



Original article

Validity of bioelectrical impedance analysis in estimation of fat-free mass in colorectal cancer patients



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SUMMARY

Background & aims: Bioelectrical impedance analysis (BIA) is an accessible and cheap method to measure fat-free mass (FFM). However, BIA estimates are subject to uncertainty in patient populations with altered body composition and hydration. The aim of the current study was to validate a whole-body and a segmental BIA device against dual-energy X-ray absorptiometry (DXA) in colorectal cancer (CRC) patients, and to investigate the ability of different empiric equations for BIA to predict DXA FFM (FFM_{DXA}). **Methods:** Forty-three non-metastatic CRC patients (aged 50–80 years) were enrolled in this study. Whole-body and segmental BIA FFM estimates (FFM_{whole-bodyBIA}, FFM_{segmentalBIA}) were calculated using 14 empiric equations, including the equations from the manufacturers, before comparison to FFM_{DXA} estimates.

Results: Strong linear relationships were observed between FFM_{BIA} and FFM_{DXA} estimates for all equations ($R^2 = 0.94$ – 0.98 for both devices). However, there were large discrepancies in FFM estimates depending on the equations used with mean differences in the ranges -6.5 – 6.8 kg and -11.0 – 3.4 kg for whole-body and segmental BIA, respectively. For whole-body BIA, 77% of BIA derived FFM estimates were significantly different from FFM_{DXA}, whereas for segmental BIA, 85% were significantly different. For whole-body BIA, the Schols* equation gave the highest agreement with FFM_{DXA} with mean difference \pm SD of -0.16 ± 1.94 kg ($p = 0.582$). The manufacturer's equation gave a small overestimation of FFM with 1.46 ± 2.16 kg ($p < 0.001$) with a tendency towards proportional bias ($r = 0.28$, $p = 0.066$). For segmental BIA, the Heitmann* equation gave the highest agreement with FFM_{DXA} (0.17 ± 1.83 kg ($p = 0.546$)). Using the manufacturer's equation, no difference in FFM estimates was observed (-0.34 ± 2.06 kg ($p = 0.292$)), however, a clear proportional bias was detected ($r = 0.69$, $p < 0.001$). Both devices demonstrated acceptable ability to detect low FFM compared to DXA using the optimal equation.

Conclusion: In a population of non-metastatic CRC patients, mostly consisting of Caucasian adults and with a wide range of body composition measures, both the whole-body BIA and segmental BIA device provide FFM estimates that are comparable to FFM_{DXA} on a group level when the appropriate equations are applied. At the individual level (i.e. in clinical practice) BIA may be a valuable tool to identify patients with low FFM as part of a malnutrition diagnosis.

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1. Introduction

Rapid loss of fat-free mass (FFM) and skeletal muscle, the major constituent of FFM, has been shown to be an independent predictor of severe toxicity following cancer treatment [1], and to negatively affect efficacy of treatment [2] and survival [3,4]. Depletion of FFM may be masked by a stable body weight or weight gain [5]. In

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cancer patients experiencing treatment-related weight loss, weight gain during or after recovery may be characterized by an increase in fat mass (FM) rather than FFM [6]. Easy available instruments that can be used in the clinic to monitor loss of FFM are therefore needed.

Dual-energy X-ray absorptiometry (DXA) is an instrument that allows for precise whole-body and regional determination of FFM by a low X-ray exposure [7]. Therefore DXA is considered one of the reference methods for measurement of body composition. Access to DXA may, however be limited in clinical practice. Bioelectrical impedance analysis (BIA) is a more easily available method for body composition analysis as it is relatively cheap, provides rapid results and requires minimal operator training. BIA may therefore be a useful tool in clinical practice to identify patients with low FFM as a part of the diagnostic criteria for malnutrition [8]. **BIA estimates body composition indirectly.** A low-voltage current is passed through the body, whereby impedance (i.e. tissue resistance and reactance) is measured. **Impedance data is then utilized in empiric equations to estimate body composition.** Such equations have been developed for different populations and incorporate impedance data with variables such as height, weight, age and gender to calculate FFM [9].

There are several types of BIA devices commercially available. Single-frequency BIA measures impedance at one frequency, usually 50 kHz, whereas multi-frequency BIA measures impedance at several frequencies. Moreover, BIA devices can be based on a whole-body or a segmental approach. With the whole-body approach the body is viewed as a cylindrical conductor with a uniform cross-sectional area. This model is demonstrated to be valid in healthy individuals with BMI within the range 16.0–34 kg/m², provided that hydration is normal and the BIA equation used is applicable to the population studied [10]. However, since it does not take into account the differences in impedance represented by the various body segments, e.g. the trunk consisting of ~50% of the body weight and only contributing to 5–12% of the whole-body resistance, it has limited validity in populations with abnormal body composition [11]. **Segmental BIA has more recently been developed to overcome the inconsistencies between the resistance and body mass of the trunk.** Additional research is however required to determine whether this model is better adapted at measuring body composition under these circumstances.

There are a large number of equations available in the literature for estimation of FFM. These equations have mostly been developed in healthy euvoletic adults with a normal body composition. Therefore, the equations may yield less reliable estimates in individuals where these conditions are not met [10]. Patients with colorectal cancer (CRC) are particularly interesting as they are vulnerable to fluid imbalance and alterations in body composition post-operatively and during chemotherapy and/or radiotherapy. CRC patients often experience symptoms such as anorexia, vomiting, diarrhoea and obstipation as a result of treatment. This may adversely affect weight status as well as influence water and electrolyte balance. Furthermore, obesity and abdominal obesity are main risk factors for CRC [12] and thus, many CRC patients will have excess body weight at the time of diagnosis.

Few studies have tested the ability of BIA to estimate FFM in cancer patients using DXA as a reference method, none of which has simultaneously compared two different BIA devices with DXA. Hence, the aim of this study was to validate two different BIA devices, a whole body BIA and a segmental BIA device, against DXA in CRC patients, and to investigate the ability of 14 different empiric equations, including the equations from the manufacturers, to predict DXA FFM (FFM_{DXA}).

2. Methods

2.1. Patients

All patients in this validation study were recruited from an ongoing randomized clinical trial, the Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study. The CRC-NORDIET study is 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 at Oslo University Hospital and Akershus University Hospital. The study is registered on the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010).

Eligible patients were women and men aged 50–80, with a confirmed CRC (ICD-10 18-20), and staged I-III according to the TNM staging system [13] when they entered the CRC-NORDIET study. Patients with pacemakers were excluded since current from the BIA device could possibly alter the pacemaker activity. To increase generalizability, we chose to include patients with abnormalities in body shape (for example amputations), obesity, orthopedic prosthesis/implants, chronic diseases and fluid disturbances (presence of oedema). All patients had undergone surgery for CRC within the last 4 years.

2.2. Measurements

All measurements took place between December 1st 2015 and February 1st 2016 at the Department of Nutrition, University of Oslo. The patients were instructed to fast overnight and until all measurements were completed. They were also encouraged to void their bladders before measurements. For each patient, all measurements were conducted in the morning in a sequential manner within a timeframe of 2 h.

2.3. BIA

BIA measures body composition indirectly by measuring the impedance of a low-voltage current passing through the body. The impedance consists of two components, resistance (R), the opposition of an ionic solution in both intra- and extracellular spaces and reactance (Xc), representing the capacitance from cell membranes [9]. Estimates of various body compartments, including FFM, are calculated from R or R and Xc values, based on equations, either incorporated in the software or reported in the literature.

Two different BIA devices were used, one whole-body single-frequency (50 KHz) BIA, BIA-101 (SMT Medical, Würzburg, Germany), hereby referred to as whole-body BIA, and a **multi-frequency segmental BIA**, Seca mBCA515 (Seca, Birmingham, United Kingdom), hereby referred to as segmental BIA. For both instruments, BIA was performed under standardized conditions according to the manufacturer's protocol. All measurements were performed with light clothing and with metal objects (e.g. jewelry, keys) being removed.

The whole-body BIA measurements were performed by placing two adhesive single-use skin electrodes (purchased from Maltron International Ltd, UK) on the right hand and foot, respectively, on the patient when lying in supine position. The device applies a current of 400 μ A at constant frequency of 50 kHz.

The segmental BIA measurements were performed on patients standing barefoot on the instrument platform. The device has an integrated scale and uses four pair of electrodes of stainless steel that are positioned at each hand and foot, through which the

current enters the limbs. The device enables segmental impedance measurements of the right arm, left arm, trunk, right leg, left leg and the right and left body side. A current of 100 μ A is applied at frequencies of 1, 1.5, 2, 3, 5, 7.5, 10, 15, 20, 30, 50, 75, 100, 200, 300, 500, 750 and 1000 kHz. In the current study, measurements at 50 kHz were utilized.

For estimation of FFM, a selection of equations was used (Tables 3A and B). These included the equations incorporated into the manufacturers software, **The Kyle (“Geneva”) equation** [14] recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) and equations previously tested in cancer populations, see Appendix 1 [14–23]. Of the 14 equations used, 11 were originally developed in healthy volunteers [14–18,20–22,24]. The equations varied with regards to the predictor variables included (e.g. R, Xc, weight, height, age and gender) and whether they were gender-specific (indicated by “**”) or not in addition to the empirically obtained parameter estimates (intercept and regression coefficients).

2.4. DXA

Total body DXA scans were performed using GE Lunar iDXA enCORE version 16 (GE Healthcare). All scans were performed using automated mode by a trained GE Lunar iDXA operator. Patients were instructed to wear a hospital gown and all jewelry was removed. Regions of interest were automatically detected by the software and verified by the operator according to instructions provided by the Lunar enCORE operator manual.

2.5. Body weight, height, body mass index (BMI) and fat-free mass index (FFMI)

Body weight was measured with light clothes and without shoes by the use of the incorporated scale in the body composition analyzer Seca mBCA515. This measured body weight was applied in both BIA devices. DXA assessment was based on the weight recorded by the DXA software according to standard procedure in the manufacturer’s manual. Height was measured by the use of a digital wireless stadiometer, Seca 285 (Seca, Birmingham, United Kingdom), and recorded in cm.

BMI (kg/m^2) was calculated based on the recorded weight and height. FFM adjusted for height, FFMI (kg/m^2), was calculated both for BIA (FFM_{BIA}) and DXA (FFM_{DXA}). To detect low FFMI, the following cut-off values were used: 15 kg/m^2 for women and 17 kg/m^2 for men [8].

2.6. Nutritional status

Nutritional status was assessed with the Patient-Generated Subjective Global Assessment (PG-SGA). This is a nutritional assessment tool, specifically designed to identify malnutrition or risk of malnutrition in cancer patients [25]. The assessment was carried out by trained registered clinical dietitians, and the scoring was controlled by one researcher (H.R). Patients were classified as either well-nourished, moderately malnourished or severely malnourished [26].

The PG-SGA form also provides information on status with regards to problems related to ascites, ankle oedema, vomiting and diarrhoea, all of which can affect the BIA raw data.

2.7. Statistical analyses

Descriptive statistics are given as median (interquartile range (Q1–Q3)) for continuous variables and number (n) (%) for categorical variables.

Differences in raw data (R, Xc and phase angle (PhA)) and FFM estimates between the various devices were tested for normality by the Shapiro–Wilk normality test and visual inspection of histograms.

To compare raw data assessed by the two BIA devices, paired sample t-tests and bivariate (Pearson’s) correlation analysis was performed.

FFM estimates derived from equations in the BIA softwares (hereby referred to as manufacturer’s equations) as well as selected previously published equations (see Appendix 1) were compared with DXA estimates using paired sample t-test and linear regression. To determine the most suitable equations, the following aspects of validity were considered: 1) Equality of means, determined by non-significant difference between mean FFM_{BIA} and FFM_{DXA} using paired sample t-tests, and 2) Ability of FFM_{BIA} to predict FFM_{DXA} , determined by high coefficients of determination (R^2) and low prediction error (SEE) using linear regression models. These equations, as well as the manufacturer’s equations were tested further for validity by constructing scatter plots, Bland–Altman plots and by calculating Lin’s concordance correlation coefficient (CCC). Bland–Altman plots were constructed to diagnose eventual bias (estimated by mean differences), limits of agreement (mean difference \pm 1.96 SD) and presence of outliers in the data. Proportional bias (e.g. variation in the vertical spread of scatter points with increasing value of FFM) was assessed by analysing the Pearson’s correlation coefficient between mean of FFM_{BIA} and FFM_{DXA} and differences in FFM_{BIA} and FFM_{DXA} . CCC, which takes both equality of means and strength of linear relationship into consideration, was calculated using the following formula: $\text{CCC} = \frac{2\rho\sigma_x\sigma_y}{\sigma_x^2 + \sigma_y^2 + (\mu_x - \mu_y)^2}$, where ρ is the correlation coefficient r between the two methods, μ_x and μ_y are the means for the two methods and σ_x^2 and σ_y^2 are the corresponding variances.

For the most suitable BIA equations, as well as the manufacturer’s equations, sensitivity and specificity for identification of low and normal FFMI was calculated using DXA as reference method [27]. Low FFMI was defined as $<17 \text{ kg}/\text{m}^2$ for men and $<15 \text{ kg}/\text{m}^2$ for women.

SPSS 21.0 for Windows (SPSS, Chicago, IL, USA) was used for all statistical analyses. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. Characteristics of the study population

All the 45 eligible patients completed the DXA scan, while 43 and 41 completed the whole-body BIA and segmental BIA assessment, respectively. Two participants were excluded from BIA measurements due to pacemakers. Furthermore, 2 patients were not able to perform the segmental BIA measurement due to upper extremity amputation and technical issues during the assessment, respectively.

Subject characteristics are shown in Table 1. Median (interquartile range (Q1–Q3)) time from surgery to assessment was 293 (190, 500) days. The participants had a wide range of BMI (18–43) kg/m^2 , FFM (33–72) kg, FM (11–63) kg and visceral adipose tissue (72–2734) g assessed by DXA. Thirty-nine percent of the women and 41% of the men were classified as abdominally obese (≥ 88 cm for women and ≥ 102 cm for men). Seventeen percent were classified as moderately malnourished according to the PG-SGA assessment tool. None of the patients were classified as severely malnourished. Regarding factors possibly contributing to altered water- and electrolyte balance, 12% had clinically visible ankle oedema, 18% had an ileostomy or a colonostomy and 29% had diarrhoea. None of the patients had ascites.

Table 1
Characteristics of the study population. Numbers are median (interquartile range (Q1–Q3)).

Variables	All subjects (n = 43) ^a	Women (n = 26) ^a	Men (n = 17) ^a
Age, years	67.0 (62.0, 71.5)	63.5 (58.0, 71.0)	69.0 (65.0, 72.0)
Race			
White, n (%)	41 (97.6)	25 (100.0)	16 (94.1)
Others, n (%)	1 (2.4)	0 (0.0)	1 (5.9)
Ostomy			
Yes, %	7 (18.4)	2 (8.7)	5 (33.3)
Time since surgery, days	293 (189.5, 499.5)	316.0 (229.0, 550.0)	278.0 (152.0, 441.0)
Nutritional status			
<i>Anthropometric measures</i>			
Height, cm	169.3 (164.5, 175.8)	165.2 (162.4, 169.3)	175.9 (170.6, 180.7)
Body weight, kg ^b	72.0 (60.3, 84.8)	61.6 (54.0, 80.5)	84.5 (71.4, 89.8)
Body weight (DXA), kg	71.7 (60.3, 84.8)	61.7 (54.1, 80.7)	83.9 (71.7, 89.9)
BMI, kg/m ^{2b}	25.8 (22.0, 28.9)	24.8 (20.7, 28.4)	27.5 (23.1, 29.5)
Waist circumference, cm	93.3 (80.6, 101.7)	83.7 (74.9, 95.6)	101.0 (93.3, 104.1)
Hip circumference, cm	97.3 (90.0, 104.0)	97.1 (89.2, 104.9)	98.6 (94.0, 103.0)
Waist/hip-ratio	0.90 (0.84, 0.99)	0.87 (0.82, 0.90)	1.01 (0.98, 1.03)
PG-SGA			
Global rating			
Well nourished, n (%)	35 (83.3)	20 (80.0)	15 (88.2)
Moderately malnourished, n (%)	7 (16.7)	5 (20.0)	2 (11.8)
Total scoring, sum	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)	3.0 (2.0, 4.0)
Ascites			
Yes, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Ankle oedema			
Yes, n (%)	5 (11.9)	4 (16.0)	1 (5.9)
Vomiting			
Yes, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea			
Yes, n (%)	12 (28.6)	8 (32.0)	4 (23.5)
Body composition (DXA)			
FFM, kg	47.6 (38.9, 55.1)	40.5 (37.8, 45.4)	60.1 (52.9, 62.2)
FM, kg	23.7 (17.1, 33.0)	22.7 (15.8, 35.3)	25.9 (18.5, 29.5)
BM, kg	2.5 (2.0, 3.0)	2.2 (1.9, 2.4)	3.1 (2.9, 3.3)
VATM, g	988.0 (477.0, 2003.0)	695.0 (215.0, 1298.0)	1949 (906.0, 2381.0)

Abbreviations: Q, Quartile; BMI, Body mass index; PG-SGA, Patient-generated Subjective global assessment; DXA, Dual energy X-ray absorptiometry; FFM, Fat-free mass; FM, Fat mass; BM, bone mass; VATM, Visceral adipose tissue mass.

^a Numbers may vary due to missing information.

^b Body weight assessed by Seca mBCA515.

Mean difference \pm SD between body weight assessed by DXA and by the weight scale used for BIA assessments (BIA–DXA) were 0.3 kg \pm 1.0 ($p = 0.046$), indicating a slight overestimation of body weight using the body composition analyser Seca mBCA515 compared to DXA.

3.2. Comparison of raw data between the two BIA devices

As raw data, i.e. the resistance and the reactance values (R and Xc, respectively), are important determinants of FFM estimates, we compared R and Xc values generated by the two BIA-devices at 50 kHz. We observed significant differences in both R and Xc values between whole-body BIA and segmental BIA. Whole-body BIA gave lower mean R values compared to segmental BIA, 547 and 622 Ohm, respectively, and higher mean Xc values, 61 and 49 Ohm, respectively (Table 2). Phase angle ((PhA), i.e. $(Xc/R) \times (180^\circ/\pi)$), an

Table 2
Comparison of resistance (R), reactance (Xc) and phase angle (PA) assessed by whole-body BIA and segmental BIA.

Variable	Whole-body BIA	Segmental BIA	Correlations		
	Mean (SD)	Mean (SD)	p^1	r	p^2
R, Ohm	546.9 (91.3)	622.2 (102.1)	<0.001	0.99	<0.001
Xc, Ohm	60.6 (13.3)	49.3 (6.9)	<0.001	0.58	<0.001
PhA	6.4 (1.3)	4.6 (0.6)	<0.001	0.57	<0.001

Abbreviations: SD, Standard deviation; r, Correlation coefficient (Spearman's); R, Resistance; Xc, Reactance; PhA, Phase angle.
 P -value: p^1 ; Paired sample t-tests, p^2 ; test for bivariate correlations (Pearson's).

indicator of functional and nutritional status, was significantly higher for whole-body BIA compared to segmental BIA, with mean PhA values of 6.4 and 4.6, respectively.

3.3. Validity of whole-body BIA to assess FFM

Whole-body BIA FFM estimates ($FFM_{\text{BIA-whole-body}}$) were calculated using different empiric equations including the equation derived from the manufacturer's software. These estimates were then compared with DXA estimates.

There was a high degree of linear relationship between BIA and DXA estimates for all equations tested with R^2 ranging from 0.94 to 0.97 (Table 3A). However, large discrepancies in FFM estimates were observed depending on the equations used, with mean differences ranging from -6.5 to 6.8 kg (Table 3A, Fig. 1A). Only three equations produced similar mean FFM values compared to DXA (i.e. not significantly different by paired t-tests). Those were the Gray*, Schols* and Segal* equations (Table 3A). Of these equations, the Schols* and Gray* equations demonstrated lower SEE (2.0 and 1.9 kg, respectively) than the Segal* equation (2.4 kg), and were hence considered more suitable.

The manufacturer, Gray* and Schols* equations were tested further for validity by constructing scatter plots (Fig. 2A–C), Bland–Altman plots (Fig. 2D–F) and by calculating CCC. Visual inspection of the scatter plots clearly revealed how FFM estimates co-varied with the corresponding DXA estimates for all equations. However, the Bland–Altman plots showed that only the Schols* equation gave satisfactory agreement with FFM_{DXA} , indicated by no

Table 3A

Evaluation of fat-free mass (FFM) measured by whole-body BIA against DXA as reference method. A comparison of different equations. N = 43^a.

Variable	Mean difference	SD	95% CI	P	R ²	SEE
Manufacturer, kg	1.46	2.16	0.80, 2.13	<0.001	0.96	2.03
Heitmann* [18,28], kg	2.41	1.75	1.87, 2.95	<0.001	0.97	1.76
Gray* [17], kg	0.36	2.99	-0.56, 1.28	0.437	0.97	1.87
Heitmann [18,28], kg	1.38	1.91	0.79, 1.97	<0.001	0.97	1.92
Schols* [23], kg	-0.16	1.94	-0.76, 0.43	0.582	0.96	1.96
Geneva [14], kg	2.66	2.42	1.92, 3.41	<0.001	0.96	2.18
Deurenberg (1991) [9,16], kg	-2.38	2.59	-3.18, -1.59	<0.001	0.95	2.29
Kyle [19], kg	-2.54	2.76	-3.39, -1.69	<0.001	0.95	2.30
Lukaski [21,28], kg	2.37	2.42	1.62, 3.11	<0.001	0.95	2.33
Lukaski* [21], kg	1.78	2.61	0.97, 2.58	<0.001	0.95	2.34
Lohman* [20,32], kg	6.81	3.27	5.80, 7.82	<0.001	0.95	2.37
Segal* [22], kg	0.40	2.37	-0.33, 1.13	0.272	0.95	2.39
Deurenberg (1990) [15], kg	-6.54	2.47	-7.29, -5.78	<0.001	0.94	2.49

Abbreviations: SD, Standard Deviation; 95% CI, 95% Confidence interval; R², R squared; SEE, Standard Error of the Estimate.

P-values: Paired sample T-test.

^a Equations included: 1) Manufacturer's equation, 2) The Geneva equation (recommended by ESPEN) and 3) Equations previously tested for validity in cancer patients. * Indicate sex-specific equations.

constant bias (i.e. fixed bias), no proportional bias and small limits of agreement (-3.96, 3.64 kg). For the manufacturer's equation, there was a small fixed bias of 1.46 (-2.77, 5.69 kg) with a tendency towards proportional bias ($r = 0.28$, $p = 0.066$). For the Gray* equation, wide limits of agreement was observed (-5.50, 6.22 kg), as well as a clear proportional bias ($r = 0.73$, $p < 0.001$), with underestimation and overestimation for low and high values of FFM, respectively. CCC values (i.e. a combined measure of equality of means and strength of linear relationship), were within the range 0.95–0.99 for all three equations (data not shown), which is considered substantial. The CCC value was higher for the Schols* equation (CCC = 0.98) than the manufacturer's and Gray* equation (CCC of 0.97 for both). Taken together, these results suggest that the Schols* equation may be superior to the other equations for estimation of FFM using whole-body BIA.

3.4. Validity of segmental BIA to assess FFM

Similar to whole-body BIA, segmental BIA FFM estimates (FFM_{BIA-segmental}) were calculated using the different empiric equations including the equation derived from the manufacturer's software, and compared with DXA estimates.

As for whole-body BIA, all equations showed strong linear agreement with DXA estimates with R² ranging from 0.94 to 0.98 (Table 3B) but large variations in FFM estimates depending on the equation used with mean differences ranging from -11.0 to 3.4 kg (Table 3B, Fig. 1B). Only two equations gave similar FFM estimates as FFM_{DXA}, the manufacturer's and the Heitmann* equations (Table 3B).

The manufacturer and Heitmann* equations were tested further for validity by constructing scatter plots (Fig. 3A–B), Bland–Altman plots (Fig. 3C–D) and by calculating CCC. The scatter plots demonstrated how FFM estimates co-varied with the corresponding FFM_{DXA} estimates for both equations. Furthermore, inspection of the Bland–Altman plots showed no fixed bias for any of the equations with limits of agreement ranging from -4.38 to 3.70 kg and -3.42 to 3.76 kg for the manufacturer's and Heitmann* equations, respectively. Whereas no proportional bias was seen for the Heitmann* equation, a clear positive association was observed for the manufacturer's equation ($r = 0.69$, $p < 0.001$) with underestimation and overestimation for low and high values of FFM, respectively. CCC values were 0.98 for both equations (data not

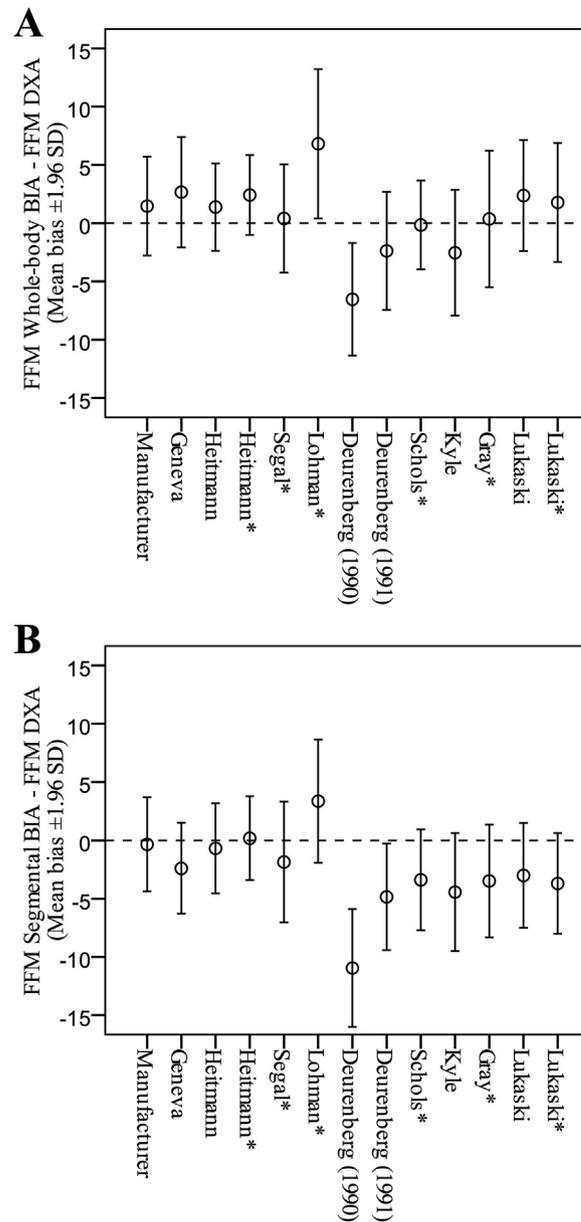


Fig. 1. Error bars showing mean difference ± 1.96 standard deviations (SD) between fat-free mass (FFM) measured by whole-body BIA and segmental BIA using various equations and FFM measured by DXA.

shown). Taken together, these results suggest that the Heitmann* equation may be the superior equation for estimation of FFM using segmental BIA.

3.5. Use of BIA-derived FFM estimates to diagnose malnutrition

The type of BIA device and equation used to assess FFM may have clinical implication for the diagnosis of malnutrition. According to the new consensus statement from ESPEN [8], malnutrition can be diagnosed by either low BMI alone or a combination of unintentional weight loss (mandatory) and low BMI or low FFMI. Using the cut-off values for FFMI, 33% of our patients were identified with low FFMI based on FFM_{DXA} (Table 4). Whole-body BIA with use of the manufacturer's equation resulted in the lowest proportion of patients with low FFMI (26%) compared to segmental BIA using the manufacturer's equation resulting in the highest

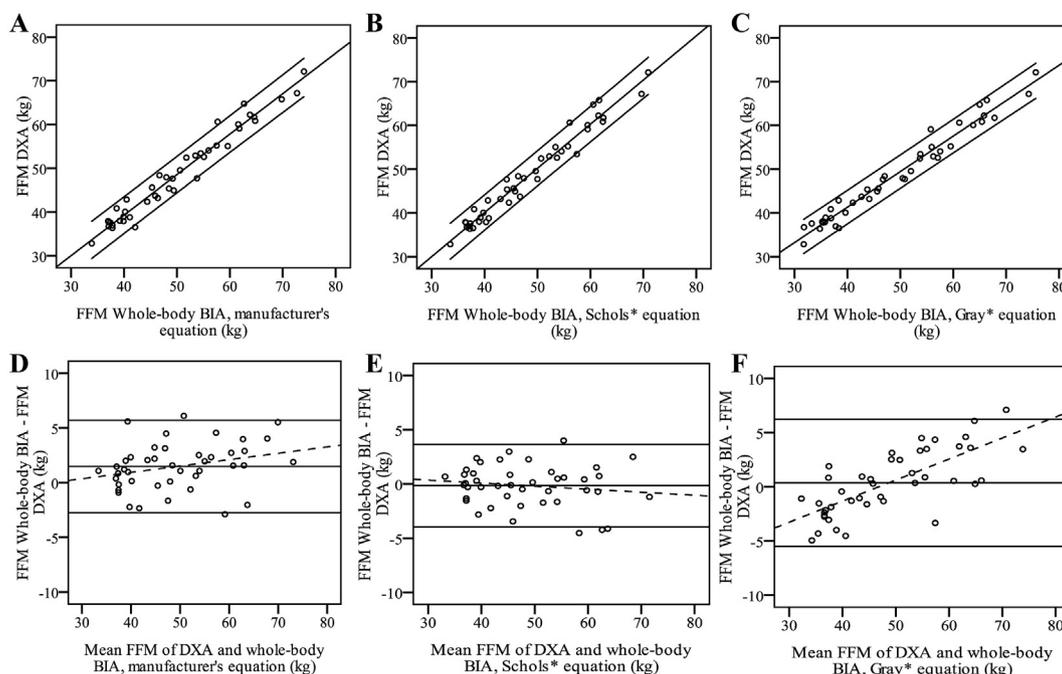


Fig. 2. Fat-free mass (FFM) assessed by DXA and whole-body BIA. A–C: Scatter plots for: A) Manufacturer's ($R^2 = 0.96$, $SEE = 2.03$), B) Schols* ($R^2 = 0.96$, $SEE = 1.96$) and C) Gray* ($R^2 = 0.97$, $SEE = 1.87$) equation. D–E: Bland–Altman plots for D) Manufacturer's; Mean difference (95% limits of agreement (± 1.96 SD)) 1.46 (–2.77, 5.69), E) Schols*; –0.16 (–3.96, 3.64) and F) Gray*; 0.36 (–5.50, 6.22) equation. The dotted lines represent the regression lines between mean FFM_{DXA} and FFM_{BIA} and differences between FFM_{BIA} and FFM_{DXA} . Pearson's correlation coefficient r (p -value); D: 0.28 ($p = 0.066$) E: –0.14 ($p = 0.356$) and F: 0.73 ($p < 0.001$).

Table 3B

Evaluation of fat-free mass (FFM) measured by segmental BIA against DXA as reference method. A comparison of different equations. $N = 41^a$.

Variable	Mean difference	SD	95% CI	P	R^2	SEE
Manufacturer [24], kg	–0.34	2.06	–0.99, 0.31	0.292	0.98	1.42
Heitmann* [18,28], kg	0.17	1.83	–0.40, 0.75	0.546	0.97	1.85
Gray* [17], kg	–3.48	2.47	–4.26, –2.71	<0.001	0.97	1.95
Heitmann* [18,28], kg	–0.69	1.97	–1.31, –0.07	0.031	0.97	1.96
Geneva [14], kg	–2.40	1.99	–3.03, –1.78	<0.001	0.96	2.00
Schols* [23], kg	–3.39	2.20	–4.09, –2.70	<0.001	0.96	2.00
Kyle [19], kg	–4.44	2.58	–5.25, –3.63	<0.001	0.96	2.11
Lukaski [21,28], kg	–3.01	2.29	–3.73, –2.29	<0.001	0.96	2.19
Lukaski* [21], kg	–3.70	2.20	–4.40, –3.01	0.001	0.96	2.20
Deurenberg (1991) [9,16], kg	–4.85	2.33	–5.59, –4.11	<0.001	0.95	2.29
Lohman* [20,32], kg	3.36	2.70	2.51, 4.21	<0.001	0.95	2.39
Deurenberg (1990) [15], kg	–10.96	2.58	–11.77, –10.14	<0.001	0.95	2.40
Segal* [22], kg	–1.86	2.64	–2.70, –1.03	<0.001	0.94	2.61

Abbreviations: SD, Standard Deviation; 95% CI, 95% Confidence interval; R^2 , R squared; SEE, Standard Error of the Estimate.

P -values: Paired sample T-test.

^a Equations included: 1) Manufacturers equation, 2) The Geneva equation (recommended by ESPEN) and 3) Equations previously tested for validity in cancer patients.

*Indicate sex-specific equations.

proportion (44%). Considering DXA as a reference method to assess FFMI, the highest sensitivity (i.e. proportion with low FFMI correctly identified as such) was seen for whole-body BIA using the Schols* equation (93%), followed by segmental BIA using the manufacturer's equation (86%). Specificity (i.e. proportion with normal FFMI correctly identified as such) was highest for whole-body BIA using the manufacturer's equation (100%), followed by segmental BIA using the Heitmann* equation (96%) and whole-body BIA using the Schols* equation (93%). The results demonstrate that type of BIA device and equation used have implications for the proportion of patients categorized with low FFMI, and consequently the ability to correctly classify patients as malnourished.

4. Discussion

To our knowledge, this is the first study to test the validity of two different BIA devices for estimation of FFM by using DXA as a reference method in CRC patients. Furthermore, our study is the first to evaluate various existing equations for estimation of FFM in order to find the most appropriate BIA equation(s) for estimating FFM in a cohort consisting solely of CRC patients.

The results of the present study show that estimating body composition from impedance data is dependent on type of BIA device and equation used. The two BIA devices tested in the current study, a whole-body BIA and a segmental BIA, resulted in significantly different R and X_c values, and hence FFM estimates, despite

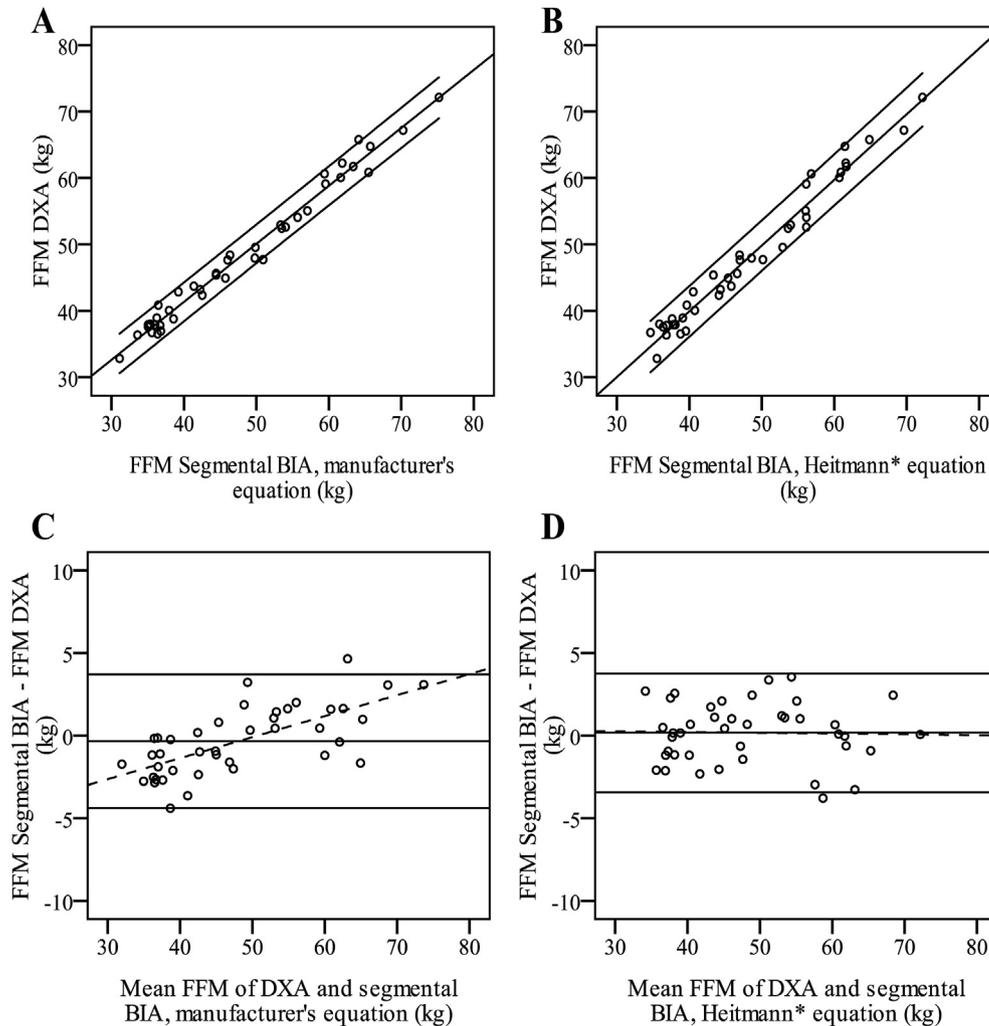


Fig. 3. Fat-free mass (FFM) assessed by DXA and segmental BIA. A–B: Scatter plots for; A) Manufacturer's ($R^2 = 0.98$, $SEE = 1.42$) and B) Heitmann* ($R^2 = 0.97$, $SEE = 1.85$) equation. C–D: Bland–Altman plots for C) Manufacturer's; Mean difference (95% limits of agreement (± 1.96 SD)) -0.34 (-4.38 , 3.70) and D) Heitmann*; 0.17 (-3.42 , 3.76) equation. The dotted lines represent the regression lines between mean FFM_{DXA} and FFM_{BIA} and differences between FFM_{BIA} and FFM_{DXA} . Pearson's correlation coefficient r (p -value); C: 0.69 ($p < 0.001$) and D: -0.03 ($p = 0.870$).

using the same equation. This suggests that the two BIA-devices should not be used interchangeably; **the accuracy of the equation will relate to the type of BIA device used in addition to population-specific factors such as age, gender, ethnicity and body composition characteristics.**

We observed a strong linear relationship between BIA and DXA estimates for all equations tested. However, there was a discrepancy in FFM estimates depending on the equations used. For whole-body BIA, mean difference in FFM estimates were in the

range -6.5 and 6.8 kg, whereas for segmental BIA, estimates varied from -11.0 to 3.4 kg. Our results are in accordance with observations reported in a newly published review article by Haverkort et al. [28], including surgical and oncological patients, and underscore that selection of BIA equation has significant implications for the accuracy of the estimates.

For whole-body BIA, the manufacturer's equation resulted in a small overestimation of FFM by 1.5 kg whereas for segmental BIA no differences were detected. Despite small or no differences at the

Table 4
Performance of whole-body and segmental BIA to detect low FFMI ($FFMI < 15$ kg/m² for women and < 17 kg/m² for men) using selected equations against DXA as reference method.

	DXA	Whole-body BIA			Segmental BIA	
		Manufacturer	Gray*	Schols*	Manufacturer	Heitmann*
Low FFMI, %	32.6	25.6	34.9	34.9	43.9	29.3
Sensitivity, %	–	78.6	78.6	92.9	85.7	78.6
Specificity, %	–	100.0	86.2	93.1	77.8	96.3
PPV, %	–	100.0	73.3	86.7	66.7	91.7
NPV, %	–	90.6	89.3	96.4	91.3	89.7

Reference values: FFMI derived from DXA measurements ($n = 43$).

Abbreviations: BIA, Bioelectrical impedance analysis; DXA, Dual energy X-ray absorptiometry; FFMI, Fat-free mass index; PPV, Positive predictive values; NPV, Negative predictive value.

group level, we observed that both devices demonstrated limitations with regards to proportional bias when using the manufacturer's equations. We cannot explore this bias further, as the equations incorporated into the BIA devices software are unknown, a phenomena referred to as black-box equations in the literature.

Most of the BIA equations available are developed in healthy individuals and consequently may not provide valid estimates in patient populations due to differences across populations, for instance with regard to body shape, fat fraction and hydration of FFM. It is therefore recommended not to use general equations without prior validation in the population of interest [9]. In absence of a CRC-specific equation, we chose to test the validity of BIA by use of the Geneva equation recommended by ESPEN and a selection of equations previously tested in cancer patients. Using a broad range of validity measures, our results suggest that the Schols* and Heitmann* equations are the most suitable equations for estimation of FFM using whole-body and segmental BIA, respectively. The Schols* equation was developed in patients with chronic obstructive pulmonary disease using deuterium dilution as the reference method [23], while the Heitmann* equation was developed in a healthy population using densitometry as the reference method [18]. The validity of the Schols* equation was tested in 51 patients with locally advanced or metastatic cancer of the lung or colorectum [29]. In contrast to our results, this study reported poor ability of BIA to estimate FFM in cancer patients. The discrepancy between our results and the results of Mourtzakis et al. [29] may be due to the older foot-to-foot BIA-device (Tanita Body Composition Analyzer TBF-300A) used by Mourtzakis et al. The validity of the Heitmann* equation was tested in a group of 26 patients who had undergone major abdominal surgery. Similar to our results, Jensen et al. found good agreement between FFM estimates derived from BIA and DXA [30].

In clinical practice, the manufacturer's equations will most often be utilized. On a group level, the use of these equations resulted in small differences in FFM for the whole-body BIA device and no difference for the segmental BIA device. On the individual level, FFM estimates were within -2.8 – 5.7 and -4.4 – 3.7 kg, using whole-body and segmental BIA, respectively, for approximately 95% of the patients. Furthermore, both equations gave proportional bias. Taken together, these findings suggest that both BIA devices may be appropriate to determine body composition of groups, however, considering the variation in measurement accuracy at the individual level, single measurements should be interpreted with care. Furthermore, one must be aware that the direction of bias may be affected by the size of the FFM compartment.

To investigate the clinical implications of using two different BIA devices, we used FFM estimates from both devices, based on the manufacturer's equation as well as the most suitable equations (i.e. the Schols* and Gray* equation for whole-body BIA and the Heitmann* equation for segmental BIA) to identify the proportion of patients with low FFMI according to the new consensus definition for malnutrition proposed by ESPEN [8]. We observed that the proportion of patients identified with low FFMI varied from 26 to 44% depending on device and equation used, with sensitivity ranging from 79 to 93%. Thus, some patients will not be correctly identified with low FFMI if a suboptimal equation is used. On the other hand, by using the optimal equation, whole-body BIA as well as segmental BIA (to a lower degree) may have acceptable ability to detect low FFM from a single measurement.

In the current study, including a high proportion of patients with obesity and abdominal obesity, we compared two different BIA devices relying on different approaches to estimate FFM; a whole-body approach and a segmental approach. For the whole-body approach, the various segments of the body will contribute differently to resistance values based on conductive mass. Hence, it

has been suggested that segmental BIA may provide more accurate estimates of FFM in patients at extremes of BMI ranges [10]. However, this has yet to be confirmed in clinical studies [31]. Our study demonstrated that both BIA devices showed good agreement with DXA when using the appropriate equation. This was demonstrated in the group as a whole, and when looking at the obese subjects only (data not shown). Hence, we could not confirm the superiority of segmental BIA over whole-body BIA in estimation of FFM in this CRC population.

A strength of our study is the unselected inclusion of patients within the study patient cohort, e.g. inclusion of patients with abnormal body shapes, obesity, presence of chronic diseases and orthopedic prosthesis/implants. In previous validation studies, patients with these conditions have often been excluded due to possible interference with the BIA measurements, resulting in highly selected patient populations. Despite our broad inclusion, we observed high agreement between FFM estimates from both BIA devices and DXA using the appropriate equation, increasing the generalizability of our results in this patient population.

5. Conclusion

In a population of non-metastatic CRC patients, mostly consisting of Caucasian adults and with a wide range of body composition measures, FFM estimates from both whole-body and segmental BIA shows good agreement with DXA when using the appropriate equation. For whole-body BIA, the highest agreement was observed for the Schols* equation, whereas for segmental BIA, the Heitmann* equation was the superior choice. At the individual level, both BIA-devices show acceptable ability to detect low FFM when using the optimal equation. We recommend using one of these combinations of device and equation for measuring FFM in this population.

Statement of authorship

HR and ASK had the main responsibility for data analysis and writing the manuscript. HR, ASK, CH, GF, HBH, SKB, 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. ASK, HR, CH, GF, HBH, SKB and IP contributed to acquisition of data. All authors contributed to the writing and final approval of the manuscript.

Conflict of interest statement

All other authors declare that they have no competing interests.

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List of abbreviations

BIA	Bioelectrical impedance analysis
BMI	Body mass index
CCC	concordance correlation coefficient
CRC	Colorectal cancer
DXA	Dual energy X-ray absorptiometry
ESPEN	European Society for Clinical Nutrition and Metabolism
FFM	Fat-free mass
FFMI	Fat-free mass index
FM	Fat mass
ICD	International classification of diseases and related health problems
NPV	Negative predictive value
N	Number
PG-SGA	Patient-generated subjective global assessment
PhA	Phase angle
PPV	Positive predictive value
R	Resistance
SD	Standard deviation
SEE	Standard error of the estimate
TNM	Tumor node metastasis
Xc	Reactance

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.clnu.2016.12.028>.

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