI was grouped into "low FFMI" (<15 kg/m^2 for women and < 17 kg/m^2 for men) and "normal FFMI" (≥ 15 kg/m^2 for women and ≥ 17 kg/m^2 for men) according to cut-off values for FFMI proposed as part of the new diagnostic criteria for malnutrition by the ESPEN[14].

Patients with sarcopenia were identified by the use of the diagnostic criteria for age-related sarcopenia as proposed by EWGSOP[8]; presence of low muscle mass (criterion 1) and low muscle function (strength (criterion 2) or performance (criterion 3)). Criterion 1, and either 2 or 3 must be present to diagnose sarcopenia. In the current study, we defined low muscle mass as low FFMI. Low muscle strength was defined as low hand grip strength according to the cut-off values published by Fried[24]. Grip strength was assessed with a hand grip dynamometer (KERN & SOHN GmbH, Balingen, Germany) as described in the manufacturer's protocol. We defined low physical performance as low gait speed **and/or** low number of sit to stands. Gait speed was measured with a 6-min walk test according to the guidelines from the American Thoracic Society[25] and gait speed < 1 m/s was defined as "low"[26]. The sit-to-stand test was performed by instructing the participants to sit on a chair with arms folded across their chest, and then to stand up and sit down as frequently as possible within 30 s, keeping both arms folded across the chest. The number of full stands was counted, and stands < 18 and < 22, i.e. the lower cut-off values for the 95 % CI for a reference population of healthy Norwegian women and men in the age of 60 years, were defined as "low"[27].

Statistical analyses

Determination of sample size was performed in accordance to a guide for sample size for sensitivity and specificity analysis published by Bujang and Adnan in 2016[28]. According to this guide, the sensitivity for a screening study must be pre-determined to be at least 0.50[28]. We estimated the prevalence of low FFM in CRC patients to be 33 %, based on our previous findings[9] . Hence, a minimum sample size of 67 patients would be needed to achieve a minimum power of 80 % in order to detect a change in sensitivity from 0.50 to 0.80, based on a significance level of 0.05. Data were checked for normality using the Kolmogorov-Smirnov test and visual inspection of the

histograms. Normally distributed data were presented as means and standard deviations, and non-normally distributed data as medians and range (minimum-maximum). Pearson chi-square test for independence or Fisher`s exact test was performed to investigate differences in proportions between groups. Mann-Whitney test was used to test differences in medians for non-normally distributed continuous variables. Independent samples t-test was used to explore differences in means for normally distributed variables. P-values (2-sided) ≤ 0.05 were considered significant. Sensitivity and specificity were calculated to evaluate PG-SGA categories and scores as an assessment tool with FFMI as reference method. All statistical analyses were performed using SPSS (IBM SPSS Statistic 22).

Results

Subject characteristics

One hundred and six patients were included in the study and assessed with the PG-SGA tool. Of these, nine patients were excluded from the analyses due to lack of data needed to determine FFMI. Of the 97 eligible patients, 28 patients (29 %) were identified with low FFMI. Subject characteristics are shown for patients with low and normal FFMI, respectively **(Table 1).**

Fifty-nine percent of the patients had colon cancer, 35 % had rectum cancer and 7 % patients had rectosigmoid cancer. The median time from CRC surgery to assessments was 4 months (range 1-15).

Patients with normal and low FFMI were compared with regard to clinical characteristics. In general, there were few differences between the groups. There were no significant differences in gender, cancer localization, TNM stage or proportions receiving neoadjuvant or adjuvant treatment between the groups. Mean BMI was found to be significantly lower in patients with low FFMI, and the proportion of underweight patients was significantly higher among patients with low FFMI compared to patients with normal FFMI ($p<0.001$). Patients with low FFMI were significantly older than patients with normal FFMI ($p=0.027$). This finding was expected since loss of FFM is associated with increased age.

Concordance between PG-SGA category and low FFMI

Based on the PG-SGA global assessment, 67 (69.1 %) and 30 (30.9 %) of 97 eligible patients were categorized as well-nourished (PG-SGA A) and moderately malnourished (PG-SGA B), respectively **(Table 2)**. No patients were categorized as severely malnourished (PG-SGA C). The proportion of patients with low FFMI estimated by BIA was significantly higher among patients classified by PG-SGA as malnourished compared to well nourished (46.7 vs 20.9 %, p=0.015) **(Table 2)**. Furthermore, median PG-SGA total score was found to be significantly higher among patients with low FFMI compared to patients with normal FFMI (5 vs 3, p=0.036). However, the sensitivity, i.e. the proportion of patients with low FFMI classified as malnourished by PG-SGA categories, was calculated to only 50.0 %. The specificity, i.e. the proportion of patients with normal FFMI classified as well nourished by PG-SGA, was found to be 76.8 %. Using the PG-SGA numerical score, 60.7 % of the patients with low FFMI were identified with score > 4, i.e. the lowest cut-off for a nutritional intervention. These results indicate that the PG-SGA global rating does not have sufficient sensitivity and specificity to detect low FFMI, however, using the PG-SGA score increase the sensitivity.

The individual components of the PG-SGA in patients with low FFMI

In order to elucidate why a significant proportion of the patients with low FFMI (estimated by BIA) was evaluated as well nourished by the PG-SGA, we investigated the individual components of the assessment tool **(Table 3)**. Regarding all patients with low FFMI independently of PG-SGA categorization, 66.7 % of the patients reported weight loss within the last 6 months, whereas only 16.7 % reported weight loss the last month, indicating that the patients experienced their weight loss earlier in the trajectory of the disease, and that the majority of the patients were maintaining or gaining weight at the time of assessment. Furthermore, 60.7 % reported a normal food intake (i.e.

unchanged or increased) the last month and 28.6 % had symptoms affecting food intake. Furthermore, 53.6 % of the patients reported having reduced activity and function level **(Table 3)**. The sensitivity of PG-SGA examination to detect muscle mass depletion (i.e. visual inspection and palpation of muscles in temporal areas, deltoids and quadriceps) was calculated. Only 64.3 % of the patients assessed with low FFMI by BIA were evaluated as muscle depleted by PG-SGA. The specificity (i.e. proportion of patients with normal FFMI correctly classified with "no deficit") was 78 %. Taken together, these findings suggest that when investigating the various components of the PG-SGA in patients with low FFMI, the majority of these patients were weight stable at the time of assessments, accompanied by a normal food intake (i.e. stable or increased) and no symptoms affecting food intake. Furthermore, the results indicate that the physical examination does not have sufficient sensitivity and specificity to detect low FFMI.

Comparison of well nourished (PG-SGA A) and malnourished (PG-SGA B) patients among patients with low FFMI

To further elucidate why a significant proportion of the patients with low FFMI was evaluated as well nourished by the PG-SGA, we selected the patients with low FFMI and compared well nourished and malnourished patients with regard to the individual components of the PG-SGA. Patients categorized as PG-SGA A had significantly lower median total PG-SGA score compared to patients categorized as PG-SGA B (3 vs 6, $p<0.001$) **(Table 3).** This finding was expected since PG-SGA category is related to the PG-SGA score. Furthermore, none of the patients with PG-SGA A reported a reduced food intake, whereas the majority of the patients categorized as PG-SGA B reported reduced food intake ($p<0.001$). We found no differences between the groups with regard to weight loss the last 6 months, weight loss the last month, presence of anorexia, presence of nutritional impact symptoms or physical function and activity. Among patients identified with

"mild to moderate deficit" by the PG-SGA physical examination, a significantly lower proportion of the patients were classified as PG-SGA A compared to PG-SGA B (27.8 vs 72.2 %, p=0.004). As PG-SGA category was set mainly based on the three components weight loss the last month, reduced food intake the last month and muscle mass depletion, these findings were quite expected, except for weight loss that did not differ between the groups. The groups did not differ with regard to BMI.

BMI according to physical examination status among patients with low FFMI

In order to investigate why a high proportion (i.e. 36 %) of the patients with low FFMI were not detected by the physical exam in the PG-SGA, we investigated if there was a difference in BMI between patients detected and patients not detected by the PG-SGA within patients with low FFMI **(Table 4)**. Mean BMI was significantly higher in patients not detected by the PG-SGA (24.6 vs 21.5, p=0.006). Furthermore, we found a significantly higher proportion of patients with overweight among these patients compared to those that were found to be muscle depleted (66.7 vs 33.3 %, p=0.025). A possible explanation for this finding may be that high BMI camouflages low muscle mass in patients with low FFMI.

Concordance between PG-SGA category and sarcopenia

In the current study, we also investigated the ability of PG-SGA to detect patients with sarcopenia. Of 97 patients included in this study, 95 patients were eligible for the diagnosis of sarcopenia, due to missing data for two patients. About twenty-two % (n= 21) of the patients were diagnosed with sarcopenia **(Table 5)**. The proportion of patients with sarcopenia did not significantly differ between patients classified by PG-SGA as well nourished and malnourished, respectively. PG-SGA

290 classified 42.9 % of the patients with sarcopenia as malnourished. With regard to the PG-SGA
291 numerical score, we found no difference in median total score when we compared sarcopenic
292 patients with non-sarcopenic patients. Furthermore, 61.9 % of the patients with sarcopenia were
293 identified with total PG-SGA score > 4, i.e. the lowest cut-off for a nutritional intervention. These
294 results were similar to the results from the analysis of patients with low and normal FFMI. The
295 sensitivity of PG-SGA to detect patients with sarcopenia was low, however, we observed increased
296 sensitivity by the use of the PG-SGA scoring.
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Discussion

In this study we investigated the concordance between PG-SGA category and low FFM among patients with non-metastatic colorectal cancer. About twenty-nine percent of the patients had low FFMI according to the cut-off values proposed by ESPEN. The PG-SGA categorization classified only 50 % of these patients as malnourished (PG-SGA B). Use of the PG-SGA total scores improved sensitivity (61 %). However, only 64 % of the patients with low FFMI assessed by BIA were evaluated as muscle depleted in the physical examination in the PG-SGA. Our results indicate that the PG-SGA does not have sufficient sensitivity to detect low FFM.

Few previous studies have examined the concordance between PG-SGA and low FFM, and to the best of our knowledge, no studies are performed in non-metastatic patients with CRC. The clinical implications of muscle depletion and sarcopenia is mainly studied in patients with metastatic cancer, however, the high percentage of patients with low FFMI in our population suggests that it may have a broader relevance[9]. Vigano and coworkers examined associations between PG-SGA scores and features of cancer cachexia in a mixed population of patients with advanced lung and gastrointestinal cancers. Although they observed that the PG-SGA score was able to predict several features of cancer cachexia, including decrease of muscle strength and loss of fat mass, PG-SGA was not able to detect differences in lean body mass[29], in agreement with our results. In patients with gynecologic cancers, FFM was not found to differ between PG-SGA categories[30]. In the study performed by Guerra and colleges, FFMI was significantly lower among malnourished patients according to the PG-SGA in a sample consisting of 455 inpatients with a broad spectrum of diagnoses[31].

Our study demonstrated poor specificity and sensitivity for the PG-SGA categories to detect low FFMI. Only half of the patients with low FFMI were classified as malnourished. Consequently, half

of the patients were missed by the use of these categories. The literature on sensitivity and specificity of PG-SGA to detect low FFM or muscle mass is scarce, however, our findings are in line with the results reported by Elkan et al, who observed that SGA, the earlier version of PG-SGA, showed poor sensitivity (46 %) in detection of low FFMI in patients with rheumatoid arthritis assessed with DXA[32]. Similar to our data, they observed a higher specificity than sensitivity for SGA.

In order to investigate why a significant proportion of the patients with low FFMI was categorized as well nourished, we investigated the individual components of the PG-SGA. We observed that the majority of the patients with low FFMI were anabolic at the time of assessments, reporting a normal food intake and no symptoms affecting food intake. Since PG-SGA is developed to detect patients with malnutrition or patients at risk of malnutrition with main focus on recent weight loss, nutritional impact symptoms and reduction in food intake, the implication of this is that patients with prior muscle mass depletion, but a stable or increasing body weight may be categorized as PG-SGA A. The majority of the patients had completed their cancer treatment, and hence were more likely to be anabolic for that reason.

Moreover, when we analyzed differences between those who were categorized as well nourished (PG-SGA A) and those who were categorized as malnourished (PG-SGA B) among patients with low FFMI, we observed differences with regard to 1) food intake and 2) proportions detected by the physical examination. A significantly higher proportion of the patients categorized as PG-SGA B reported reduced food intake, and a significantly higher proportion of these patients were detected with muscle mass depletion, compared to the patients categorized as PG-SGA A. Since reduced food intake and muscle mass depletion constitute two of the three components that were

emphasized in the PG-SGA categorization, it provides a plausible explanation for why these patients were categorized as PG-SGA B.

We observed that use of the PG-SGA total score improved sensitivity compared to PG-SGA categories, suggesting that the scoring is better at capturing patients with low FFMI. It should, however, be mentioned that the physical examination only in minor extent contributes to the total PG-SGA score, with the maximum score of 3 points indicating severe adipose and muscle deficit. Hence, patients with low FFMI may hypothetically have a low total score, i.e. a total score below the lowest cut-off for an intervention.

Although a significantly higher proportion of the patients categorized as malnourished by PG-SGA were detected as muscle depleted by the physical examination (i.e. visual inspection and palpation of muscles in temporal areas, deltoids and quadriceps) compared to well nourished patients, the sensitivity and specificity was found to be low. In order to elucidate why many patients were missed by the physical examination in the PG-SGA, we hypothesized that muscle mass depletion could be more difficult to detect in patients with high BMI. In the current study, BMI was found to be significantly higher in those patients who were not identified as muscle depleted (as indicated by loss of bulk and tone in selected muscles examined by visual inspection and palpation) by the PG-SGA physical examination. Furthermore, we observed a higher proportion of overweight patients among these patients compared to those who were captured as depleted. Based on these findings, we conclude that PG-SGA is not sensitive enough to detect muscle mass depletion, particularly in overweight and obese patients. Studies utilizing imaging analyses have confirmed that excessive muscle wasting can be obscured in patients with excessive fat mass[5, 33], with CT images demonstrating equal low total muscle amounts in obese and underweight patients. With a growing prevalence of overweight and obesity in several patient populations, including cancer populations, it is important to be aware of this limitation in the application of PG-SGA.

Monitoring weight loss, nutritional impact symptoms and reduction in food intake are important aspects of the nutritional assessments of cancer patients. However, since an ongoing loss of muscle mass may be masked by a stable or increased body weight, particularly in overweight and obese patients[6], assessing and monitoring body weight and food intake is not sufficient. Increase of body weight in terms of body fat rather than FFM may lead to sarcopenic obesity, a syndrome that entails the combined health risks of both sarcopenia and obesity. This highlights the importance of including appropriate tools to identify low FFM as part of the nutritional evaluation. As PG-SGA seems not be sensitive enough to detect muscle mass depletion, we suggest that the tool should be supplemented by muscle mass assessments by BIA or other methods.

In the current study we chose to use the FFMI cut-off values recently proposed by ESPEN, to determine low FFM. Since these cut-offs were published in 2015, validation studies have confirmed the prognostic impact of the malnutrition criteria on clinical outcomes[34] and survival [35].

Our estimates of FFM were generated from BIA. Compared to imaging techniques such as DXA, CT and magnetic resonance imaging (MRI) that measure lean body mass and muscle mass with high precision, BIA measures these compartments indirectly by measuring the impedance of the current applied to the body. The impedance data (i.e. resistance and reactance) is utilized in empiric equations to calculate FFM. One of the main limitations with BIA is that these empirical equations are developed in healthy euvolemic adults with a normal body composition, and may therefore provide less reliable estimates in individuals with disturbances in fluids and alterations in body composition, such as cancer patients. There are currently few studies that have investigated the validity of BIA in estimation of FFM in cancer patients. However, the BIA used in the current study was previously validated against DXA in a subgroup of CRC patients included in the CRC-

NORDIET study, and use of the equation incorporated in the BIA software for calculation of FFM showed good agreement with DXA estimates of FFM[9].

Similar to the results from the analysis of patients with low FFMI, we observed low sensitivity of the PG-SGA categories in detection of patients diagnosed with sarcopenia, and furthermore, increased sensitivity by the use of the PG-SGA scores. Although PG-SGA is primarily developed to identify patients with malnutrition and increased risk of malnutrition and not sarcopenia, our study demonstrates that a high proportion of patients diagnosed with sarcopenia who need to be further evaluated for nutritional therapy, are considered "no need for nutritional intervention" by the PG-SGA.

Patients identified with low FFMI who have not fully developed sarcopenia, is particularly interesting as target for nutritional intervention. According to the European Working Group on Sarcopenia in Older People (EWGSOP), low muscle mass without the presence of reduced strength or physical performance, corresponds to the stage "presarcopenia". Identifying these patients and selecting appropriate treatment, may prevent further loss of muscle mass and inhibit progressive functional impairment.

Although PG-SGA does not perform sufficient sensitivity to detect low FFM, it covers several important aspects of malnutrition and sarcopenia. Hence, PG-SGA may be useful to characterize nutritional problems in patients where low FFM has been documented by the use of BIA or other methodology. It rapidly provides a detailed overview of the patient`s nutritional status as the assessment takes only approximately 5 minutes. Furthermore, the PG-SGA scoring may be useful in the follow up of these patients, by using the scores to monitor changes during and after nutritional therapy. In addition, PG-SGA score has been shown to predict clinical outcomes[29], quality of life[36] and survival[29, 37] in cancer patients.

To our knowledge, this is the first study that has evaluated the concordance between the PG-SGA and low FFM in colorectal cancer patients. Since PG-SGA is widely used and accepted as an assessment tool in oncology it is important to be aware of its strengths and limitations.

Conclusion

In the present study, we found low concordance between the nutritional assessment tool PG-SGA and low FFMI. PG-SGA classified only half of the patients with low FFMI as malnourished/suspected malnourished Use of the total PG-SGA score increased the sensitivity. However, only 64.3 % of the patients with low FFMI were detected by the physical examination which is part of the PG-SGA. In clinical practice, PG-SGA scores should be supplemented by muscle mass assessments by BIA or other methods in order to more accurately identify low FFM in this patient group.

List of abbreviations

BIA: Bioelectrical impedance analysis; BMI: Body mass index; CRC: Colorectal cancer; CT: Computed tomography; DXA: Dual energy x-ray absorptiometry; ESPEN: European Society for Clinical Nutrition and Metabolism; EWGSOP: European Working Group on Sarcopenia in Older People; FFM: Fat-free mass; FFMI: Fat-free mass index; ICD: International classification of diseases and related health problems; MRI: Magnetic resonance imaging; PG-SGA: Patient-generated subjective global assessment; RCT: Randomized clinical trial; TNM: Tumor node metastasis.

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Statement of authorship

HR had the main responsibility for data analysis and writing the manuscript. HR, CH, SKB, AROFV, HBH, ASK, KR, IP, SS and RB contributed to the conception and the design of the study, analysis and interpretation of the data and drafting of the manuscript. HR, CH, SKB, AROFV, HBH, ASK, KR and IP contributed to acquisition of data. All authors contributed to the writing and final approval of the manuscript.

Conflict of interest statement

R.B is a shareholder in the company Vitas AS. All other authors declare that they have no competing interests.

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References

1. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36:11-48.
2. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15:2920-6.
3. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107:931-6.
4. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31:1539-47.
5. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9:629-35.
6. Prado CM, Siervo M, Mire E, Heymsfield SB, Stephan BC, Broyles S, et al. A population-based approach to define body-composition phenotypes. Am J Clin Nutr. 2014;99:1369-77.
7. Thibault R, Pichard C. The evaluation of body composition: a useful tool for clinical practice. Ann Nutr Metab. 2012;60:6-16.
8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412-23.
9. Raeder H, Kvaerner AS, Henriksen C, Florholmen G, Henriksen HB, Bohn SK, et al. Validity of bioelectrical impedance analysis in estimation of fat-free mass in colorectal cancer patients. Clin Nutr. 2017.
10. Black D, Mackay C, Ramsay G, Hamoodi Z, Nanthakumaran S, Park KG, et al. Prognostic Value of Computed Tomography: Measured Parameters of Body Composition in Primary Operable Gastrointestinal Cancers. Ann Surg Oncol. 2017.
11. Baldwin C, Spiro A, Ahern R, Emery PW. Oral nutritional interventions in malnourished patients with cancer: a systematic review and meta-analysis. J Natl Cancer Inst. 2012;104:371-85.
12. Bourdel-Marchasson I, Blanc-Bisson C, Doussau A, Germain C, Blanc JF, Dauba J, et al. Nutritional advice in older patients at risk of malnutrition during treatment for chemotherapy: a two-year randomized controlled trial. PLoS One. 2014;9:e108687.
13. Ravasco P, Monteiro-Grillo I, Camilo M. Individualized nutrition intervention is of major benefit to colorectal cancer patients: long-term follow-up of a randomized controlled trial of nutritional therapy. Am J Clin Nutr. 2012;96:1346-53.
14. Cederholm T, Bosaeus I, Barazzoni R, Bauer J, Van Gossum A, Klek S, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. Clin Nutr. 2015;34:335-40.
15. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN J Parenter Enteral Nutr. 2014;38:940-53.
16. Patient-Generated Subjective Global Assessment [23.05.2017]. Available from: http://pt-global.org/.
17. Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the Patient-Generated Subjective Global Assessment. Current opinion in clinical nutrition and metabolic care. 2017;20:322-9.

18. Sealy MJ, Nijholt W, Stuiver MM, van der Berg MM, Roodenburg JL, van der Schans CP, et al. Content validity across methods of malnutrition assessment in patients with cancer is limited. Journal of clinical epidemiology. 2016;76:125-36.
19. Thompson KL, Elliott L, Fuchs-Tarlovsky V, Levin RM, Voss AC, Piemonte T. Oncology Evidence-Based Nutrition Practice Guideline for Adults. J Acad Nutr Diet. 2017;117:297-310.e47.
20. AJCC Cancer Staging [23 May 2017]. Available from: https://cancerstaging.org.
21. Henriksen HB, Raeder H, Bohn SK, Paur I, Kvaerner AS, Billington SA, et al. The Norwegian dietary guidelines and colorectal cancer survival (CRC-NORDIET) study: a food-based multicentre randomized controlled trial. BMC Cancer. 2017;17:83.
22. The Clinical Guide to Oncology Nutrition. In: C.G. MPDaP, editor. Chicago, Illinois: The American Dietetic Association; 2000.
23. Sealy MJ, Ottery FD, van der Schans CP, Roodenburg JLN, Jager-Wittenaar H. Evaluation of change in dietitians' perceived comprehensibility and difficulty of the Patient-Generated Subjective Global Assessment (PG-SGA) after a single training in the use of the instrument. Journal of human nutrition and dietetics : the official journal of the British Dietetic Association. 2017.
24. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56.
25. ATS statement: guidelines for the six-minute walk test. AmJRespirCrit Care Med. 2002;166:111-7.
26. Cesari M, Kritchevsky SB, Newman AB, Simonsick EM, Harris TB, Penninx BW, et al. Added value of physical performance measures in predicting adverse health-related events: results from the Health, Aging And Body Composition Study. J Am Geriatr Soc. 2009;57:251-9.
27. Tveter AT, Dagfinrud H, Moseng T, Holm I. Health-related physical fitness measures: reference values and reference equations for use in clinical practice. Arch Phys Med Rehabil. 2014;95:1366-73.
28. Bujang MA, Adnan TH. Requirements for Minimum Sample Size for Sensitivity and Specificity Analysis. J Clin Diagn Res. 2016;10:Ye01-ye6.
29. Vigano AL, di Tomasso J, Kilgour RD, Trutschnigg B, Lucar E, Morais JA, et al. The abridged patient-generated subjective global assessment is a useful tool for early detection and characterization of cancer cachexia. J Acad Nutr Diet. 2014;114:1088-98.
30. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. Am J Clin Nutr. 2008;87:1678-85.
31. Guerra RS, Fonseca I, Sousa AS, Jesus A, Pichel F, Amaral TF. ESPEN diagnostic criteria for malnutrition - A validation study in hospitalized patients. Clin Nutr. 2016.
32. Elkan AC, Engvall IL, Tengstrand B, Cederholm T, Hafstrom I. Malnutrition in women with rheumatoid arthritis is not revealed by clinical anthropometrical measurements or nutritional evaluation tools. Eur J Clin Nutr. 2008;62:1239-47.
33. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15:6973-9.
34. Sanz-Paris A, Gomez-Candela C, Martin-Palmero A, Garcia-Almeida JM, Burgos-Pelaez R, Matia-Martin P, et al. Application of the new ESPEN definition of malnutrition in geriatric diabetic patients during hospitalization: A multicentric study. Clin Nutr. 2016;35:1564-7.
35. Rondel AL, Langius JA, de van der Schueren MA, Kruizenga HM. The new ESPEN diagnostic criteria for malnutrition predict overall survival in hospitalised patients. Clin Nutr. 2016.

36. Isenring E, Bauer J, Capra S. The scored Patient-generated Subjective Global Assessment (PG-SGA) and its association with quality of life in ambulatory patients receiving radiotherapy. Eur J Clin Nutr. 2003;57:305-9.
37. Persson C, Sjoden PO, Glimelius B. The Swedish version of the patient-generated subjective global assessment of nutritional status: gastrointestinal vs urological cancers. Clin Nutr. 1999;18:71-7.

573 **Table1.** Characteristics of the population

	N	Normal FFMI (n=69)	Low FFMI* (n=28)	p[a]
Age				
Mean (years) (std)	97	64.9 (8.2)	68.1 (5.3)	0.027
Gender, n (%)				0.058
Women	46	28 (60.9)	18 (39.1)	
Men	51	41 (80.4)	10 (19.6)	
Cancer localization, n (%)				0.264
Colon cancer	54	36 (66.7)	18 (33.3)	
Rectosigmoid cancer	6	6 (100)	0 (0)	
Rectum cancer	32	23 (71.9)	9 (28.1)	
TNM stage, n (%)				0.199
Stage 1	10	8 (80.0)	2 (20.0)	
Stage 2	46	36 (78.3)	10 (21.7)	
Stage 3	33	20 (60.6)	13 (39.4)	
Neoadjuvant treatment, n (%)				0.531
No	81	59 (72.8)	22 (27.2)	
Yes	14	9 (64.3)	5 (35.7)	
Adjuvant treatment, n (%)				
None	74	55 (74.3)	19 (25.7)	0.512
Ongoing	16	10 (62.5)	6 (37.5)	
Completed	5	3 (60.0)	2 (40.0)	
BMI				
Mean (kg/m^2) (std)	97	27.2 (4.3)	22.6 (3.0)	<0.001
BMI categories, n (%)				<0.001
Underweight (BMI < 20)	8	1 (12.5)	7 (87.5)	
Normal range (BMI 20-24,9)	32	20 (62.5)	12 (37.5)	
Overweight (BMI 25-29,9)	43	34 (79.1)	9 (20.9)	
Obese (BMI >30)	14	14 (100)	0 (0)	

574 Abbreviations: FFMI, Fat-free mass index; TNM, Tumor node metastasis; BMI, Body mass index
575 [a]Independent samples t-test, chi-square test for independence or Fisher`s exact test, significance level $p \leq 0.05$
576 *Low FFMI defined as FFMI < 17 kg/m^2 for men and < 15 kg/m^2 for women[14].
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580 **Table 2.** Global rating and PG-SGA scoring according to normal and low FFMI

	N	Normal FFMI (n=69)	Low FFMI* (n=28)	P[a]
Global rating, n (%)				0.015
Well nourished (A)	67	53 (79.1)	14 (20.9)	
Moderately malnourished (B)	30	16 (53.3)	14 (46.7)	
Severely malnourished (C)	0	0 (0)	0 (0)	
Total PG-SGA score				0.146
PG-SGA score < 4, n (%)	53	42 (79.2)	11 (20.8)	
PG-SGA score 4-8, n (%)	35	22 (62.9)	13 (37.1)	
PG-SGA score ≥ 9, (%)	9	5 (55.6)	4 (44.4)	
Median (range)	97	3 (1-17)	5 (1-20)	0.036

581 Abbreviations: PG-SGA, Patient-generated subjective global assessment; FFMI, Fat-free mass index
582 [a]Mann-Whitney test, chi-square test for independence or Fisher`s exact test, significance level $p \leq 0.05$
583 *Low FFMI defined as FFMI < 17 kg/m^2 for men and < 15 kg/m^2 for women[14].
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586 **Table 3.** Comparison of PG-SGA A and PG-SGA B among patients with low FFM with regard to the
587 various components of the PG-SGA and BMI

		Patients with low FFMI*		
	N	**Patients with PG-SGA A (n=14)**	**Patients with PG-SGA B (n=14)**	**P[a]**
PG-SGA score, median (range)	28	3 (1-8)	6 (3-20)	<0.001
Weight loss last 6 months, n (%)				0.420
Yes	18	8 (44.4)	10 (55.6)	
No	9	6 (66.7)	3 (33.3)	
Weight loss last month, n (%)				0.596
Yes	4	1 (25.0)	3 (75.0)	
No	20	10 (50.0)	10 (50.0)	
Presence of anorexia, n (%)				0.481
Yes	2	0 (0)	2 (100)	
No	26	14 (53.8)	12 (46.2)	
Food intake, n (%)				<0.001
Normal	17	14 (82.4)	3 (17.6)	
Reduced	11	0 (0)	11 (100)	
Symptoms, n (%)				0.209
Yes	8	2 (25.0)	6 (75.0)	
No	20	12 (60.0)	8 (40.0)	
Physical function and activity, n (%)				0.058
Normal	13	9 (69.2)	4 (30.8)	
Reduced	15	5 (33.3)	10 (66.7)	
Physical examination, n (%)				0.004
No deficit	10	9 (90.0)	1 (10.0)	
Mild to moderate deficit	18	5 (27.8)	13 (72.2)	
Severe depletion	0	0 (0)	0 (0)	
BMI, mean (std)	28	23.4 (3.0)	21.8 (3.0)	0.184
BMI categories, n (%)				0.623
Underweight (BMI < 20)	7	3 (42.9)	4 (57.1)	
Normal range (BMI 20-24,9)	12	5 (41.7)	7 (58.3)	
Overweight (BMI 25-29,9)	9	6 (66.7)	3 (33.3)	
Obese (BMI >30)	0	0 (0)	0 (0)	

588 Abbreviations: FFMI, Fat-free mass index; PG-SGA: Patient-generated subjective global assessment; BMI: Body mass index.
589 [a]Mann-Whitney test (PG-SGA score), independent samples t-test (BMI), chi-square test for independence or Fisher`s exact test
590 significance level $p \leq 0.05$
591 *Low FFMI defined as FFMI < 17 kg/m^2 for men and < 15 kg/m^2 for women[14].
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Table 4. BMI according to physical examination status in the PG-SGA among patients with low FFMI.

		Low FFMI*		
	N	**No deficit (n=10) by the PG-SGA**	**Mild to moderate deficit (n=18) by the PG-SGA**	**p[a]**
BMI, mean (std)	28	24.6 (2.7)	21.5 (2.7)	0.006
BMI categories, n (%)				0.025
BMI < 20	7	0 (0)	7 (100)	
BMI 20-24,9	12	4 (33.3)	8 (66.7)	
BMI 25-29,9	9	6 (66.7))	3 (33.3)	
BMI >30	0	0 (0)	0 (0)	

Abbreviations: FFMI, Fat-free mass index; PG-SGA: Patient-generated subjective global assessment; BMI, Body mass index.
[a]Independent-samples t-test, chi-square test for independence or Fisher`s exact test, significance level $p \leq 0.05$
*Low FFMI defined as FFMI <17 kg/m^2 for men and < 15 kg/m^2 for women[14].

Table 5. Global rating and PG-SGA scoring according to sarcopenia and no sarcopenia

	N	**No sarcopenia (n=74)**	**Sarcopenia* (n=21)**	**p[a]**
Global rating, n (%)				0.127
Well nourished (A)	67	55 (82.1)	12 (17.9)	
Moderately malnourished (B)	28	19 (67.9)	9 (32.1)	
Severely malnourished (C)	0	0 (0)	0 (0)	
Total PG-SGA score				0.162
PG-SGA score < 4, n (%)	52	44 (84.6)	8 (15.4)	
PG-SGA score 4-8, n (%)	34	23 (67.6)	11 (32.4)	
PG-SGA score ≥ 9, n (%)	9	7 (77.8)	2 (22.2)	
Median (range)	95	3 (1-17)	4 (1-20)	0.092

Abbreviations: PG-SGA: Patient-generated subjective global assessment.
[a]Mann-Whitney test, chi-square test for independence or Fisher`s exact test, significance level $p \leq 0.05$
*Sarcopenia was diagnosed based on EWGSOP diagnostic criteria[8].