Original article

Use of bioelectrical impedance analysis to monitor changes in fat-free mass during recovery from colorectal cancer— a validation study

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SUMMARY

Background & aims: Although previous research show high correlation between fat-free mass (FFM) measured by bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA), the validity of BIA to track longitudinal changes in FFM is uncertain. Thus, the aim of this study was to validate the ability of BIA to assess changes in FFM during 6 months of recovery from non-metastatic colorectal cancer (CRC).
Methods: A total of 136 women and men (50–80 years) with stage I-III CRC and a wide range of baseline FFM (35.7–73.5 kg) were included in the study. Body composition was measured at study baseline within 2–9 months of surgery and again 6 months later. Whole-body BIA FFM estimates (FFM_{BIA}) were calculated using three different equations (manufacturer's, Schols' and Gray's) before comparison to FFM estimates obtained by DXA (FFM_{DXA}).
Results: Correlation between changes in FFM_{BIA} and FFM_{DXA} was intermediate regardless of equation ($r \approx 0.6$). The difference in change of FFM_{BIA} was significant compared to FFM_{DXA}, using all three equations and BIA overestimated both loss and gain. However, BIA showed 100% sensitivity and about 90% specificity to identify individuals with ≥5% loss in FFM, using all three equations. Sensitivity of FFM_{BIA} to detect a smaller loss of FFM (60–76%) or a gain in FFM of ≥5% (33–62%) was poor.
Conclusion: In a well-nourished population of non-metastatic CRC patients, a single-frequency whole-body BIA device yielded imprecise data on changes in FFM, regardless of equation. BIA is thus not a valid option for quantifying changes in FFM in individuals. However, BIA could be used to identify patients with loss in FFM ≥5% in this population. The validity of BIA to monitor changes in FFM warrants further investigation before implementation in clinical praxis.

1. Introduction

Colorectal cancer (CRC) is among the most common cancers worldwide and a leading cause of cancer deaths [1]. The incidence of CRC is still increasing in many countries including Norway [2]. CRC mortality has decreased due to implementation of screening programs and improved treatment, and 5-year survival is approximately 65% in high-income countries [3].

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Malnutrition frequently occurs in patients with cancer diagnosis, and can have severe impact on the outcome. Especially low muscle mass and fat-free mass (FFM) is associated with increased mortality [4], reduced tolerance to adjuvant chemotherapy [5] and post-surgical complications [6]. Further, loss of muscle mass during recovery from localised CRC is associated with higher all-cause and cancer-specific mortality [7]. Weight loss is a poor predictor of loss in muscle mass [8]. Thus, tracking changes in body composition could be valuable in both clinical and research settings. However, detecting change in muscle mass requires high precision in the body composition assessment.

Dual-energy *X-ray* absorptiometry (DXA) has high precision in measuring different body compartments [9–12], and is therefore one of the preferred methods for body composition assessment. DXA is however often not available for measurement of body composition alone and more inexpensive and readily available methods would be preferable at least in a clinical setting. Bioelectrical impedance analysis (BIA) is an easy and non-invasive bedside method used to measure body composition as two components: FFM and fat mass (FM). The method assesses body composition by sending an electrical current through the body. In order to reduce the measurement error, standardized measurement procedure is of utmost importance. Errors to the BIA method are dependent on the device, the operator, the subject, the measurement procedure and the environmental conditions [13]. In addition, BIA estimates of body composition are dependent on the use of equations appropriate for the population [14].

Previous results from our research group show that in CRC, FFM derived from BIA is highly correlated with FFM by DXA and produce similar estimates at the group level [14]. However, measurement uncertainty is high at the individual level, raising the question whether BIA is sufficiently precise to track changes in FFM over time. In addition, patients with CRC may be subject to anatomical and physiological changes due to treatment or the underlying disease. These changes may affect the conductivity of the body and hence the measurement of FFM by BIA, and could differ with time. To ensure that BIA is suitable to identify small but clinically relevant changes in FFM in an oncological setting, a validation study is needed.

The aim of the current study was to validate the ability of a whole-body BIA, compared to DXA, to track and identify changes in FFM during 6 months in a heterogeneous group of non-metastatic CRC patients in recovery from surgery.

2. Materials and methods

2.1. Patients and eligibility

Patients included in the current study were recruited from the ongoing randomized controlled trial, The Norwegian Dietary Guidelines and Colorectal Cancer Survival (CRC-NORDIET) study [15]. Eligibility criteria for this study included age 50–80 years, presence of a newly diagnosed primary invasive CRC (ICD-10 C18-20), histologically confirmed adenocarcinoma and TNM stage I-III.

Participants from the CRC-NORDIET study with available BIA and DXA measurements at study baseline, and at 6-month follow-up were included in the current validation study. The only exclusion criterion was ascites at baseline (N = 3), as BIA is unreliable in this state [16]. Participants were recruited in the period March 2012 to December 2018.

2.2. Ethics

The CRC-NORDIET study is carried out in accordance with the Declaration of Helsinki. Signed informed consent was provided by all participants prior to enrollment. The study is 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 at www.ClinicalTrials.gov (NCT01570010).

2.3. Data collection

All measurements were conducted at the Department of Nutrition, University of Oslo. Patients were instructed to fast overnight and until all measurements were completed. All measurements were conducted in the morning, in a sequential manner

Table 1
Baseline characteristics of the study participants.

	N	Mean ± SD or N (%)
Female gender	136	65 (47.8)
Age, years	136	66.5 ± 7.8
Smoker	136	11 (8.1)
Highest education level attained	127	
Primary Level		10 (7.9)
Secondary level		59 (46.5)
University level		58 (45.7)
Employment status	127	
Employed		41 (32.3)
Unemployed		1 (0.8)
Retired		68 (53.5)
Sick leave or disability benefits		17 (13.4)
Marital status	125	
Married or living with partner		94 (75.2)
Single		10 (8.0)
Widowed		6 (4.8)
Divorced		15 (12.0)
PG-SGA category	136	
A: well nourished		118 (86.8)
B: moderately malnourished		18 (13.2)
C: severely malnourished		0 (0)
Anthropometric measures	136	
Height, cm		172.8 ± 8.7
Body weight, kg		80.8 ± 16.7
BMI, kg/m^2		27.0 ± 4.9
Waist circumference, cm		94.7 ± 14.0
Hip circumference, cm		102 ± 9.8
Waist/hip-ratio		0.92 ± 0.1
Bioelectrical impedance data	136	
Phase angle (PhA) 50 kHz		6.5 ± 1.4
Reactance (Xc) 50 kHz		58.2 ± 15.2
Resistance (R) 50 kHz		516.8 ± 85.7
DXA body composition data	136	
Fat mass, kg		27.5 ± 10.1
Fat-free mass, kg		52.5 ± 10.4
BMI-categories	136	
<16 kg/m^2		0 (0)
< 18.5 kg/m^2		1 (0.7)
18.5–24.9 kg/m^2		50 (36.8)
25–29.9 kg/m^2		54 (39.7)
≥30 kg/m^2		31 (22.8)
≥34 kg/m^2		10 (7.4)
Ankle edema	133	35 (26.3)
Tumor localization	136	
C18 Colon		85 (62.5)
C19 Rectosigmoid		7 (5.1)
C20 Rectum		44 (32.4)
TNM-stage	125	
I		46 (36.8)
II		46 (36.8)
III		33 (26.4)
Time since surgery, days	136	170 ± 48
Adjuvant treatment	136	23 (16.9)
Ostomy	126	37 (29.4)

Abbreviations: BMI, Body Mass Index; TNM, Tumor Nodes Metastases; PG-SGA, Patient-Generated Subjective Global Assessment; DXA, dual-energy x-ray absorptiometry.
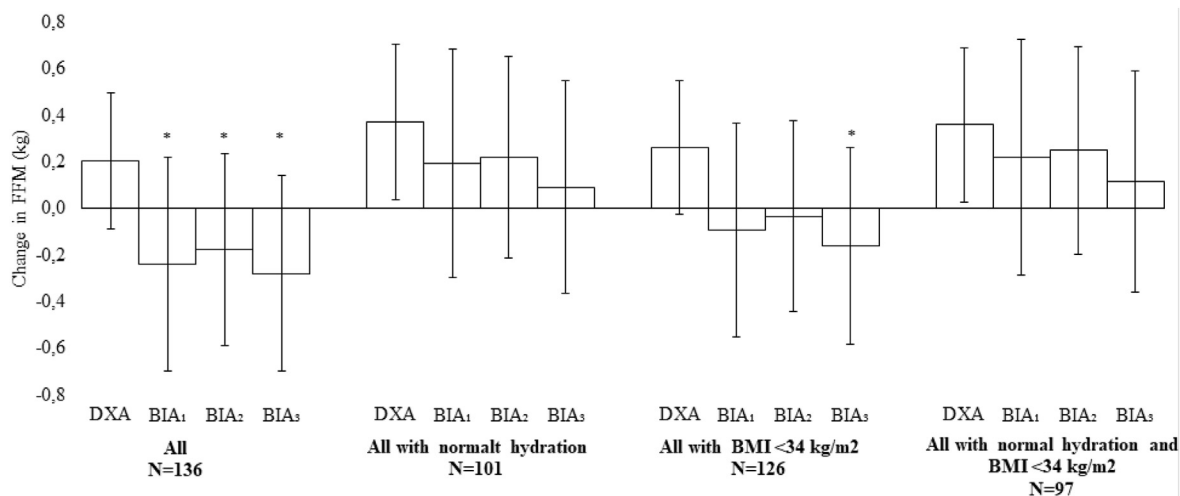
Fig. 1. Changes in FFM from baseline to 6-months follow-up estimated by DXA, and BIA using three different equations. Abbreviations: FFM, fat-free mass; DXA, Dual X-ray absorptiometry; BIA, Bioelectrical impedance analysis. Bars represent mean and error bars 95% confidence intervals. BIA_1: manufacturer's equation; BIA_2: Schol's equation; BIA_3: Gray's equation. *P < 0.05 compared to DXA.

within a 2 h timeframe. Clinicopathological data were retrieved from medical records. Information on socioeconomic variables, including work situation, education and marital status, were assessed using questionnaires.

2.4. Body composition assessment

For all measurement procedures of body composition, participants were measured wearing light clothing without metal objects such as jewellery or watches.

The Lunar iDXA (GE Healthcare Lunar, Buckinghamshire, United Kingdom) was used to measure total FFM and total fat mass (FM). All measurements were performed by a trained operator according to a standardized protocol.

A single frequency, whole-body BIA (BIA-101, SMT Medical, Würzburg, Germany) was used to quantify FFM and FM. The device utilizes a current of 400 μA at a constant frequency of 50 kHz. Measurements were performed by placing two adhesive skin electrodes at least 5 cm apart on the right hand and on the right foot of the patient in the supine position, in accordance with the manufacturer's protocol. Three different equations were utilized in the calculation of FFM: the manufacturer's equation, Schol's equation used by Steiner [17] and Gray's equation [18]. These equations were selected as they yielded the highest concordance with FFM measured by DXA in a previous, cross sectional study in the same population [14]. FM was calculated as body weight minus FFM.

2.5. Anthropometry

Body weight was measured by use of a digital measuring station, Seca 285 (Seca, Birmingham, United Kingdom). Body weight was recorded to the nearest 0.1 kg. To account for clothing, 0.5 kg was subtracted from body weight. Height was measured using either a mechanical height rod (Kern MSF-200) or a digital stadiometer (Seca 285). Height was recorded to the nearest 0.1 cm. BMI was calculated as kg/m^2 based on recorded weight and height. Waist circumference was measured at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Hip circumference was measured at the widest part of the hip. Waist and hip circumferences were recorded to the nearest 0.1 cm.

2.6. Nutritional status

Nutritional status was assessed by use of the Norwegian version of the Patient-Generated Subjective Global Assessment (PG-SGA) (15-004 v10.13.16) [19], with permission from the copyright holder. Based on the results, the patients were categorized as either well-nourished (PG-SGA A), moderately malnourished (PG-SGA B) or severely malnourished (PG-SGA C). Signs of ascites and ankle edema were assessed and recorded. The assessment and scoring of PG-SGA were carried out by trained clinical dietitians, as described previously [20].

2.7. Statistical analyses

Differences between FFM and FM by DXA (FFM_{DXA} and FM_{DXA}) and BIA (FFM_{BIA} and FM_{BIA}) were calculated as BIA minus DXA. Descriptive statistics are given as mean ± SD for continuous variables. Categorical variables are presented as number (n) and percent (%). Continuous variables were tested for normality by visual inspection of histograms and Q-Q-plots. FM_{BIA} and FFM_{BIA} were compared to FM_{DXA} and FFM_{DXA} using Bland Altman-plots, scatter plots, correlation analysis, linear regression analysis and Wilcoxon signed ranks test. Sensitivity analyses were conducted, excluding those with altered hydration status (ankle edema), and BMI <16 kg/m^2 or >34 kg/m^2 (none of the participants had BMI <16 kg/m^2) [21], at baseline. The specificity and sensitivity of BIA to detect loss or gain in FFM or FM at 5%, 2.5% and 1% was analyzed using DXA as reference. Significance was accepted at p < 0.05. Software SPSS Statistics version 25 (Armonk, New York: IBM Corp.) was used for all statistical analyses.

3. Results

Patient characteristics are shown in Table 1. Out of the 158 patients included at data extraction, N = 16 had missing DXA or BIA data at one or both time points. In addition, six participants were excluded - three due to implausible BIA readings and three due to ascites. Thus, 136 participants were included in the analyses.

At baseline, mean FFM_{DXA} was 60.4 kg (69%) among men and 43.9 kg (62%) among women. Only 13% of the participants were
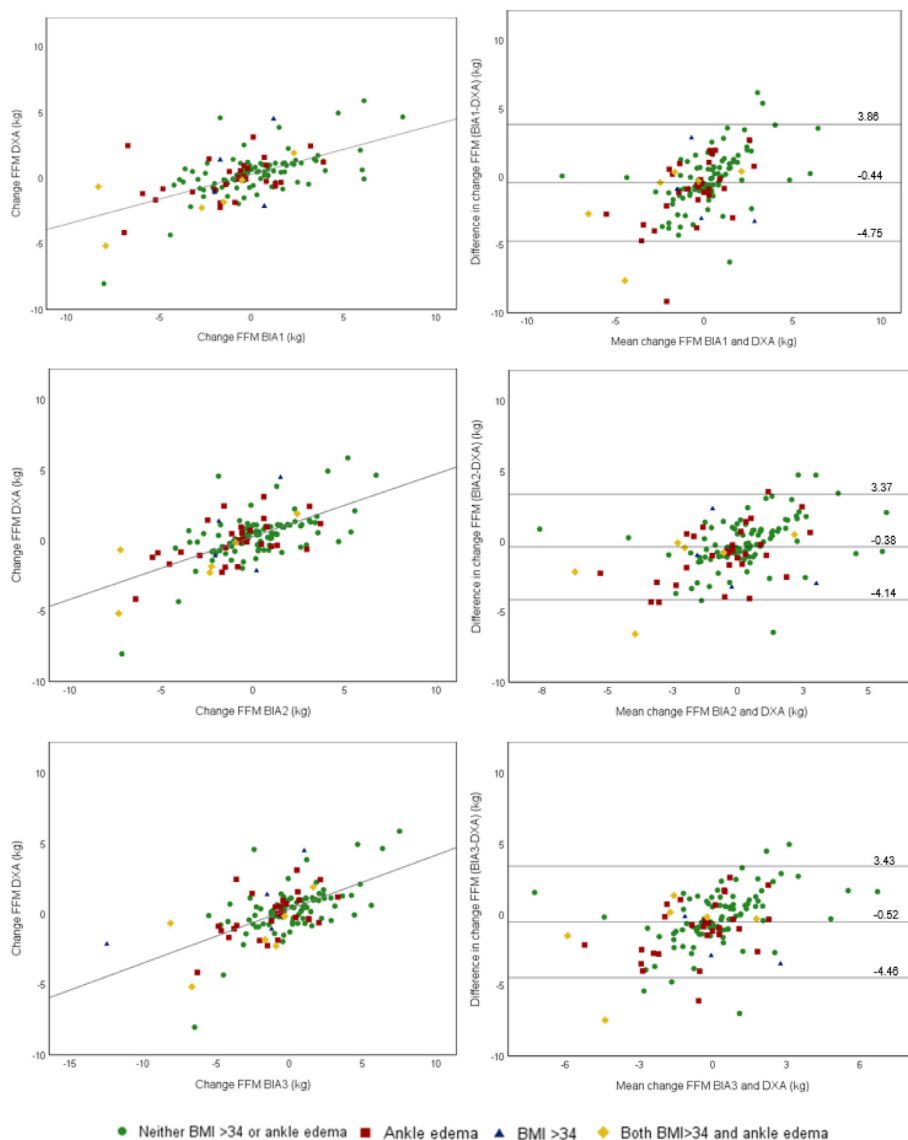
Fig. 2. Agreement between changes in fat-free mass (FFM) during 6-months follow-up assessed by Dual energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA), using three different equations. BIA1: manufacturer's equation; BIA2: Schol's equation; BIA3: Gray's equation.

categorized as malnourished by PG-SGA. One participant (0.7%) was underweight according to BMI at baseline.

Cross sectional analyses at baseline and 6 months follow up showed correlation between FFM_{DXA} and FFM_{BIA} to be r = 0.96–0.97 (depending on equation) and r = 0.96, respectively (all p < 0.001). At baseline, FFM_{BIA} differed from FFM_{DXA} by 1.7 kg, 0.9 kg and −0.3 kg using the equation by the manufacturer, Gray and Schols, respectively. At 6 months follow-up, difference was 1.3 kg, 0.3 kg and −0.7 kg.

At the 6-month follow up visit, mean ± SD weight change was 0.8 ± 3.8 kg with a range of -19 − 10 kg.

3.1. Changes in fat-free mass

Mean ± SD FFM_{DXA} increased by 0.2 ± 1.7 kg or 0.5 ± 3.0% during the 6-months follow-up. In contrast, FFM_{BIA} by all three equations estimated a mean loss in FFM, averaging from −0.2 ± 2.5 to −0.4 ± 2.7 kg (Fig. 1). The difference in change of FFM_{BIA} was significant compared to FFM_{DXA}, using all three equations.

The correlation between changes of FFM_{DXA} and FFM_{BIA} was r = 0.60 using the manufacturer's equation, r = 0.63 using Schol's equation and r = 0.60 using Gray's equation. The narrowest limits of agreement were seen for FFM_{BIA} by Schol's equation at −4.75-3.37. In addition, Bland Altman plots showed a proportional bias where FFM_{BIA} by all equations overestimated both loss and gain, compared to FFM_{DXA} (Fig. 2).

The performance of the BIA to identify individuals who had lost FFM was highest for Schols equation. Sensitivity to detect a loss in FFM of ≥5%, 2.5% and 1% was 100%, 73% and 76%, respectively. Specificity was 92%, 75% and 66%. Sensitivity to detect a gain in FFM of ≥5%, 2.5% and 1% was also highest for Schols equation at 50%, 62%, 58%, respectively, while specificity was 90%, 82% and 82% (Table 3).

Sensitivity analyses excluding participants with ankle edema and/or extreme BMI improved the concurrence between FFM_{DXA} and FFM_{BIA} (Table 2). However, neither correlation nor limits of agreement changed substantially. The mean difference between change in FFM_{BIA} and FFM_{DXA} was reduced in the sensitivity

Table 2
Change in fat-free mass from baseline to 6 months follow up according to BIA using three different equations, compared to DXA.

	Difference from DXA Mean ±SD[a]	R	LoA lower	LoA higher	R^2	SEE
All participants (N = 136)						
BIA, manufacturers equation	−0.44 ± 2.20*	0.60***	−4.75	3.86	0.36	1.40
BIA, Schol's equation	−0.38 ± 1.92*	0.64***	−4.14	3.37	0.40	1.35
BIA, Gray's equation	−0.52 ± 2.01*	0.60***	−4.46	3.43	0.36	1.39
All with normal hydration (N = 101)						
BIA, manufacturers equation	−0.18 ± 2.02	0.60***	−4.13	3.78	0.36	1.37
BIA, Schol's equation	−0.15 ± 1.80	0.60***	−3.69	3.38	0.37	1.37
BIA, Gray's equation	−0.32 ± 1.92	0.59***	−4.09	3.44	0.35	1.38
All with BMI 16−34 (N = 126)						
BIA, manufacturers equation	−0.36 ± 2.13	0.59***	−4.53	3.81	0.35	1.33
BIA, Schol's equation	−0.30 ± 1.85	0.63***	−3.93	3.33	0.38	1.30
BIA, Gray's equation	−0.42 ± 1.95*	0.60***	−4.24	3.39	0.36	1.32
All with normal hydration and BMI 16−34 (N = 97)						
BIA, manufacturers equation	−0.14 ± 1.99	0.62***	−4.03	3.75	0.39	1.31
BIA, Schol's equation	−0.11 ± 1.77	0.62***	−3.58	3.35	0.39	1.30
BIA, Gray's equation	−0.24 ± 1.90	0.61***	−3.97	3.48	0.37	1.32

Abbreviations: BIA, Bioelectrical impedance analysis; DXA, Dual X-ray absorptiometry; R, correlation coefficient, R2 = coefficient of determinations; LoA, Limits of Agreement.
*P<0.05, **<0.01, ***<0.001 compared to DXA
[a] BIA-DXA for all variables.

Table 3
Performance of a whole-body single frequency BIA to detect DXA identified changes in fat-free mass during 6 months.

	All (N = 136)			All with normal hydration (N = 101)			All with BMI 16−34 (N = 126)			All with normal hydration and BMI 16−34 (N = 97)		
	N (%)	Sensitivity (%)	Specificity (%)	N (%)	Sensitivity (%)	Specificity (%)	N (%)	Sensitivity (%)	Specificity (%)	N (%)	Sensitivity (%)	Specificity (%)
Lost ≥ 1% FFM	37 (27)			21 (21)			31 (3)			19 (20)		
BIA[1]		73.0	66.7		61.9	66.3		71.0	66.3		63.2	66.7
BIA[2]		75.7	65.7		66.7	68.8		74.2	66.3		68.4	69.2
BIA[3]		70.3	64.6		57.1	66.3		67.7	64.2		57.9	66.7
Gained ≥ 1% FFM	57 (42)						54 (43)			43 (44)		
BIA[1]		56.1	78.5		60.0	76.8		55.6	77.8		60.5	77.8
BIA[2]		57.9	82.3		60.0	80.4		57.4	80.6		60.5	79.6
BIA[3]		57.9	81.0		60.0	78.6		57.4	79.2		60.5	77.8
Lost ≥ 2.5% FFM	15 (11)			7 (7)			11 (9)			6 (6)		
BIA[1]		66.7	75.2		57.1	77.7		63.6	75.7		66.7	78.0
BIA[2]		73.3	75.2		57.1	77.7		72.7	76.5		66.7	79.1
BIA[3]		60.0	76.9		57.1	78.7		63.6	77.4		66.7	79.1
Gained ≥ 2.5% FFM	21 (15)			16 (16)			19 (15)			15 (16)		
BIA[1]		57.1	81.7		62.5	80.0		57.9	80.4		66.7	79.3
BIA[2]		61.9	81.7		68.8	80.0		57.9	80.4		66.7	79.3
BIA[3]		57.1	81.7		62.5	80.0		57.9	80.4		66.7	79.3
Lost ≥ 5% FFM	4 (3)			2 (2)			3 (2)			2 (2)		
BIA[1]		100.0	90.9		100.0	93.9		100.0	91.1		100.0	93.7
BIA[2]		100.0	92.4		100.0	96.0		100.0	92.7		100.0	95.8
BIA[3]		100.0	90.9		100.0	93.9		100.0	91.1		100.0	93.7
Gained ≥ 5% FFM	12 (9)			9 (9)			11 (9)			8 (8)		
BIA[1]		42.0	91.1		44.0	89.1		45.0	90.4		50.0	88.8
BIA[2]		50.0	90.3		56.0	89.1		55.0	89.6		63.0	88.8
BIA[3]		33.0	94.4		44.0	93.5		36.0	93.9		50.0	93.3

Abbreviations: FFM, Fat-free mass; BIA, Bioelectrical impedance analysis; DXA, Dual X-ray absorptiometry.
BIA[1]: manufacturer's equation; BIA[2]: Schol's equation; BIA[3]: Gray's equation.

analyses, particularly when participants with ankle edema were excluded (Fig. 1). Sensitivity analyses did not show substantial improvements in the ability of the BIA to detect changes in FFM (Table 3).

3.2. Changes in fat mass

During the 6-month follow up, mean ± SD change in FM_{DXA} was 0.6 ± 2.6 kg. BIA overestimated changes in FM by approximately 0.4−0.5 kg depending on equation, with intermediate correlation (Supplementary Table 1). FM_{BIA} could identify individuals with ≥5% loss in FM with acceptable precision, but not smaller losses or gain in FM (Supplementary Table 2). Sensitivity analyses excluding

participants with ankle edema and/or extreme BMI slightly improved the performance of FM_{BIA} (Supplementary Tables 1 and 2), particularly when participants with ankle edema were excluded.

4. Discussion

The results from this longitudinal study show that a single-frequency whole-body BIA device yields imprecise data on changes in FFM, regardless of equation. However, the BIA was able to identify those who had lost ≥5% of FFM with reasonable accuracy. The BIA showed poor performance in identifying gain in FFM or losses smaller than 5%. Since FFM loss around 5% is associated with increased mortality in CRC stage I-III [7], this degree of loss is

likely to be of clinical relevance in this population. However, BIA derived changes in FFM should be interpreted with caution at the individual level. Results for change in FM were similar to those of FFM, and should also be interpreted with caution.

In this group of predominantly well-nourished patients with CRC, correlation and concordance between change in FFM_{BIA} and FFM_{DXA} were moderate, with little improvement in sensitivity analyses. Very few studies have previously validated the ability of a whole-body single-frequency BIA to assess changes in body composition over time, compared to DXA. Similar to our findings, previous results show high imprecision of FFM_{BIA} to track changes at the individual level (limits of agreement of $\pm3{-}4$ kg) compared to DXA, in healthy subjects during loss [22] or gain [23] in FFM. Among obese individuals during weight loss, correlation between change in FFM_{BIA} and FFM_{DXA} was intermediate at r = 0.35, but varied greatly with DXA scanner [22]. A high concurrence (r = 0.84) between change in FFM_{BIA} and FFM_{DXA} has been observed in a small group of patients with head and neck cancer in recovery, despite wide limits of agreements in cross sectional analyses at both time points [24]. However, changes in FFM in the study were large at -2 kg (corresponding to -3.5%), compared to $+0.2$ kg in the current study. As the results of the current study show that BIA have higher validity in detecting losses, the large loss in FFM is a probable explanation for the disparate results.

Only small differences between the equations used to estimate FFM_{BIA} were found. The Schol's equation only slightly outperformed the equations by the manufacturer or Gray, with the highest concurrence with FFM_{DXA}. However, the differences were small, in particular in comparison with the manufacturer's equation. Thus, the relevance of the improvement in precision by opting for the equation by Schols instead of the manufacturer could be questioned.

The presence of ankle edema seemed to affect the estimation of FFM_{BIA}, more so than high BMI. Excluding individuals with ankle edema slightly improved the correlation and yielded somewhat narrower limits of agreement. Large alterations to hydration status such as ascites is known to affect the validity of BIA [16]. The current results indicate that also smaller shifts in hydration status affect the validity of BIA. FFM_{BIA} could be used to track group level changes in FFM, expressed as mean or median, when participants with ankle edema were excluded.

4.1. Limitations and strengths

This study has some limitations. Firstly, we used a single frequency BIA device, and our results cannot be generalized to multifrequency BIA devices. Secondly, the patients included in this study were generally well nourished and group level changes in both bodyweight and FFM were small. Strengths of this work include the assessment of ascites and ankle edema. In addition, standardized operation procedures for all measurements in the study likely minimized procedure related bias.

5. Conclusion

In conclusion, in a well-nourished population of non-metastatic CRC patients, a single-frequency whole-body BIA device yielded imprecise data on changes in FFM, regardless of equation. BIA is thus not a valid option for quantifying changes in FFM in individuals. However, BIA could be used to identify patients with loss in FFM $\geq5\%$ in this population. The validity of BIA to monitor changes in FFM warrants further investigation before implementation in clinical praxis.

Statement of authorship

ASK, MS and LB had the main responsibility for data analysis and writing the manuscript. RB, ASK, LB and MS, HBH contributed to the conception and the design of the validation study, analysis and interpretation of the data and drafting of the manuscript. ASK, LB, MS, HBH, AJS, CH, SKB, IP and HR contributed to acquisition of data. RB, HBH, CH, IP, SKB, SS and GW designed the CRC-NORDIET study, participated in the interpretation of results and critically revised the manuscript. All authors contributed to the writing and final approved the final manuscript.

Declaration of competing interest

Rune Blomhoff is a shareholder of Vitas, Oslo, Norway. The remaining authors declare that there are no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.09.021.

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