Clinical Nutrition ESPEN 43 (2021) 360–368

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Quantification of adipose tissues by Dual-Energy X-Ray Absorptiometry and Computed Tomography in colorectal cancer patients

Dena Helene Alavi [a, *], Hege Berg Henriksen [a], Peter Mæhre Lauritzen [b], Ane Sørlie Kværner [a, c], Tomas Sakinis [d], Torgrim Mikal Langleite [a], Christine Henriksen [a], Siv Kjølsrud Bøhn [e], Ingvild Paur [f], Gro Wiedswang [g], Sigbjørn Smeland [h, i], Rune Blomhoff [a, j]

[a] Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway
[b] Division of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway
[c] Section for Colorectal Cancer Screening, Cancer Registry of Norway, Oslo, Norway
[d] Medical Division, Radiology & Nuclear Medicine, Neuroimaging Research Group, Oslo University Hospital, Oslo, Norway
[e] Faculty of Chemistry, Biotechnology and Food Science, Norwegian University of Life Sciences, Ås, Norway
[f] Norwegian National Advisory Unit on Disease-Related Malnutrition, Oslo University Hospital, Oslo, Norway
[g] Department of Gastrointestinal Surgery, Oslo University Hospital, Ullevål, Norway
[h] Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway
[i] Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[j] Department of Clinical Service, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway

ARTICLE INFO

Article history:
Received 14 January 2021
Accepted 30 March 2021

Keywords:
Visceral adipose tissue
Adipose tissue
Inter- and intramuscular adipose tissue
Dual-energy X-ray absorptiometry
Computed tomography
Colorectal cancer

SUMMARY

Background & aims: Excess adipose tissue may affect colorectal cancer (CRC) patients' disease progression and treatment. In contrast to the commonly used anthropometric measurements, Dual-Energy X-Ray Absorptiometry (DXA) and Computed Tomography (CT) can differentiate adipose tissues. However, these modalities are rarely used in the clinic despite providing high-quality estimates. This study aimed to compare DXA's measurement of abdominal visceral adipose tissue (VAT) and fat mass (FM) against a corresponding volume by CT in a CRC population. Secondly, we aimed to identify the best single lumbar CT slice for abdominal VAT. Lastly, we investigated the associations between anthropometric measurements and VAT estimated by DXA and CT.

Methods: Non-metastatic CRC patients between 50-80 years from the ongoing randomized controlled trial CRC-NORDIET were included in this cross-sectional study. Corresponding abdominal volumes were acquired by Lunar iDXA and from clinically acquired CT examinations. Also, single CT slices at L2-, L3-and L4-level were obtained. Agreement between the methods was investigated using univariate linear regression and Bland–Altman plots.

Results: Sixty-six CRC patients were included. Abdominal volumetric VAT and FM measured by DXA explained up to 91% and 96% of the variance in VAT and FM by CT, respectively. Bland–Altman plots demonstrated an overestimation of VAT by DXA compared to CT (mean difference of 76 cm^3) concurrent with an underestimation of FM (mean difference of −319 cm^3). A higher overestimation of VAT ($p = 0.015$) and underestimation of FM ($p = 0.036$) were observed in obese relative to normal weight subjects. VAT in a single slice at L3-level showed the highest explained variance against CT volume ($R^2 = 0.97$), but a combination of three slices (L2, L3, L4) explained a significantly higher variance than L3 alone ($R^2 = 0.98$, $p < 0.006$). The anthropometric measurements explained between 31-65% of the variance of volumetric VAT measured by DXA and CT.

Conclusions: DXA and the combined use of three CT slices (L2-L4) are valid to predict abdominal volumetric VAT and FM in CRC patients when using volumetric CT as a reference method. Due to the poor

Abbreviations: CRC, colorectal cancer; DXA, Dual-Energy X-Ray Absorptiometry; CT, Computed Tomography; VAT, visceral adipose tissue; FM, fat mass; SAT, subcutaneous adipose tissue; IMAT, inter- and intramuscular adipose tissue; ISCD, International Society for Clinical Densitometry; PG-SGA, Patient-Generated Subjective Global Assessment.

* Corresponding author. Sognsvannsveien 9, Domus Medica, 0372 Oslo, Norway.
E-mail address: d.h.alavi@medisin.uio.no (D.H. Alavi).

https://doi.org/10.1016/j.clnesp.2021.03.022

performance of anthropometric measurements we recommend exploring the added value of advanced body composition by DXA and CT integrated into CRC care.

1. Introduction

Excess adipose tissue is an established risk factor for the development of colorectal cancer (CRC) [1,2], in addition to influence CRC prognosis [3,4] and treatment [5]. However, not all adipose tissues are alike as they have several structural and functional differences [6,7]. Visceral adipose tissue (VAT) is in general more metabolically active compared to subcutaneous adipose tissue (SAT) [8,9]. Also, inter- and intramuscular adipose tissue (IMAT) is associated with insulin resistance, loss of strength and mobility dysfunction [10,11]. After CRC surgery patients may experience a shift in body composition towards decreasing skeletal muscle mass and increasing amounts of adipose tissue [12]. Quantification of the individual's adipose tissues and muscle mass allows risk-stratification and personalized treatment [13,14].

Anthropometric measurements such as BMI are commonly used, but neither able to distinguish different adipose tissues from one another nor muscle [7]. Thus, appropriate clinical follow up of CRC patients calls for accurate tools that can monitor shifts in body composition, including different adipose tissues [12].

Advanced imaging methods like Computed Tomography (CT) and Dual-Energy X-Ray Absorptiometry (DXA) are examples of such tools. Abdominal CT is a part of standard oncological care, but is rarely used for body composition purposes in the clinic despite being considered a reference standard [15]. In research the assessment of adipose tissues by CT has typically been performed by a single lumbar slice and not by volumetric measures. This mainly due to the comprehensive post-processing in lack of automated quantifying software. Therefore, volumetric CT data consisting of multiple continuous single slices is, although considered a reference standard, unattainable in most settings. There is limited evidence on which lumbar landmark is superior for estimation of abdominal adipose tissues in a CRC population.

Although mainly used in research, DXA is a non-invasive, low-cost, and easily applicable method for studying body composition [15,16]. While CT provides three-dimensional imaging, DXA is two-dimensional [15]. Therefore, the DXA software uses geometrical assumptions to estimate VAT by subtracting the SAT layer from total fat mass (FM) in the abdominal area [17,18]. Due to the location of IMAT, deep to SAT, we hypothesize that DXA at least partly detect IMAT and misclassifies it as VAT. Following surgical resection, anatomical changes in CRC patients may challenge DXA's geometrical assumptions for distinguishing fat masses. Therefore, validation of DXA in a pure CRC population is necessary.

The aim of this study was to compare DXA's measurement of abdominal VAT and FM against a corresponding volume measured by CT in a CRC population. Secondly, we investigated the ability of single slices at the lumbar level (L2-L4) to predict abdominal volumetric VAT by CT (VAT_{CT}). Finally, we examined the association between anthropometric measurements (BMI, waist circumference, and waist/hip ratio) and abdominal VAT_{DXA} and VAT_{CT}.

2. Materials and methods

2.1. Subjects and inclusion criteria

A sub-population from the ongoing randomized controlled trial, CRC-NORDIET [19], was enrolled in the current cross-sectional study. The CRC-NORDIET study included patients, 50–80 years of age, who were diagnosed with CRC stage I-III and treated surgically [19]. The CRC patients could both have finished treatment or received adjuvant treatment at the time of inclusion. The baseline in the CRC-NORDIET study takes place two to nine months post-operatively and includes a DXA scan. CT scans are not performed in the CRC-NORDIET study, but are clinically acquired as a part of the routine six months post-operative follow up at the hospital. Inclusion in the current study required 1) participation at baseline in the CRC-NORDIET study and 2) a maximum of 45 days between the DXA scan conducted at baseline and the routine CT scan performed six months postoperatively. The time limit of 45 days was imposed to avoid substantial changes in body composition between DXA and CT scan.

2.2. DXA

DXA scans were obtained using Lunar iDXA (GE Healthcare Lunar, Buckinghamshire, UK) and the software enCORE ™ version 16 including the application CoreScan. Subjects were scanned at baseline in CRC-NORDIET by trained personnel and the scan was performed in line with the protocol of the International Society for Clinical Densitometry (ISCD) [20]. The system was calibrated daily prior to scans and subjects were fasting and wearing light clothing. The region-of-interest (hereafter referred to as the abdominal volume) was individually defined as 20% of the distance from the iliac crest towards the lowest point of the mandible (gnathion) (Fig. 1). Abdominal volumes of VAT, SAT and FM were retrieved from the DXA scans.

2.3. CT

Clinically indicated CT scans were acquired at Oslo University Hospital, Ullevål and Akershus University Hospital as part of the routine follow up six months after CRC surgery. From these CT scans we extracted image volumes corresponding to the individually DXA-defined abdominal volume (Fig. 1). These image volumes consisted of 29–35 consecutive 3 mm axial CT slices. In addition to the entire volume, single axial mid-vertebral CT slices were extracted at the 2nd, 3rd and 4th lumbar vertebrae (L2, L3, and L4).

2.3.1. Segmentation of CT slices

Segmentation of VAT, IMAT, SAT and SM in CT slices was performed (Fig. 1) with the sliceOmatic software package (v 5.0 rev. 7b, Tomovision, Magog, QC, Canada) in accordance with the Alberta protocol. Abdominal volumetric FM $_{CT}$ was defined as the sum of VAT_{CT}, $IMAT_{CT}$ and SAT_{CT}. An in-house software based on

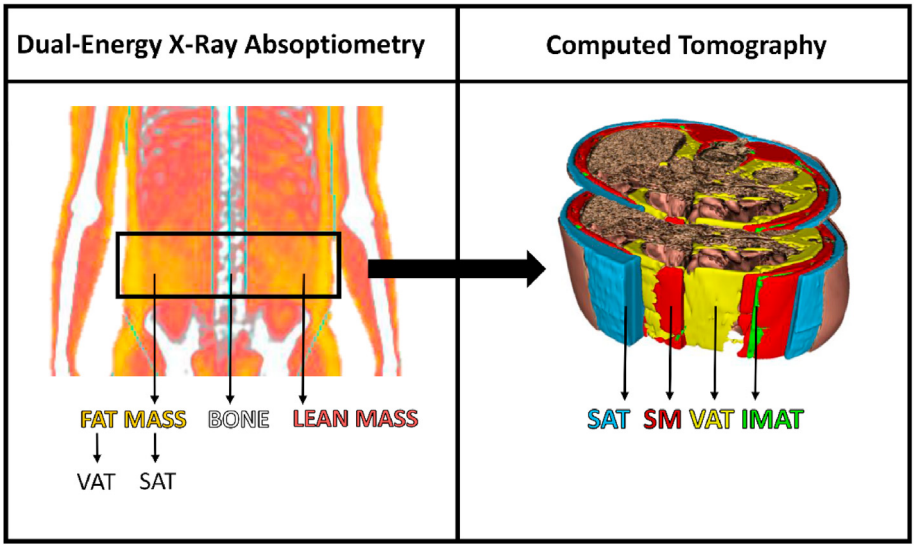

Fig. 1. An illustration of the various body compartments in the corresponding abdominal volume obtained by DXA (illustrated as the area inside the black rectangle) and CT, respectively. Abbreviations: DXA, Dual-Energy X-ray Absorptiometry; CT, Computed Tomography; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMAT, inter- and intramuscular adipose tissue; SM, skeletal muscle mass.

convolutional neural networks, BodySegAI, was used for automatic and more efficient segmentation process. Quality assurance with semi-manual corrections was conducted after segmentation by BodySegAI, as this software was under validation. All CT data were segmented by a single operator (DHA) under the supervision of an experienced radiologist (PML).

2.4. Anthropometric measurements

BMI, waist circumference and waist/hip ratio were performed in accordance with standardized protocols [19]. Data on self-reported weight change were obtained from the Patient-Generated Subjective Global Assessment (PG-SGA), a nutrition assessment tool validated for use in cancer patients [21,22]. Weight change data were only used for subjects that performed a CT scan prior to the DXA scan, as the PG-SGA is retrospective and was completed the same day as the DXA scan. Subjects with ≤7 days between the DXA- and CT scan were classified as weight stable, which was defined as alterations in weight less than ±1 kg.

2.5. Statistical analyses and sample size calculation

Data were analyzed using SPSS (IBM SPSS Statistics 25). Normality was checked by visual inspection of histograms and Q–Q plots and tested using the Shapiro–Wilk normality test. Characteristics of the study population are presented by median and percentiles (25^{th} and 75^{th}) and count (n) and percentage. Scatter plots with coefficients of determination (R^2) were constructed to examine the degree of covariance between fat masses estimated by DXA, CT and anthropometric measurements. To quantify potential differences between volumetric fat masses by DXA and CT, as well as visualize potential patterns in data, Bland–Altman plots with predetermined limits of agreement were created (mean difference±1.96xSD) [23]. Comparisons of VAT_{DXA} and VAT_{CT} were performed with and without the inclusion of $IMAT_{CT}$ in VAT_{CT} and tested using the Paired Samples T-test. The Mann–Whitney U-test with Bonferroni correction was used to examine differences between DXA and CT measurements across median VAT or BMI within the boxplots. The whiskers represents the minimum and maximum values (Q1/Q3 ± (1.5x interquartile range)). Regression equations and Pearson's correlation coefficients were provided for the associations. When predicting the difference between methods, the mean difference was expressed on the y-axis and mean VAT or BMI on the x-axis. Pairwise comparisons by Meng, Rosenthal, and Rubin were performed to examine the potential differences between correlations for the single slices [24]. Bonferroni corrections were applied. The sample size calculation was based on correlation coefficients from previous validation studies of VAT_{DXA} [2,18,25]. One-sided z-test for Fisher's z-transformation of r was used to calculate the sample size required for detecting a Pearson's correlation coefficient of r = 0.9 or higher, with a power of 0.8 and a significance level of alpha = 0.05. Assuming the true correlation was >0.95, a sample size of 51 subjects was sufficient.

2.6. Ethical statement

The CRC-NORDIET study was approved by the Regional Committees for Medical and Health Research Ethics (REC Protocol Approval 2011/836) and the data protection officials at Oslo University Hospital and Akershus University Hospital. The study is carried out in accordance with the Helsinki Declaration and informed consents were obtained from the participants. The CRC-NORDIET study is registered on the National Institutes of Health Clinical Trials (www.ClinicalTrials.gov; Identifier: NCT01570010).

3. Results

3.1. Patient characteristics

Hundred-and-thirty-five subjects were available at baseline in the CRC-NORDIET study. Fifty-two were excluded as they exceeded the 45 day limit between baseline DXA and postoperative CT scan. Another 17 subjects were excluded due to lack of CT-data in electronic patient records leaving a total of 66. Characteristics of the study population are shown in Table 1. The median age was 64 years, and the median BMI was 26.5 kg/m^2 for men and women combined. The median number of days between the CT and DXA scan was 17 days. Weight change data were available for 70% of the subjects, and most reported weight stability.

Table 1
The characteristics of study population.

	Total n = 66		Male n = 31		Female n = 35	
	Median	p25, p75	Median	p25, p75	Median	p25, p75
Age (y)	64.0	(61,68)	64.0	(61,68)	64	(60,71)
BMI (kg/m^2)	26.5	(23,29)	27.0	(25,30)	26.3	(23,30)
Weight (kg)	77.9	(69,93)	85.5	(77,99)	72.0	(66,81)
Waist circumference (cm)	94.1	(85,103)	98.5	(94,110)	86.5	(81,95)
Waist/hip ratio	0.9	(0.9,1.0)	1.0	(1.0,1.0)	0.9	(0.8,0.9)
VAT_{CT} (cm^3) [1]	994	(560,1786)	1754	(973,2454)	662	(423,1227)
VAT_{DXA} (cm^3) [1]	1230	(707,1996)	1706	(1082,2610)	769	(623,1310)
FM_{CT} (cm^3) [1]	2954	(2199,4255)	3361	(2669,4403)	2596	(1867,3501)
FM_{DXA} (cm^3) [1]	2511	(2005,3524)	2956	(2322,3766)	2378	(1782,3336)
$IMAT_{CT}$ (cm^3) [1]	102	(66,153)	102	(74,164)	102	(62,151)
Days between DXA and CT scan	16.5	(6,34)	14.0	(7,34)	19.0	(6,37)
Days between DXA scan and cancer operation	189	(154,221)	188	(152,211)	193	(176,226)
	n (%)		n (%)		n (%)	
Self-reported weight change [2]						
Reduced	0 (0)		0 (0)		0 (0)	
Stabile	38 (58)		15 (48)		23 (66)	
Increased	8 (12)		3 (10]		5 (14]	
Unknown	20 (30)		13 (42)		7 (20)	
Tumour localization						
C18 Colon	41 (62)		17 (55)		24 (69)	
C19 Rectosigmoid	5 (8)		4 (13)		1 (3)	
C20 Recti	20 (30)		10 (32)		10 (29)	
TNM stage						
I	14 (21)		8 (26)		6 (17)	
II	23 (35)		13 (42)		10 (29)	
III	29 (44)		10 (32)		19 (54)	
Received adjuvant chemotherapy	5 (8)		3 (10)		2 (6)	

Median and percentiles (25th, 75th), count (n) and percent of total (%) are presented. [1] Results given for the abdominal volume. [2] Weight change defined as ±1 kg one month before the DXA scan, information obtained from the PG-SGA. Abbreviations: VAT, visceral adipose tissue; CT Computed Tomography; DXA, Dual-Energy X-ray Absorptiometry; FM, fat mass; IMAT, inter- and intramuscular adipose tissue; TNM stage, tumour, node and metastasis stage.

3.2. Assessment of VAT and FM by DXA and CT

Scatter plots with coefficients of determination (R^2) and Bland–Altman plots of VAT_{DXA} against VAT_{CT} (excluding and including IMAT) are presented in Fig. 2. The coefficient of determination between abdominal volumetric VAT_{DXA} and VAT_{CT} was $R^2 = 0.89$ excluding IMAT, and $R^2 = 0.91$ IMAT included. The Bland–Altman plots demonstrated a mean overestimation of VAT_{DXA} compared to VAT_{CT} of 201 cm^3. The mean difference between methods was significantly reduced when including IMAT to VAT_{CT} in the comparison with VAT_{DXA} (from 201 cm^3 to 76 cm^3, $p < 0.001$). The Bland–Altman plots illustrated increased variation between the methods for VAT above 1000 cm^3.

Scatter plot and Bland–Altman plot for abdominal volumetric FM between DXA and CT is presented in Fig. 3. The coefficient of determination between methods was $R^2 = 0.96$. The Bland–Altman plot shows a mean underestimation by DXA of −319 cm^3 for abdominal underestimation with the increasing size of the FM compartment.

To examine whether DXA's accuracy for VAT and FM measurements was related to the level of body fatness, differences between DXA and CT were investigated across BMI and VAT categories (Fig. 4). Fig. 4A shows the difference between methods across VAT categories. There were no significant differences between groups (all p-values>0.05). Fig. 4B shows the difference between methods across BMI categories. DXA demonstrated a significantly higher overestimation of VAT in obese versus normal weight subjects (median and 25th,75th percentile: 397.0 cm^3 (120.2, 741.5) vs. 77.3 cm^3 (−116.7, 265.1), $p = 0.015$). Concurrently, an increased underestimation of FM was seen in obese versus normal weight subjects (median and 25th, 75th percentile: −426.8 cm^3 (−760.7, −173.6) vs. −128.2 (−300.1, −42.1), $p = 0.036$).

Linear regression analysis showed that with every 100 cm^3 increase in mean VAT (IMAT not included) the difference between DXA and CT increased with 16 cm^3 ($y = 17.39 + 0.16x$, $r = 0.44$, significant regression equation p-value<0.001). Regression equations for differences between methods for VAT (IMAT not included) and FM across BMI showed that for every unit increase in BMI, mean difference between DXA and CT increased with 31.8 cm^3 for VAT ($y = -663.5 + 31.8x$, $r = 0.45$, significant regression equation p-value<0.001), and −18.4 cm^3 for FM ($y = 180.2-18.4x$, $r = 0.30$, significant regression equation $p = 0.014$).

3.3. CT single slice predictions

Associations between measurements of VAT single slices against abdominal volumes by CT and DXA are presented in Table 2. Overall, the single slice at L3-level demonstrated the highest explained variance among the single slices against the corresponding abdominal volumetric alternative by CT and DXA ($R^2 = 0.87–0.97$). However, a combination of three slices at L2, L3-and L4-level demonstrated statistically significant higher explained variance ($R^2 = 0.90–0.98$) than from a single L3 slice ($p = 0.006$-<0.001 for all comparisons).

3.4. Anthropometric measurements

The relationships between BMI, waist circumference, and waist/hip ratio and abdominal volumes of VAT_{CT} and VAT_{DXA} are described in Fig. 5. BMI, waist circumference and waist/hip ratio explained 31, 64, and 52%, respectively of the variability in volumetric abdominal VAT_{CT}. Similarly, the anthropometric measurements described 39, 65 and 43%, respectively of the variability in abdominal volumetric VAT_{DXA}.

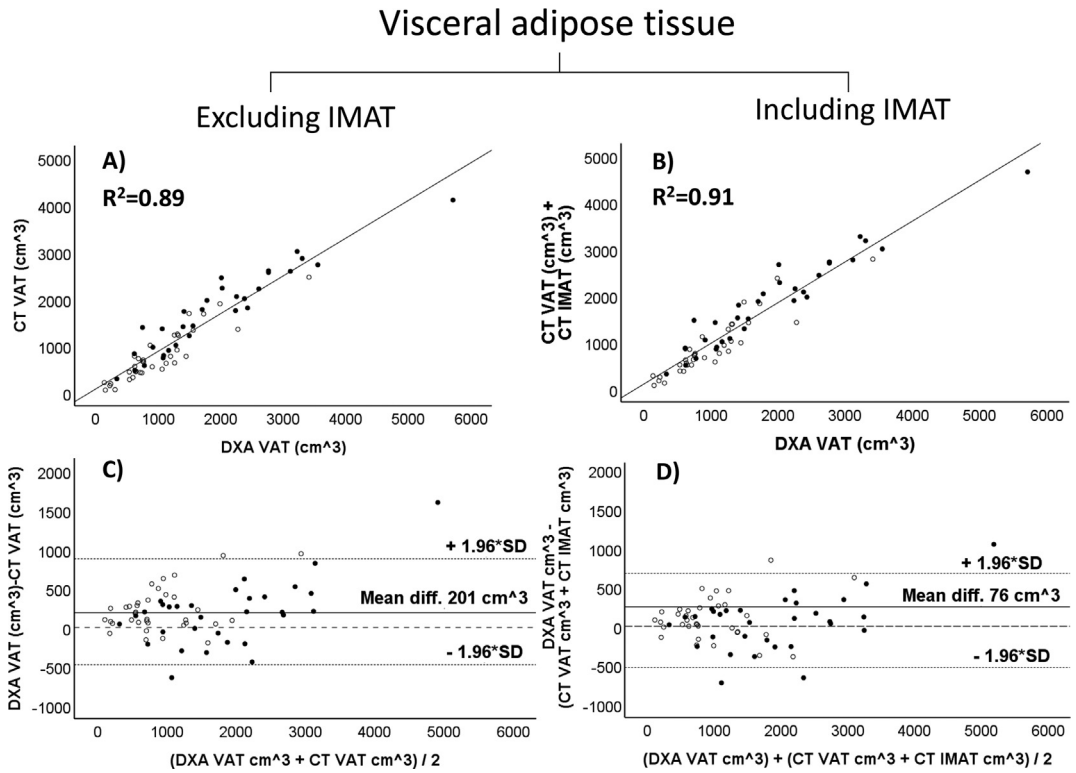

Fig. 2. Comparing DXA and CT in the assessment of abdominal volumetric VAT, excluding and including IMAT in scatter plots and Bland Altman plots. Men are annotated by black dots and females by white dots. In the Bland Altman plots the differences between methods are shown on the y-axis and mean VAT is on the x-axis. Abbreviations: VAT, visceral adipose tissue; IMAT, inter- and intramuscular adipose tissue, CT Computed Tomography; DXA, Dual-Energy X-ray Absorptiometry.

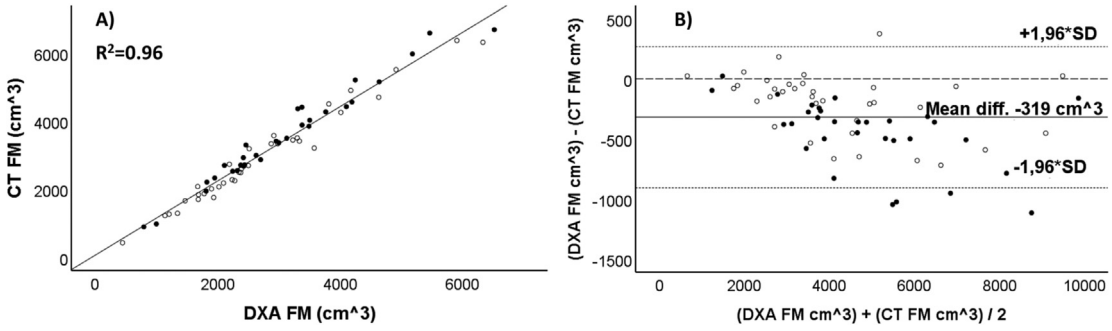

Fig. 3. Scatter plot with coefficient of determination (R^2) and a Bland–Altman plot comparing DXA and CT in the assessment of abdominal volumetric FM. Men are annotated by black dots and females by white dots. In the Bland-Altman plot, the differences between methods are shown on the y-axis and mean VAT on the x-axis. Abbreviations: CT, Computed Tomography; DXA, Dual-Energy X-ray Absorptiometry; FM, fat mass.

4. Discussion

The main finding of this study is that DXA is a valid tool for the measurement of abdominal volumetric VAT and FM in CRC patients compared to reference method CT. The difference between methods for VAT was 76 cm^3 including IMAT and 201 cm^3 excluding IMAT, which is small in relation to the total VAT in the subjects (i.e. median VAT_{DXA} is 1230 cm^3). The results are in line with similar validation studies in healthy subjects [2,18]. Coletta et al. conducted a validation study using cancer patients [26]. However, their results are not comparable to us as they used two different region-of-interests for VAT_{DXA} and VAT_{CT}, in contrast to the corresponding volumes in this study. In addition to high validity, DXA also need to be precise (provide high repeatability) [27]. A precision study conducted on the same Lunar iDXA machine with CRC patients revealed high precision (%CV = 3.56) and a least significant change in VAT of 149 cm^3. Values below 149 cm^3 can be attributed to measurement variability in the DXA machine itself rather than a systematic difference between DXA and CT [44]. Similarly, a mean difference of −319 cm^3 in FM is a small amount relative to the total abdominal FM (i.e. median FM_{DXA} is 2511 cm^3).

The degree of fatness may influence the validity of DXA. We observed a higher overestimation of VAT ($p = 0.015$) concurrent with an underestimation of FM ($p = 0.036$) in obese versus normal weight subjects by DXA. To demonstrate, the mean difference between methods (DXA minus CT) was 97 cm^3 and 337 cm^3 for subjects with low (500 cm^3) and high amounts (2000 cm^3) of VAT using the regression equations. A BMI of 23 and 30 kg/m^2 present a

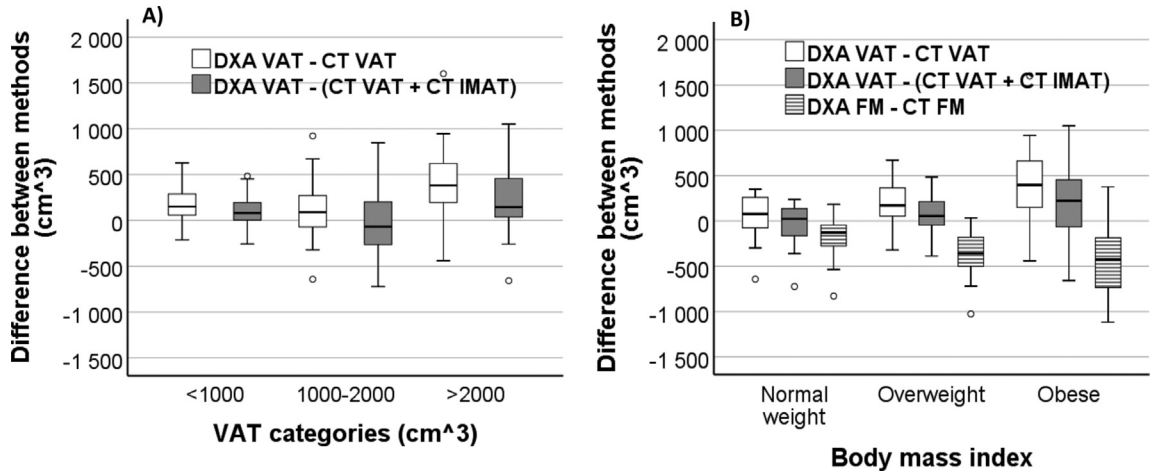

Fig. 4. Boxplots representing the differences between DXA and CT across groups. A) The difference between methods for the assessment of abdominal volumetric VAT (y-axis) across mean VAT categories (DXA VAT + CT VAT (+CT IMAT)/2 on x-axis). B) The difference between methods for the assessment of abdominal volumetric VAT and FM (on y-axis) stratified by WHO BMI categories (accordingly normal weight: 18.5–24.9 kg/m^2, overweight: 25.0–29.9 kg/m^2 and obese subjects: 30.0–34.9 kg/m^2) on the x-axis. Abbreviations: Dual-Energy X-ray Absorptiometry; VAT, visceral adipose tissue; CT, Computed Tomography; DXA; IMAT, inter- and intramuscular adipose tissue, FM, fat mass.

Table 2
Abdominal volumetric visceral adipose tissue versus single slice samples of body compartments with coefficients of determination (R^2).

Abdominal volumes vs. single slices	Level of CT single slice and slice combinations							
	L2	L3	L4	L2+L3	L2+L4	L3+L4	L2+L3+L4	p-value L3 vs. L2+L3+L4
n	65	66	46	65	45	46	45	
VAT_{CT} volume (cm^3) vs. VAT_{CT} single slice	0.94	0.97	0.94	0.97	0.97	0.97	0.98	0.006*
VAT_{DXA} volume (cm^3) vs. VAT_{CT} single slice	0.82	0.87	0.86	0.86	0.89	0.90	0.90	0.004*
VAT_{DXA} volume (cm^3) vs. VAT_{CT} + $IMAT_{CT}$ single slice	0.86	0.87	0.87	0.88	0.91	0.91	0.92	<0.001*

Abbreviations CT, Computed Tomography; VAT, visceral adipose tissue; DXA, Dual-Energy X-Ray Absorptiometry; IMAT, inter- and intramuscular adipose tissue. *p-value calculated by pairwise comparisons proposed by Meng, Rosenthal and Rubin.

difference between methods of 68 cm^3 and 291 cm^3 for VAT and −254 and −387 cm^3 for FM, respectively. Caution should therefore be taken when comparing subjects with very high and low amounts of VAT measured by DXA, as well as subjects in underweight or normal weight versus obese BMI groups. However, patients are rarely subject to extreme changes in BMI, even in the event of disease related malnutrition with 10% weight loss [28]. DXA can therefore safely be used in the follow-up of most patients in clinical practice.

Anthropometric measurements are not sensitive for determining the distribution of adipose tissues and muscle mass [7]. In this study, the anthropometric measurements described approximately half of the variation (31–65%) of volumetric VAT measured by DXA and CT. A study using similar instructions for WC and hip circumference measurement as us in obese and overweight patients showed that the mean difference in measurements between observers was not clinically significant [29]. We do not expect precision errors to influence our results. The risk of several cancers, cardiovascular diseases and other lifestyle-related conditions are generally found to be more associated with VAT than overall FM [30,31]. Therefore, we suggest looking beyond the commonly used anthropometric measurements like BMI. For instance, CT is integrated into cancer care for CRC patients. By using CT scans from electronic journals we can retrieve information about body composition without providing extra radiation exposure [15]. This is a unique opportunity to introduce more personalized treatment and follow-up on body composition in cancer care. In other patient groups without clinical CT data, we propose greater use of DXA. DXA is often available at hospitals as it is the main modality for diagnosis and management of osteoporosis [32], but is rarely in use for VAT or FM assessment. With DXA one can perform a whole-body scan, while whole-body estimates derived from single CT-slices usually require the use of prediction equations [33] which introduce additional uncertainty. Therefore, whole body measurement by DXA might be superior to estimates derived from a single CT slice, despite CT being described as more accurate than DXA [15]. In a clinical practice, both DXA and CT may contribute to the evaluation of nutritional status, tailoring of nutritional support or intervention [32,34] optimizing treatment [13,35] and may influence survival [4,5].

In this study we compared DXA and CT's quantification of VAT, with and without the inclusion of IMAT. There are several reasons why IMAT might partly be included in DXA's estimate of VAT. First, DXA can differentiate FM and lean fractions in areas where bone is not present [16,36]. In a whole-body scan, bones are present in 30–45% of the pixels [37,38]. In the abdominal volumes applied in the current study even less bone is present, as only the spine is displayed. Secondly, DXA does not segment or classify IMAT separately, but it is most likely included in other DXA measures of adipose tissue. The DXA software identify VAT by subtracting SAT from total FM in the android region [17,18,39]. We propose that DXA detect IMAT at some extent and embed this

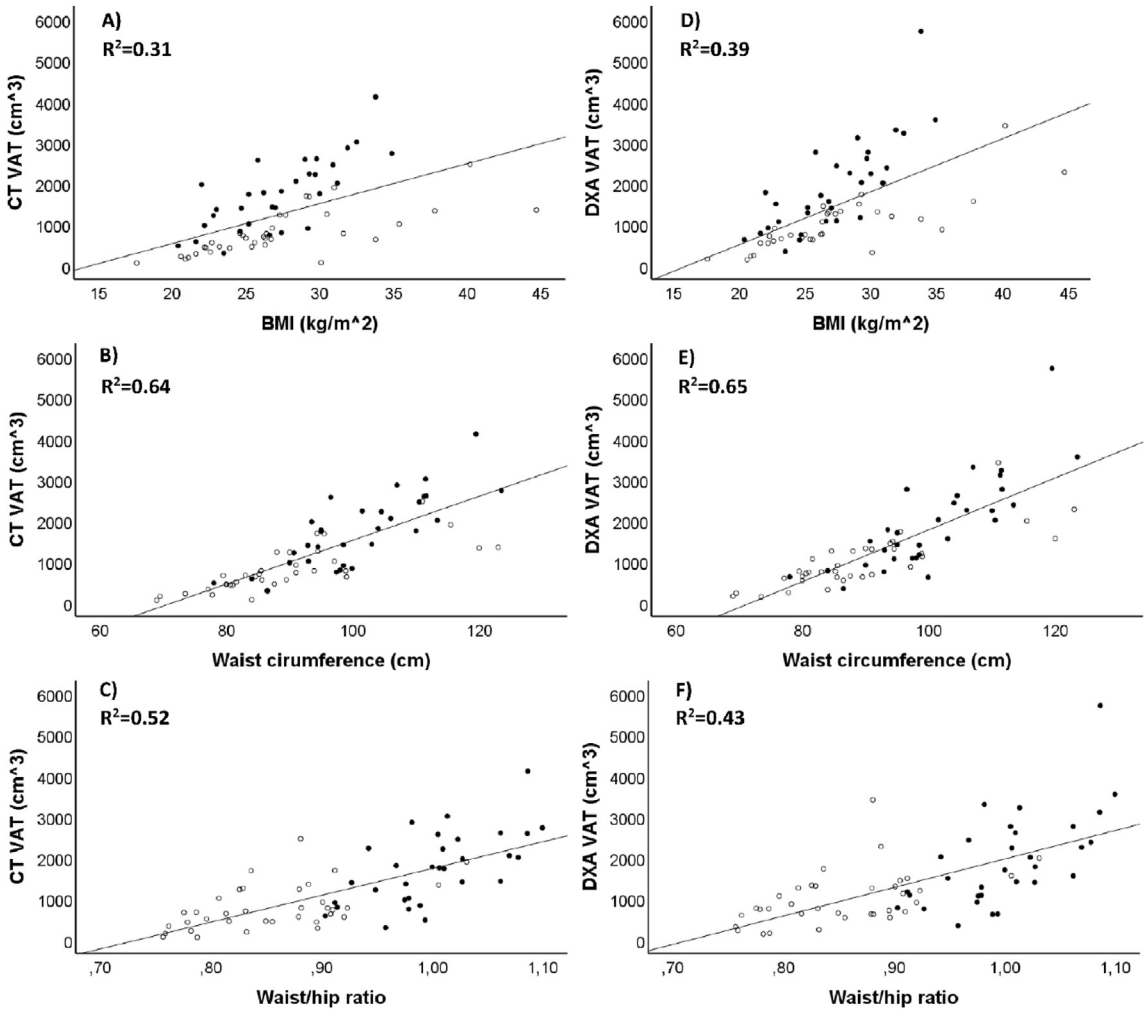

Fig. 5. Coefficient of determination (R^2) between the BMI, waist circumference and waist/hip ratio and abdominal volumetric VAT_{CT} (A–C) and VAT_{DXA} (D–F). Men are annotated by black dots and females by white dots. Abbreviations: CT Computed Tomography; VAT, visceral adipose tissue; DXA, Dual-Energy X-Ray Absorptiometry.

adipose tissue within VAT. This is supported by the increased explained variance (from 89% to 91%) and less mean difference between the methods (from 201 cm^3 to 76 cm^3, $p < 0.001$) when adding $IMAT_{CT}$ to VAT_{CT} in the comparison against VAT_{DXA}. Thus, we assume that it is likely that DXA detects parts of IMAT, especially in individuals in which fat has replaced large amounts of muscle. However, more research such as cadaver and phantom studies is needed to confirm this hypothesis, and quantify the exact amounts of IMAT that is detected by DXA.

VAT measurements obtained by CT have typically been derived from a single slice. This is due to time-consuming segmentation in lack of a quantifying software [33,40]. We showed that a single slice at the L3-level was superior across the lumbar slices (explained 87–97% of volumes), similar to results from other studies [41,42]. However, the combination of three slices at L2, L3, and L4-level demonstrated significantly better explained variance (explained 90–98% of volumes) than a single L3 slice alone ($p < 0.006$ for all comparisons). Accordingly, future body composition measurement by CT should aim against using multiple slices or volumetric approaches. This requires automatic software, which will be one of our next objectives. Until then, we suggest the combination of three slices at different lumbar localizations (L2, L3, L4). This will manage the shortcomings of the single slice approach while reducing the labour-intensive work of acquiring volumetric CT data in a non-automatic manner.

The time-frame between the scans is a limitation of this study, and we cannot rule out changes in the patient's body composition in the days between the DXA and CT scan. However, additional analysis showed that time did not statistically impact the difference between methods in a univariate regression model (data not shown). Only five out of 66 patients received chemotherapy and most of the patients reported no weight change. Also, our population with TNM I-III can be considered quite stabile compared to patients with more advanced CRC. The CT segmentation was performed by a single operator and followed the established Alberta protocol. A previous study demonstrated low level of operator dependability for CT body composition segmentation which suggest that our results are reproducible [43]. Strengths of this study includes the archived power of 80%, according to our sample size estimation. As far as we know, this is the first study to investigate corresponding volumes of VAT and abdominal FM from DXA and CT in a pure CRC population.

We conclude that DXA and the combined use of three lumbar CT slices (L2-L4) are valid tools for the estimation of abdominal VAT and FM in CRC patients, when using volumetric CT as reference method. We suggest further exploration of the increased use of

DXA and CT in standard cancer care as this may add great clinical value.

Statement of authorship (CRediT)

Dena Helene Alavi: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Roles/Writing - original draft, Writing - review & editing, Hege Berg Henriksen: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing - review & editing. Peter Mæhre Lauritzen: Conceptualization, Data curation, Investigation, Methodology, Project administration; Resources, Supervision, Validation, Writing - review & editing. Ane Sørlie Kværner: Conceptualization, Data curation, Investigation, Supervision, Writing - review & editing. Tomas Sakinis: Data curation, Resources, Software. Torgrim Mikal Langleite: Project administration, Data curation, Resources, Writing - review & editing. Christine Henriksen: Conceptualization, Writing - review & editing. Siv Kjølsrud Bøhn: Conceptualization, Project administration (of the CRC-NORDIET study), Writing - review & editing. Ingvild Paur: Conceptualization, Project administration (of the CRC-NORDIET study), Writing - review & editing. Gro Wiedswang: Conceptualization, Resources, Writing - review & editing. Sigbjørn Smeland: Conceptualization, Resources, Writing - review & editing. Rune Blomhoff: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Writing - review & editing.

Funding sources

This project has received funding from the Throne Holst Nutrition Research Foundation, Norwegian Cancer Society, South Eastern Norway Regional Health Authority.

Declaration of competing interest

RB is a shareholder of AS Vitas. All the other authors declares no conflict of interests.

References

[1] World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report, revised 2018. Diet, nutrition, physical activity and colorectal cancer. 2017. Accessed 12.01.20 at dietandcancerreport.org.
[2] Lin H, Yan H, Rao S, Xia M, Zhou Q, Xu H, et al. Quantification of visceral adipose tissue using lunar dual-energy X-ray absorptiometry in Asian Chinese. Obesity 2013;21(10):2112–7.
[3] Kim B, Kim BC, Nam SY, Nam JH, Ryu KH, Park BJ, et al. Visceral adipose tissue volume and the occurrence of colorectal adenoma in follow-up colonoscopy for screening and surveillance. Nutr Canc 2017;69(5):739–45.
[4] Xiao J, Mazurak VC, Olobatuyi TA, Caan BJ, Prado CM. Visceral adiposity and cancer survival: a review of imaging studies. Eur J Canc Care 2018;27(2):e12611.
[5] Lee CS, Murphy DJ, McMahon C, Nolan B, Cullen G, Mulcahy H, et al. Visceral adiposity is a risk factor for poor prognosis in colorectal cancer patients receiving adjuvant chemotherapy. J Gastrointest Canc 2015;46(3):243–50.
[6] Arner P. Not all fat is alike. Lancet 1998;351(9112):1301–2.
[7] World Cancer Research Fund/American Institute for Cancer Research. reportContinuous Update Project Expert Report 2018. Body fatness and weight gain and the risk of cancer. (Accessed 25.02.20 at dietandcancerreport.org).
[8] Ibrahim MM. Subcutaneous and visceral adipose tissue: structural and functional differences. Obes Rev 2010;11(1):11–8.
[9] Lee SW, Son JY, Kim JM, Hwang SS, Han JS, Heo NJ. Body fat distribution is more predictive of all-cause mortality than overall adiposity. Diabetes Obes Metabol 2018;20(1):141–7.
[10] Addison O, Marcus RL, Lastayo PC, Ryan AS. Intermuscular fat: a review of the consequences and causes. Internet J Endocrinol 2014;2014:309570.
[11] Waters DL. Intermuscular adipose tissue: a brief review of etiology, association with physical function and weight loss in older adults. Ann Geriatr Med Res 2019;23(1):3–8.
[12] Hopkins JJ, Reif R, Bigam D, Baracos VE, Eurich DT, Sawyer MM. Change in skeletal muscle following resection of stage I-iii colorectal cancer is predictive of poor survival: a cohort study. World J Surg 2019;43(10):2518–26.
[13] Malietzis G, Aziz O, Bagnall NM, Johns N, Fearon KC, Jenkins JT. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. Eur J Surg Oncol 2015;41(2):186–96.
[14] Malietzis G, Currie AC, Athanasiou T, Johns N, Anyamene N, Glynne-Jones R, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. Br J Surg 2016;103(5):572–80.
[15] Yip C, Dinkel C, Mahajan A, Siddique M, Cook GJ, Goh V. Imaging body composition in cancer patients: visceral obesity, sarcopenia and sarcopenic obesity may impact on clinical outcome. Insights Imaging 2015;6(4):489–97.
[16] Plank LD. Dual-energy X-ray absorptiometry and body composition. Curr Opin Clin Nutr Metab Care 2005;8(3):305–9.
[17] Ergun DL, Rothney MP, Oates MK, Xia Y, Wacker WK, Binkley NC. Visceral adipose tissue quantification using Lunar Prodigy. J Clin Densitom 2013;16(1):75–8.
[18] Kaul S, Rothney MP, Peters DM, Wacker WK, Davis CE, Shapiro MD, et al. Dual-energy X-ray absorptiometry for quantification of visceral fat. Obesity 2012;20(6):1313–8.
[19] 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. Br J Canc 2017;17(1):83.
[20] Hangartner TN, Warner S, Braillon P, Jankowski L, Shepherd J. The Official Positions of the International Society for Clinical Densitometry: acquisition of dual-energy X-ray absorptiometry body composition and considerations regarding analysis and repeatability of measures. J Clin Densitom 2013;16(4):520–36.
[21] Jager-Wittenaar H, Ottery FD. Assessing nutritional status in cancer: role of the patient-generated subjective global assessment. Curr Opin Clin Nutr Metab Care 2017;20(5):322–9.
[22] Patient-generated subjective global assessment. (Accessed 15.02.20 at http://pt-global.org/).
[23] Giavarina D. Understanding Bland altman analysis. Biochem Med 2015;25(2):141–51.
[24] Meng X-l, Rosenthal R, Rubin DB. Comparing correlated correlation coefficients. Phychol Bull 1992;111(1):172–5.
[25] Choi YJ, Seo YK, Lee EJ, Chung YS. Quantification of visceral fat using dual-energy x-ray absorptiometry and its reliability according to the amount of visceral fat in Korean adults. J Clin Densitom 2015;18(2):192–7.
[26] Coletta AM, Klopp AH, Fogelman D, Parikh AM, Li Y, Garg N, et al. Dual-Energy X-ray absorptiometry compared to computed tomography for visceral adiposity assessment among gastrointestinal and pancreatic cancer survivors. Sci Rep 2019;9(1):11500.
[27] Bland JM, Altman DG. Measuring agreement in method comparison studies. Stat Methods Med Res 1999;8(2):135–60.
[28] 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(3):335–40.
[29] Sebo P, Herrmann FR, Haller DM. Accuracy of anthropometric measurements by general practitioners in overweight and obese patients. BMC Obes 2017;4:23.
[30] Neeland IJ, Ross R, Després JP, Matsuzawa Y, Yamashita S, Shai I, et al. Visceral and ectopic fat, atherosclerosis, and cardiometabolic disease: a position statement. Lancet Diabetes Endocrinol 2019;7(9):715–25.
[31] Bardou M, Barkun AN, Martel M. Obesity and colorectal cancer. Gut 2013;62(6):933–47.
[32] Thibault R, Pichard C. The evaluation of body composition: a useful tool for clinical practice. Ann Nutr Metab 2012;60(1):6–16.
[33] Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metabol 2008;33(5):997–1006.
[34] Thibault R, Genton L, Pichard C. Body composition: why, when and for who? Clin Nutr 2012;31(4):435–47.
[35] Kværner AS, Harnæs H, Alavi DH, Bärebring L, Henriksen HB, Guren MG, et al. Should calculation of chemotherapy dosage for bowel cancer be based on body composition? Tidsskr Nor Laegeforen 2020;140(8).
[36] Toombs RJ, Ducher G, Shepherd JA, De Souza MJ. The impact of recent technological advances on the trueness and precision of DXA to assess body composition. Obesity 2012;20(1):30–9.
[37] Laskey MA. Dual-energy X-ray absorptiometry and body composition. Nutrition 1996;12(1):45–51.
[38] Bazzocchi A, Ponti F, Albisinni U, Battista G, Guglielmi G. DXA: technical aspects and application. Eur J Radiol 2016;85(8):1481–92.
[39] Micklesfield LK, Goedecke JH, Punyanitya M, Wilson KE, Kelly TL. Dual-energy X-ray performs as well as clinical computed tomography for the measurement of visceral fat. Obesity 2012;20(5):1109–14.
[40] Tchernof A, Despres JP. Pathophysiology of human visceral obesity: an update. Physiol Rev 2013;93(1):359–404.
[41] Irlbeck T, Massaro JM, Bamberg F, O'Donnell CJ, Hoffmann U, Fox CS. Association between single-slice measurements of visceral and abdominal

subcutaneous adipose tissue with volumetric measurements: the Framingham Heart Study. Int J Obes 2010;34(4):781–7.
[42] Faron A, Luetkens JA, Schmeel FC, Kuetting DLR, Thomas D, Sprinkart AM. Quantification of fat and skeletal muscle tissue at abdominal computed tomography: associations between single-slice measurements and total compartment volumes. Abdom Radiol 2019; 44(5):1907–16.
[43] Kjønigsen LJ, Harneshaug M, Fløtten A-M, Karterud LK, Petterson K, Skjolde G, et al. Reproducibility of semiautomated body composition segmentation of abdominal computed tomography: a multiobserver study. Eur Radiol Exp 2019;3(1):42.
[44] Henriksen HB. Precision of Lunar Dual-Energy X-ray Absorptiometry (iDXA) in measuring body composition among Norwegian colorectal cancer patients and healthy subjects. Clin Nutrn ESPEN. Submitted.