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Original article

Contrast-enhancement influences skeletal muscle density, but not skeletal muscle mass, measurements on computed tomography

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SUMMARY

Background & aims: Low skeletal muscle mass and density have recently been discovered as prognostic and predictive parameters to guide interventions in various populations, including cancer patients. The gold standard for body composition analysis in cancer patients is computed tomography (CT). To date, the effect of contrast-enhancement on muscle composition measurements has not been established. The aim of this study was to determine the effect of contrast-enhancement on skeletal muscle mass and density measurements on four-phase CT studies.

Design: In this observational study, two observers measured cross-sectional skeletal muscle area corrected for patients' height (skeletal muscle index [SMI]) and density (SMD) at the level of the third lumbar vertebra on 50 randomly selected CT examinations with unenhanced, arterial, and portal-venous phases. The levels of agreement between enhancement phases for SMI and SMD were calculated using intra-class correlation coefficients (ICCs).

Results: Mean SMI was 42.5 (±9.9) cm^2/m^2 on the unenhanced phase, compared with 42.8 (±9.9) and 43.6 (±9.9) cm^2/m^2 for the arterial and portal-venous phase, respectively (both $p < 0.01$). Mean SMD was lower for the unenhanced phase (30.9 ± 8.0 Hounsfield units [HU]) compared with the arterial (38.0 ± 9.9 HU) and portal-venous (38.7 ± 9.2 HU) phase (both $p < 0.001$). No significant difference was found between SMD in the portal-venous and arterial phase ($p = 0.161$). The ICCs were excellent (≥0.992) for all SMIs and for SMD between the contrast-enhanced phases (0.949). The ICCs for the unenhanced phase compared with the arterial (0.676) and portal-venous (0.665) phase were considered fair to good.

Conclusions: Statistically significant differences in SMI were observed between different enhancement phases. However, further work is needed to assess the clinical relevance of these small differences. Contrast-enhancement strongly influenced SMD values. Studies using this measure should therefore use the portal-venous phase of contrast-enhanced CT examinations.

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1. Introduction

The involuntary loss of skeletal muscle mass, quality and function is considered to be a result of aging (i.e. sarcopenia), or as part of muscle wasting syndromes (i.e. cancer cachexia, chronic diseases, bed rest) [1–3]. Low skeletal muscle mass has recently been identified as a prognostic factor for treatment outcome and survival in various populations, such as in cancer and liver transplant

Abbreviations: HU, Hounsfield units; ICC, intraclass correlation coefficient; SDC, smallest detectable change; SEM, standard error of the measurement.

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patients [4,5]. Furthermore, it is associated with an increased risk of postoperative complications, chemotherapy toxicity and increased hospital expenditure [4,6–8]. Low skeletal muscle density, a measure for intramuscular adipose content, has recently been described as a risk factor for mortality in patients with lymphoma, melanoma, metastatic renal cell carcinoma, pancreatic carcinoma, and metastatic gastric cancer [9–13]. Body composition measures may guide future interventions to manage skeletal muscle wasting and to increase patients' resistance towards stressors, such as surgery and chemotherapy [14].

The gold standard and most used modality to assess body composition is computed tomography (CT) due to its wide availability, especially in cancer patients [15–17]. Excellent inter-observer and intra-observer agreement, as well as excellent comparability of various commonly used software programs for skeletal muscle mass measurement have previously been described [18]. However, the effect of contrast-enhancement on skeletal muscle mass and density measurements remains unclear. It is well-known that contrast-enhancement may influence tissue attenuation [19] and may consequently influence skeletal muscle mass and density measurements. Nevertheless, various enhancement phases have been used in studies that investigated the association between CT-assessed skeletal muscle mass and density and outcome measures [9–12,20]. Therefore, the aim of this study was to compare skeletal muscle mass and density measurements on CT between different contrast-enhancement phases.

2. Materials and methods

2.1. Patients

A total of 50 patients with cancer or evaluated for liver transplantation in Erasmus MC University Medical Center between 2009 and 2015 with available multiphase (unenhanced, arterial, portal-venous) abdominal CT examinations were randomly selected retrospectively. Patients with CTs on which part of the cross-sectional skeletal muscle area was not depicted (e.g. due to obesity) or with artefacts (e.g. due to prostheses) were excluded. Date of birth, sex, body weight, and body height were collected from the electronic patient files within a month of the CT- examination. Body mass index (BMI) was calculated and patients were categorized as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9) or obese (BMI ≥30.0) according to the World Health Organization (WHO) definitions [21]. Approval from the local medical ethical committee was obtained and the study has been performed according to the 1964 Declaration of Helsinki and its later amendments.

2.2. CT scanning protocol

All CT examinations were performed according to a standardized protocol. First, an unenhanced phase was obtained. Afterwards, intravenous (IV) contrast administration in an antecubital vein followed by saline flush of 20 ml was performed using a power injector. The contrast material used was Visipaque 320 mgI/ml (GE Healthcare, Cork, Ireland), adapted to a patient's body weight. Patients with body weight <80 kg received 120 ml contrast medium, whereas patients with body weight ≥80 kg received 150 ml contrast medium. Phases acquired were the arterial phase, determined using a bolus-tracking technique, followed by the portal-venous phase acquired 70 s after contrast administration. For the arterial phase, a region of interest (ROI) was placed in the upper abdominal aorta; when the threshold of +100 HU was reached, scanning started with a delay of 15 s. Estimated time after administration of the bolus was 30–35 s for the arterial phase. The portal-venous phase was obtained with a fixed delay of 70 s after administration of the contrast material. Axial reconstructions were created with a slice thickness of 3 mm in all phases. No adverse reactions were noted during contrast administration. All images were transferred to our local picture archiving and communication system (PACS).

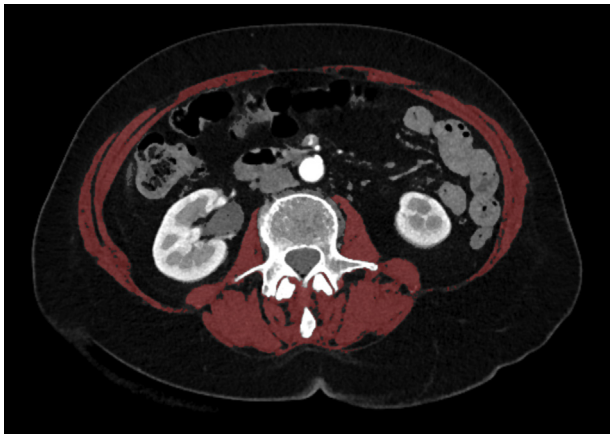

Fig. 1. Example of skeletal muscle mass and density measurement on a contrast-enhanced CT slice in the portal-venous phase at the level of the third lumbar vertebra (L3). The cross-sectional skeletal muscle area of this 71-year-old woman with a body mass index of 24.7 kg/m^2 was 95.6 cm^2, resulting in a skeletal muscle index of 33.1 cm^2/m^2. The mean skeletal muscle attenuation was 33 Hounsfield units. According to the cut-off values of Martin et al. [24], this patient is considered to have both sarcopenia and low skeletal muscle density.

An experienced abdominal radiologist (FEJAW) confirmed the different phases of contrast-enhancement per patient. Furthermore, the mean intraluminal attenuation (in HU) of the aorta was measured for every phase per patient.

2.3. Skeletal muscle mass and density measurements

The cross sectional muscle area (CSMA) was measured at the level of the third lumbar vertebra for the various contrast-enhancement phases (i.e. unenhanced, arterial, portal-venous).

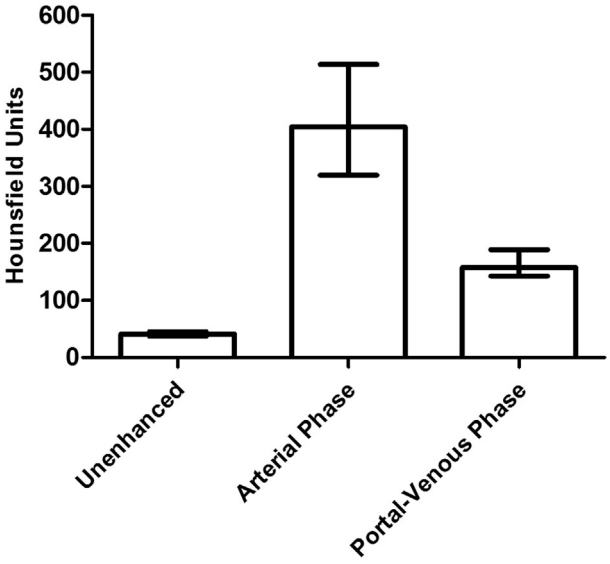

Fig. 2. Median intraluminal aorta attenuation per contrast-enhancement phase. The whiskers represent the interquartile range.

Table 1
Differences in skeletal muscle mass and skeletal muscle density measurements using unenhanced, arterial, and portal-venous phases on CT.

	Skeletal muscle area (cm^2)					Skeletal muscle mass (cm^2/m^2)					Skeletal muscle density (HU)				
	Mean difference (cm^2)	p-Value	ICC	SEM (cm^2)	SDC (cm^2)	Mean difference (cm^2/m^2)	p-Value	ICC	SEM (cm^2/m^2)	SDC (cm^2/m^2)	Mean difference (HU)	p-Value	ICC	SEM (HU)	SDC (HU)
Unenhanced – arterial phase	−0.9	0.011	0.997 (0.994–0.998)	0.14	0.38	−0.3	0.007	0.996 (0.992–0.998)	0.05	0.14	−7.2	<0.001	0.676 (−0.077–0.896)	2.42	6.72
Unenhanced – portal-venous phase	−3.1	<0.001	0.994 (0.778–0.999)	0.15	0.42	−1.1	<0.001	0.992 (0.743–0.998)	0.06	0.17	−7.8	<0.001	0.665 (−0.059–0.903)	1.83	5.06
Arterial phase – portal-venous phase	−2.2	<0.001	0.996 (0.953–0.999)	0.12	0.35	−0.7	<0.001	0.995 (0.940–0.999)	0.05	0.13	−0.6	0.161	0.949 (0.911–0.971)	0.68	1.90

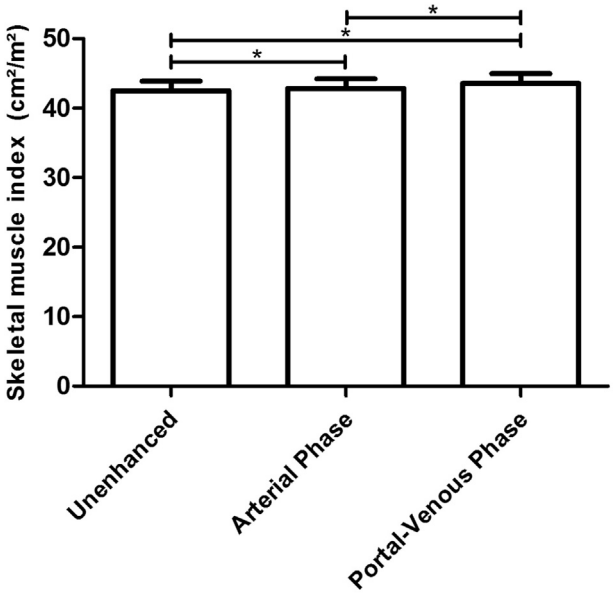

Fig. 3. Mean skeletal muscle index per contrast-enhancement phase. The whiskers represent the standard error of the mean. * indicates statistically significant difference.

The selected slice was the one on which both transversal processes were visible. Two observers (HJWS and KMV) who were blinded for patient characteristics performed all measurements as previously described [22]. An in-house developed software program (FatSeg, developed by the Biomedical Imaging Group Rotterdam of Erasmus MC, Rotterdam, The Netherlands, using MeVisLab [Mevis Medical Solutions, Bremen, Germany]) was used (Fig. 1). A previous study indicated excellent comparability between this and other frequently used software programs (i.e. sliceOmatic, OsiriX, and ImageJ) for body composition analyses [23]. The inner and outer contours of the CSMA (including the psoas, rectus abdominis, transversus abdominis, internal and external abdominal oblique muscles) were manually outlined and the tissue within the threshold of −30 to +150 Hounsfield units (HU) was selected. CSMA was corrected for patients' body height squared, as is common for body composition measures, resulting in the skeletal muscle index (SMI, cm^2/m^2). The mean HU value was recorded as a measure of skeletal muscle density. Low skeletal muscle mass was defined using previously described cut-off values: skeletal muscle index <41 cm^2/m^2 for women regardless of BMI, and <43 and <53 cm^2/m^2 for men with BMI <25.0 and ≥25.0 kg/m^2, respectively. The definition for low skeletal muscle density was identical for men and women: a skeletal muscle attenuation <41 for patients with BMI <25.0 kg/m^2 and <33 for patients with BMI ≥25.0 kg/m^2 [24].

2.4. Statistical analysis

Normality of data was tested using the Shapiro–Wilk test. Continuous data are presented as median with interquartile range (IQR) or mean with standard deviation (SD ±), depending on the normality of distribution. Categorical data are presented as counts with percentages. Differences between the different contrast-enhancement phases were tested using a paired t-test or Wilcoxon signed rank test, again depending on the normality of the distribution of the data. The agreement between observers (i.e. inter-observer agreement) and between contrast-enhancement phases (i.e. inter-enhancement phase agreement) were calculated using intra-class correlation coefficients (ICCs) with 95% confidence intervals (CIs) using a two-way mixed single measures model with

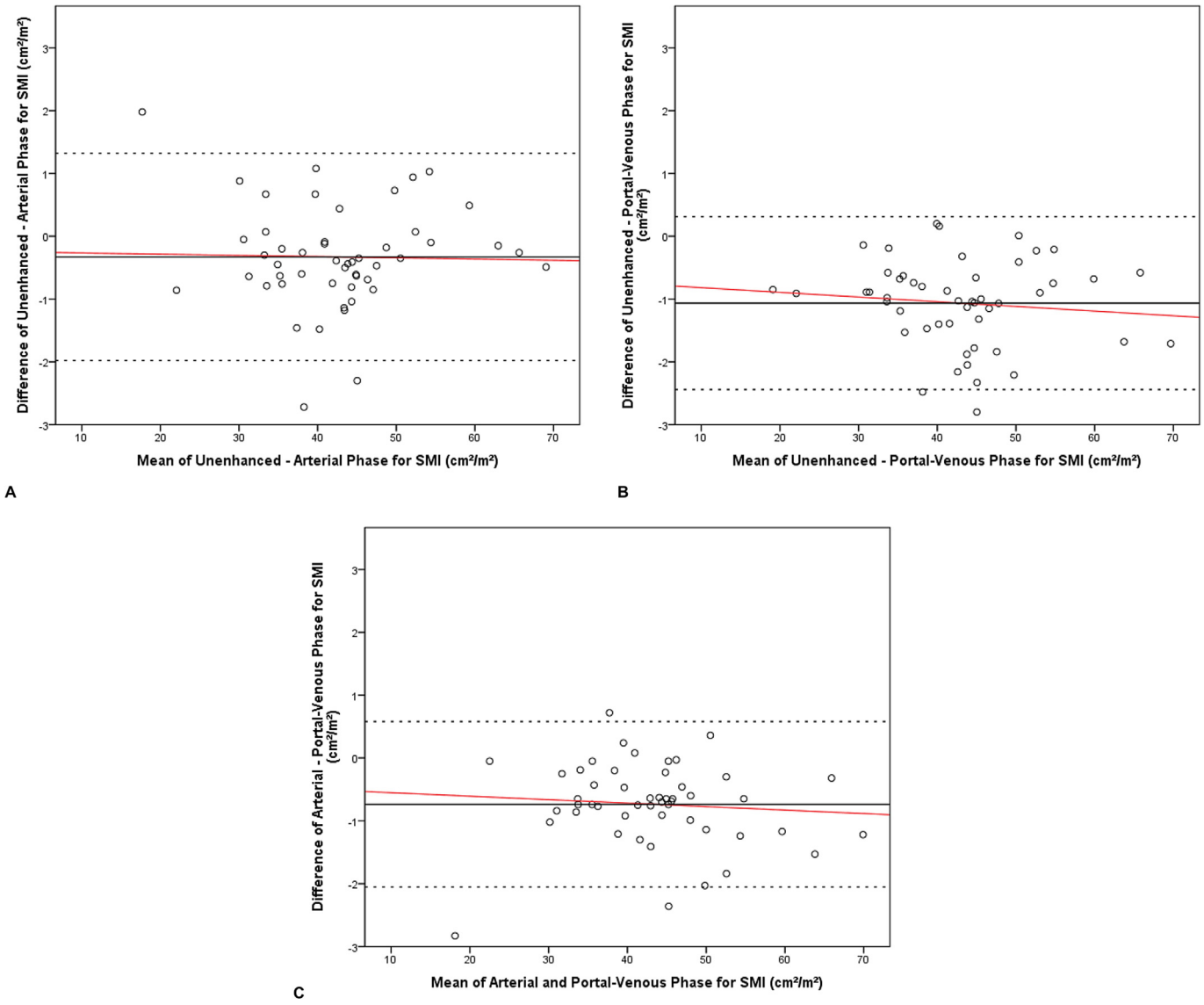

Fig. 4. Bland Altman plots with 95% limits of agreement for the comparison of the cross sectional muscle area (SMI in cm^2/m^2) of the unenhanced with arterial phase (A), unenhanced with the portal-venous phase (B) and arterial with the portal-venous phase (C). The solid black line represents the mean difference, the striped lines represent the mean ± 1.96 standard deviations, and the red line represents the regression slope. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

absolute agreement. Bland and Altman plots with 95% CI were generated to investigate the agreement between contrast-enhancement phases [25]. Linear regression was used to test for proportional systematic bias [26]. Smallest detectable changes (SDC), expressing the smallest detectable difference considered a "real" change in paired measures, were calculated for both skeletal muscle mass and density for the different contrast-enhancement phases using the following formula:

$$Change\,[in\,skeletal\,muscle\,mass\,or\,density] \pm \left(1.96 \times \frac{SEM\,change}{\sqrt{k}}\right),$$

in which k is the number of measurements and SEM stands for standard error of the measurement [27]. The SEM is calculated using the following formula:

$$Standard\ Deviation\ [SD]\ \times\ \sqrt{1 - ICC}.$$

The agreement on sarcopenia assessment between observers and contrast-enhancement phases was calculated using Cohen's κ coefficients. ICCs and Cohen's κ's ranging from 0.00 to 0.49 were interpreted was poor, whereas coefficients ranging from 0.50 to 0.74 and 0.75 to 1.00 were interpreted as fair to good and excellent, respectively [28].

The average of the two measurements by the two observers was used. Two-sided p-values <0.05 were considered statistically

Table 2
Cohen's κ's for the assessment of low skeletal muscle mass and low skeletal muscle density using unenhanced, arterial, and portal-venous phases on CT.

	Unenhanced phase		Arterial phase	
	Low mass	Low density	Low mass	Low density
Arterial phase	0.959	0.400	–	–
Portal-venous phase	0.920	0.266	0.879	0.680

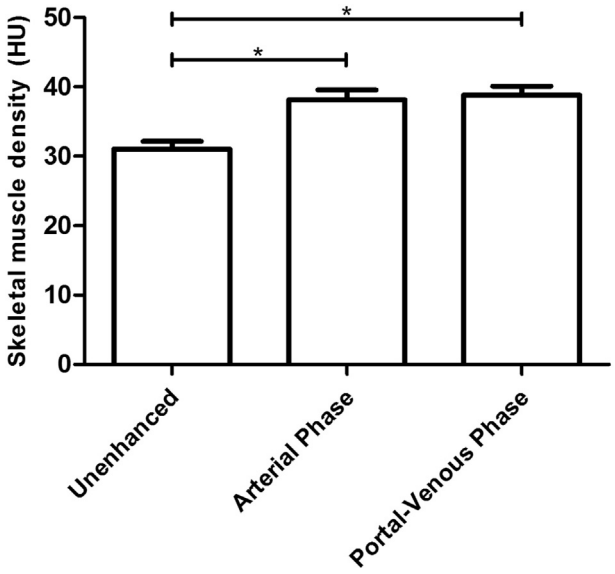

Fig. 5. Mean skeletal muscle density per contrast-enhancement phase. The whiskers represent the standard error of the mean. * indicates statistically significant difference.

significant. All statistical analyses were performed using SPSS for Windows (IBM Corp., Armonk, NY, USA), version 22.

3. Results

3.1. Patient and CT characteristics

The study cohort consisted of 23 (46%) females and 27 (54%) males with a mean BMI of 24.2 (±4.0) kg/m^2. In total, 19 (38%) patients had a BMI ≥25 kg/m^2 and 4 (8%) patients were considered obese (i.e. BMI ≥30 kg/m^2). All baseline characteristics are shown in Supplementary Table 1. The median intraluminal attenuation of the aorta was 41 (IQR 37–45) HU in CT images without contrast-enhancement, 404 (IQR 320–514) HU in the arterial contrast-enhancement phase, and 158 (IQR 143–189) HU in the venous contrast-enhancement phase (Fig. 2). The inter-observer ICCs were 0.999 for all contrast-enhancement phases for the skeletal muscle area, and ≥0.980 for the skeletal muscle density.

3.2. Skeletal muscle mass measurements

An overall difference in SMI was found between the three contrast-enhancement phases ($F(2, 98) = 56.174$, $p < 0.001$). The mean skeletal muscle index was 42.5 ± 9.9 cm^2/m^2 in the unenhanced phase, which was significantly lower compared with the arterial phase (42.8 ± 9.9 cm^2/m^2, $p = 0.021$) and the portal-venous phase (43.6 ± 9.9 cm^2/m^2, $p < 0.001$) (Table 1, Fig. 3). A significant difference was also observed between the arterial and portal-venous phase (42.8 versus 43.6 cm^2/m^2, $p < 0.001$). Bland Altman plots with 95% limits of agreement for the SMI are shown in Fig. 4. There was no proportional systematic bias for any comparison. The ICCs were excellent (all >0.99) for all comparisons (Table 1). Comparable results were found when using the cross-sectional muscle area (CSMA, Supplementary Fig. 1). According to the cut-off values defined by Martin et al. [24], 22 (44%) patients were considered to have low skeletal muscle mass using unenhanced CT, compared with 21 (42%) patients using the arterial phase and 24 (48%) patients using the portal-venous phase. This resulted in excellent Cohen's κ's of 0.959 (unenhanced versus arterial phase), 0.920 (unenhanced versus portal-venous phase), and 0.879 (arterial versus portal-venous phase) (Table 2).

3.3. Skeletal muscle density measurements

An overall significant difference in skeletal muscle density between the three contrast-enhancement phases was found ($F(1.649, 80.813) = 150.167$, $p < 0.001$). The mean skeletal muscle density was lower in the unenhanced phase (30.9 ± 8.0 HU) compared with the arterial (38.0 ± 9.9 HU) and portal-venous (38.7 ± 9.2 HU) phase (both $p < 0.001$), but not between the two latter (38.0 versus 38.7 HU, $p = 0.483$) (Table 1, Fig. 5). Mean skeletal muscle density did not significantly differ between patients receiving 120 or 150 ml of contrast medium in any contrast-enhancement phase. Bland Altman plots with 95% limits of agreement for the skeletal muscle density are shown in Fig. 6. There was a proportional systematic bias for the comparison of the unenhanced phase with the arterial ($p = 0.001$) and portal-venous ($p = 0.007$) phase, but not for the comparison of the arterial with the portal-venous phase ($p = 0.113$). The ICCs for the unenhanced phase compared with the arterial (0.676) and portal-venous (0.665) phase were considered fair to good, whereas the ICC between the arterial and portal-venous phase was considered excellent (0.949). The SDCs for skeletal muscle density measurements were considerably higher than for skeletal muscle mass measurements. The mean difference in skeletal muscle density between the arterial and venous contrast-enhancement phases (−0.6 HU) was within the SDC (1.90 HU) (Table 1). According to the cut-off values defined by Martin et al. [24], 40 (80%) patients were considered to have low skeletal muscle density using unenhanced CT, compared with 25 (50%) patients using the arterial phase and 19 (38%) patients using the portal-venous phase. This resulted in Cohen's κ's of 0.400 (unenhanced versus arterial phase), 0.266 (unenhanced versus portal-venous phase), and 0.680 (arterial versus porta-venous phase) (Table 2).

4. Discussion

This is the first study to demonstrate differences in CT-based skeletal muscle mass and skeletal muscle density measurements due to different stages of contrast-enhancement in multiphase CT. Importantly, although statistically significant differences in skeletal muscle mass were found between contrast-enhancement phases, these could be considered as not clinically relevant in contrast with the differences found for skeletal muscle density measurements.

The influence of CT-assessed sarcopenia on treatment outcome has increasingly gained interest last years. Sarcopenia is associated with increased vulnerability, postoperative complications and mortality, chemotherapy toxicity, and overall survival [4,5]. Recently, skeletal muscle density has been identified as a prognostic factor in various populations, whereas skeletal muscle mass was not [9–12,20]. Skeletal muscle density, expressed as the mean Hounsfield unit value of the selected skeletal muscle area, is correlated with skeletal muscle lipid content [29]. Furthermore, low skeletal muscle mass is associated with increased (dose-limiting) chemotherapy toxicity [8,30–32], and may be a superior measure to dose chemotherapy rather than body surface area which is currently being used [33].

Particularly in cancer patients, CT is considered the gold standard to measure skeletal muscle mass and density because it is routinely being performed (i.e. for diagnosis, treatment planning, and treatment evaluation) and consequently widely available [1,15,34]. CT-based assessment of skeletal muscle mass is an easy and reliable method correlated with total body skeletal muscle mass and known for its excellent inter- and intra-observer agreement [18,35]. However, previous studies on the association

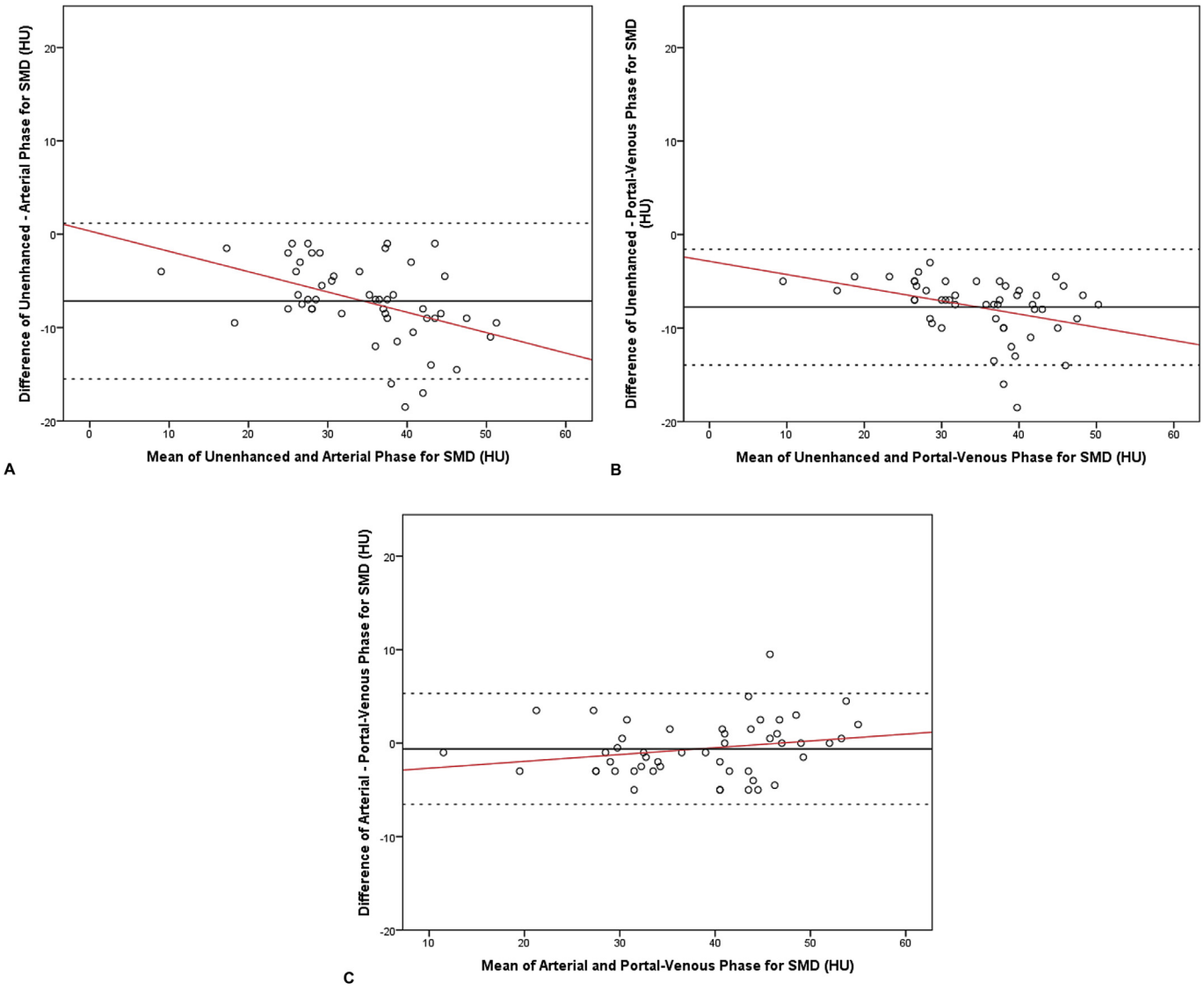

Fig. 6. Bland Altman plots with 95% limits of agreement for the comparison of the mean skeletal muscle density (SMD in Hounsfield units [HU]) of the unenhanced with arterial phase (A), unenhanced with the portal-venous phase (B) and arterial with the portal-venous phase (C). The solid black line represents the mean difference, the striped lines represent the mean ± 1.96 standard deviations, and the red line represents the regression slope. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

between skeletal muscle density and treatment outcome, did not report whether unenhanced or contrast-enhanced CT images were used to measure skeletal muscle density [9–12,20]. Results should therefore be interpreted with caution. To increase comparability within and between studies, based on our results, we recommend performing measurements in portal-venous contrast-enhanced phase CT examinations, as this phase is routinely being performed in cancer patients. Moreover, identification of various tissues is easier on contrast-enhanced CT examinations due to increased attenuation differences. When previously established cut-off values (e.g. those defined by Martin et al. [24]) are used, measuring skeletal muscle density on unenhanced or contrast-enhanced CT may lead to over- or underestimating the number of patients with low skeletal muscle density, respectively. This explains the poor Cohen's κ's for the classification of patients' skeletal muscle density in the current study. Therefore, we recommend to at least report the contrast-enhancement phase used to measure skeletal muscle mass and density. Ultimately, one should seek for consensus which contrast-enhancement phase should preferably be used.

Recently, promising results to reverse cancer-induced skeletal muscle wasting have been described in animal studies [36]. Currently, multiple trials are being performed in humans to investigate drugs for the treatment of cachexia [37]. However, the general opinion is that treatment of cachexia should be multimodal, of which nutritional intervention is one modality [14,38,39]. Treatment strategies may be adapted as well, depending on the cancer-induced muscle loss. Body composition measures assessed on CT may guide the indication and effectiveness of these therapies.

Although all CTs used for this study have been performed within a relatively short time frame (2009–2015) in one center only, the possible use of different type of CT scanners may have led to differences in observations between patients. Indeed, there is a difference in density measurements between different vendors. However, all examinations included in this study were performed on Siemens (Erlangen, Germany) CT scanners. All scanners were calibrated daily and calibrated using a phantom monthly. Furthermore, we used identical scanning protocols for all patients, reducing differences in measurements resulting from technique

variation. Nevertheless, variations on these protocols may have occurred.

Contrast distribution depends on various factors, such as cardiac output, vascular status [40], which were unknown for the current study population, and body weight and body lean mass. However, one may expect that the influence of these factors on the uptake of contrast medium by skeletal muscles of the core is minimal in rest. Also, scanning protocols using thresholds to start scanning correct for this. Consequently, these influences may be considered negligible. After all, we did not find significant differences in mean skeletal muscle density between patients receiving 120 ml or 150 ml of contrast medium. Furthermore, each patient formed its reference in this study as paired t-tests were used. Moreover, the variation in aortic intraluminal attenuation measurements in each contrast phase was relatively small. Contrary to a previous study [18], consecutive measures in the various contrast-enhancement phases were not performed on identical slices, since patients' movements and differences in breath-hold may have led to variations in the level on which measurements were performed. These factors could, however, better be controlled for in a future prospective study. Although single-slice cross-sectional areas are strongly correlated with whole body skeletal muscle mass, this remains an estimation only, which may introduce a potential error of several kilograms. Inter-observer variation may have led to measurement differences, although the inter-observer agreement for skeletal muscle mass measurements is excellent [18] and the mean of the two observers was used for analyses to further minimize inter-observer differences.

In conclusion, significant and clinically relevant differences in skeletal muscle density were observed between contrast-enhancement phases, whereas significant but not clinically relevant differences were found in skeletal muscle mass measurements. We recommend using the portal-venous phase of contrast-enhanced CT for studies that describe the association between skeletal muscle density and outcome measures to improve comparability of studies.

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None.

Authors' contributions

Design of the study: JLAvV, RRJCvdB, FEJAW, JNMIJ.
Data collection: JLAvV, SL, HJS, KV.
Data analysis: JLAvV, RRJCvdB.
Data interpretation: JLAvV, RRJCvdB, SL, FEJAW, JNMIJ, MK, WJN, RWFdB.
Development of research tool: MK, WJN.
Writing of the manuscript: JLAvV, RRJCvdB.
Critical revisions of the manuscript: All authors.

Conflict of interest statement

W.J. Niessen is co-founder and shareholder of Quantib BV.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.clnu.2017.07.007.

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