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CONTRAST MEDIA

Prospective multicenter study on personalized and optimized MDCT contrast protocols: results on liver enhancement

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Abstract

Objective To determine a personalized and optimized contrast injection protocol for a uniform and optimal diagnostic level of liver parenchymal enhancement, in a large patient population enrolled in a multicenter study.

Methods Six hundred ninety-two patients who underwent a standardized multi-phase liver CT examination were prospectively assigned to one contrast media (CM) protocol group: G1 (100 mL fixed volume, 37 gI); G2 (600 mgI/kg of total body weight (TBW)); G3 (750 mgI/kg of fat-free mass (FFM)), and G4 (600 mgI/kg of FFM). Change in liver parenchyma CT number between unenhanced and contrast-enhanced images was measured by two radiologists, on 3-mm pre-contrast and portal phase axial reconstructions. The enhancement histograms were compared across CM protocols, specifically according to a target diagnostic value of 50 HU. The total amount of iodine dose was also compared among protocols by median and interquartile range (IQR). The Kruskal-Wallis and Mann-Whitney *U* tests were used to assess significant differences ($p < 0.005$), as appropriate.

Results A significant difference ($p < 0.001$) was found across the groups with liver enhancement decreasing from median over-enhanced values of 77.0 (G1), 71.3 (G2), and 65.1 (G3) to a target enhancement of 53.2 HU for G4. Enhancement IQR was progressively reduced from 26.5 HU (G1), 26.0 HU (G2), and 17.8 HU (G3) to 14.5 HU (G4). G4 showed a median iodine dose of 26.0 gI, significantly lower ($p < 0.001$) than G3 (33.9 gI), G2 (38.8 gI), and G1 (37 gI).

Conclusions The 600 mgI/kg FFM-based protocol enabled a diagnostically optimized liver enhancement and improved patient-to-patient enhancement uniformity, while significantly reducing iodine load.

Key Points

- *Consistent and clinically adequate liver enhancement is observed with personalized and optimized contrast injection protocol.*
- *Fat-free mass is an appropriate body size parameter for correlation with liver parenchymal enhancement.*
- *Diagnostic oncology follow-up liver CT examinations may be obtained using 600 mgI/kg of FFM.*

Keywords Multidetector computed tomography · Abdomen · Contrast media · Liver, body composition

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Abbreviations

BMI	Body mass index
CM	Contrast media
CT	Computed tomography
FFM	Fat-free mass
MDCT	Multidetector CT scanner
TBW	Total body weight

Introduction

Hepatic imaging represents an important part of abdominal computed tomography (CT). Major clinical indications are

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suspicion, detection, and characterization of primary or metastatic hepatic lesions, tumor staging and monitoring treatment response, and diagnosis of diffuse liver diseases, assessment of vascular and biliary obstruction, and preoperative evaluation for surgical resection.

With the advent of multidetector CT (MDCT) scanners, images of the liver can be acquired with isotropic spatial resolution and high temporal resolution, thus improving the detection of subtle lesions and allowing multiple phases acquisition [1]. Multiple phase acquisition takes advantage of the dual (arterial and portal venous) blood supply to the liver. Indeed, after intravenous (i.v.) contrast media (CM) administration, opacification of the hepatic arteries (arterial phase) is expected after 15–25, while enhancement in the portal venous system occurs between 45 and 55 s, followed by hepatic venous parenchymal enhancement at 60–80 s (portal phase) [2].

As each hepatic enhancement phase is obtained for a specific clinical application, scanning protocols aim at maximal enhancement of specific structures at each phase, while minimizing the influence of others that will enhance during a subsequent phase [2].

The liver is therefore an extensively studied body organ for contrast protocol optimization. CT contrast enhancement of the liver is dependent on several factors, being patient-related (cardiac output, gender, age, body habitus- body weight, lean body mass (LBM), fat-free mass (FFM)-, renal function), scanner related (scan duration, delay, direction, tube voltage), or CM related (iodine concentration, dose, rate, saline flush, viscosity, temperature, injection type- monophasic, dual-phase) [2].

Although extensive literature has been published on personalizing the contrast protocol based on patient habitus [3–19], most of these studies did not account for different CM concentrations or kVp settings. As a consequence, the personalized protocols allowed improving liver enhancement uniformity across patients but were not always optimized to the desired diagnostic level, considered 50 Hounsfield Unit (HU) [2]; a value below 30 HU is also being considered insufficient as it diminishes the conspicuity of lesions [20].

The purpose of our study was to identify the most appropriate personalized contrast injection protocol to reach a uniform and optimal diagnostic level of liver parenchymal enhancement, in a large patient population enrolled in a multicenter study.

Material and methods

The study was approved by our regional ethical committee, waiving a specific written consent as a general research agreement is submitted to all patients at admission and contrast volume administration remains in legally defined ranges.

Patient data collection

From September 2017 to August 2020, CT data from consecutive adult patients were collected in a multicenter multivendor prospective study. Inclusion criteria consisted of an abdominal CT referral for cancer staging and follow-up as well as liver lesion characterization and follow-up examinations. Patients with fatty liver (< 40 HU or attenuation difference with spleen > 10HU on unenhanced CT [21]), cirrhotic (surface and parenchymal regenerative, siderotic, or dysplastic nodularity, signs of portal hypertension [22]) or fibrotic liver changes (wedge-shaped regions of hypoattenuation on non-contrast CT, hypoattenuating on the arterial and portal venous phases [23]), and hemochromatosis (marked homogeneous increase in liver density (> 75–130 HU), with portal vessels and hepatic veins of low attenuation relative to the liver on non-contrast CT [24]) were excluded, due to the dysmetabolic impact on parenchymal attenuation. All patients underwent a hepatic dynamic CT, including at least an unenhanced and a portal venous phase scanning.

Scanning protocol

Prior to this study, the adult (> 16 years) CT acquisition protocols of 11 CT scanners (2 Philips Ingenuity, 2 GE Optima CT520, 6 GE Revolution EVO, 1 GE Revolution Frontier) of 8 centers of the Swiss Groupe 3R (3R, Réseau Radiologique Romand), were harmonized and optimized, based on clinical indication and body mass index (BMI) [25].

Automatic tube current modulation of the x-ray tube current was used, while the setting of the tube voltage was manually selected to 100, 120, or 140 kVp. Specifically, 120kVp was the tube voltage used by default in most of our centers at the beginning of the study; however, during the process of contrast protocol optimization, the tube voltage was reduced to 100kVp for all patients except for patients with a BMI > 30. One hundred forty kilovoltage peak was used only for 3 patients with BMI > 33.

The other scanning parameters were detector configuration 64 × 0.625 mm, pitch 1, collimation 40 mm, gantry rotation time 0.4–0.5 s, large body field of view. The reconstruction algorithms were iDose level 3 and kernel Standard (B) for the Philips scanners and ASIR 70% or True Fidelity High and kernel Standard for the GE systems.

All examinations were performed using a real-time low-dose (100 kVp, 40 mA, 0.5 s) bolus-tracking program (Smart Prep; GE Medical Systems, Bolus Tracking, Philips) initiated 15 s after contrast medium injection to determine the CT acquisition starting time. Twenty-five (25) s after reaching a threshold of 120HU in a region-of-interest placed in the

supra-diaphragmatic aorta, the equilibrium phase was initiated, and the portal phase acquisition performed at 80 s after the injection start.

All CT scanners were connected to a dose monitoring system (DoseWatch, GE Healthcare), equipped with a contrast management module for contrast volume and concentration data collection.

Contrast protocol

Iopamidol (Iopamiro, Bracco) 370 mgI/mL or iohexol (Accupaque, GE Healthcare) 350 mgI/mL) contrast media and saline flush (30mL) were injected with the same dual mechanical power injector (Bayer, Medrad Stellant class IV) at a fixed injection rate respectively of 3.5 mL/s and 3 mL/s. An antecubital 21-G 32-mm plastic intravenous catheter was used.

To identify the optimal contrast protocol for a homogenous and optimal liver enhancement, patients were prospectively assigned to one of the four groups (Table 1). In group (G) 1, a fixed volume injection based on the assumption of a standard size patient was used as a baseline. In G2 and G3, we implemented personalized contrast protocols as reported in the literature. Finally, after analysis of G1–3 data, an optimal contrast injection protocol was identified and implemented (G4). Note that the data of G1 were collected after the data collection of G2 and G3, as we missed a baseline to compare the results of the personalized protocols.

The total body weight (TBW) and fat-free mass (FFM) were assessed at the time of examination. FFM was measured using a BIA-ACC impedance meter (BioTekna). Two skin electrodes at a measured distance of 5 cm were placed on the patient 3rd metacarpal and 3rd metatarsal level. The measured FFM was automatically estimated, exported in Excel format, and combined with the Excel output of the dose and contrast management systems, by using the examination identification number.

Iodine concentration and iodine concentration scaling factors at different kVp

To rule out the effect of contrast media concentration differences and kVp settings on liver enhancement associated with each personalized CM protocol investigated, iodine concentration scaling factors for all kVp settings were calculated. For this purpose, two anthropomorphic phantoms (QRM) of medium (correlating to a non-overweight patient with a BMI ≤ 25) and large size (correlating to an overweight patient with a BMI > 25) were used (Fig. 1). Each phantom contained 6 syringes; five rods were filled with contrast agent (Iopamidol 370 mg/mL) with different iodine concentrations (ranging between 0.5 and 8 mgI/mL [2, 26]) obtained by saline dilution (0.9% NaCl, Baxter).

The sixth rod was filled with saline solution only. Images were acquired over the complete clinical kVp range available on all CT scanners (80, 100, 120, and 140 kVp), using the liver lesion follow-up protocol, to obtain scanner-specific iodine concentration scaling factors. On ten axial slices, the HU value was registered for each iodine concentration and the water.

By using regression analysis, the relation of kVp and iodine concentration with HU was used to estimate iodine concentration scaling factors with respect to a clinical routine kVp reference of 100. Finally, the obtained scaling factors were averaged across different scanners of the same model.

Quantitative image quality evaluation: contrast enhancement index of normal parenchyma

To assess the impact on image quality of the different contrast protocols, liver parenchymal enhancement was measured on a clinical workstation (Advantage Windows Server version 3.0 and 3.2, GE Healthcare). Two independent senior radiologists placed circular regions of interest (ROIs) of identical size (range 20–30 mm in diameter),

Table 1 Overview of the study phases for the patient data collection. *TBW*, total body weight; *FFM*, fat-free mass

Period	Group (G)	Contrast protocol	Group (G), number of patients	Reference
March 2019–July 2019	G1	100 mL fixed contrast volume	G1, 201	Based on the assumption of a standard size patient
September 2017–December 2017	G2	600 mgI/kg of TBW	G2, 91	From [15]
January 2018–August 2018	G3	750 mgI/kg FFM	G3, 272	From [4]
December 2019–August 2020	G4	600mgI/kg of FFM	G4,126	As optimization of the protocol used in G3

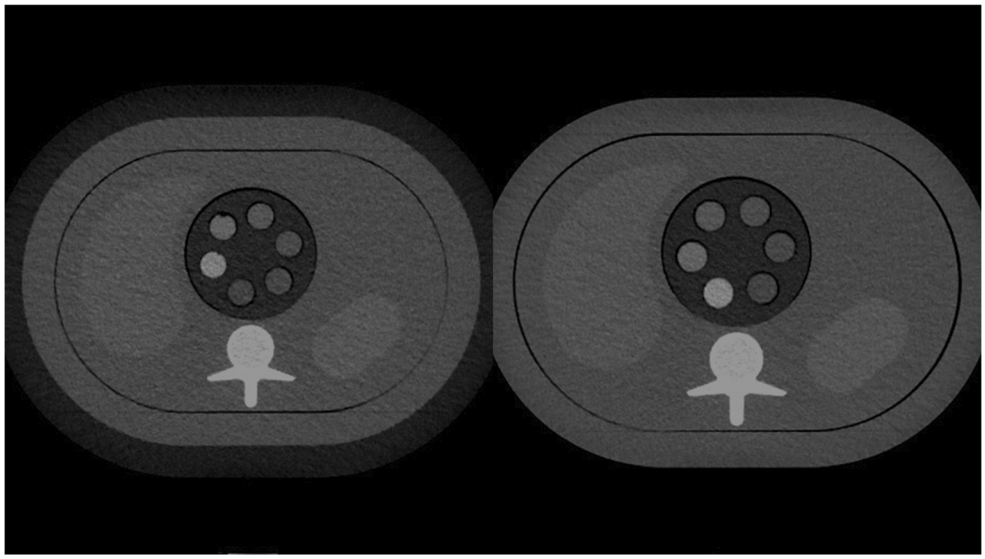

Fig. 1 An example of quantitative measurements performed on liver segments III and VI

locations (liver segments III and VI), and scan table position on unenhanced and portal phase 3-mm thickness axial reconstructions (Fig. 2).

The level of enhancement was determined by the contrast enhancement index (CEI) of normal parenchyma (NP) (CEI_{NP}), consisting of attenuation (HU) difference between portal and unenhanced parenchyma

$$CEI_{NP} = \sum ROI \frac{HUportal}{N} - \sum ROI \frac{HU\ unenhancement}{N}$$

In order to compare liver parenchymal enhancement among the four groups and to eliminate the enhancement differences due to CM concentration and kVp, the measured CEI_{NP} of each patient was rescaled to the reference 100kVp using the calculated iodine concentration scaling factor.

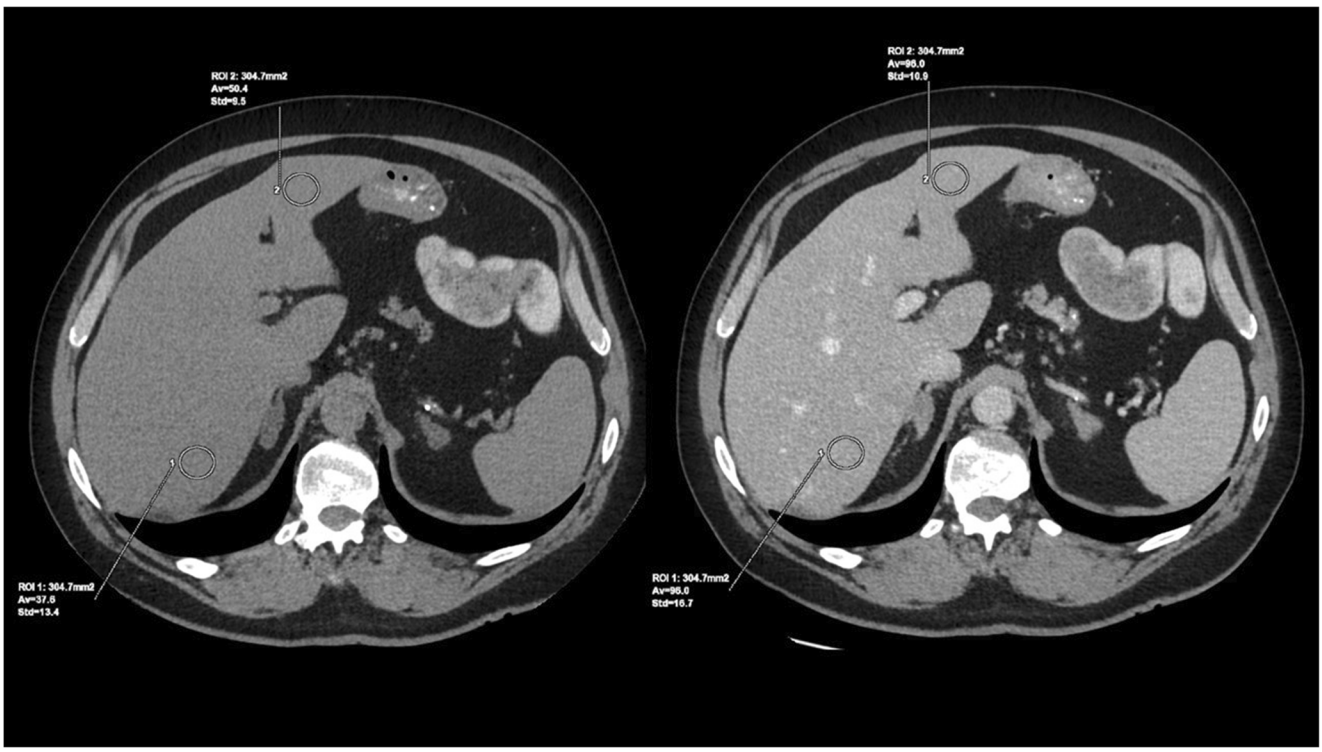

Fig. 2 The QRM phantom medium (left) and large (right) scanned on a GE Revolution EVO at 100 kV, with the 6 rods filled with contrast and saline media

Table 2 Patient characteristics stratified per group of contrast protocol injection

Characteristic	G1	G2	G3	G4	*p* value
Number of patients (male/female)	201 (87/114)	93 (37/56)	272 (114/158)	126 (46/80)	
Mean age (y) ± standard deviation (male/female)	64 ± 14 (66/62)	62 ± 17 (70/57)	60 ± 15 (61/59)	62 ± 15 (62/63)	0.03
Height (cm) ± standard deviation (male/female)	168 ± 9 (175/163)	167 ± 7 (174/163)	168 ± 9 (175/163)	168 ± 8 (175/164)	0.82
Weight (kg) ± standard deviation (male/female)	73 ± 16 (81/66)	67 ± 13 (75/62)	72 ± 16 (80/66)	71 ± 14 (78/66)	0.02
BMI ± standard deviation (male/female)	26 ± 5 (27/25)	24 ± 4 (25/23)	26 ± 5 (26/25)	25 ± 5 (25/25)	0.02

Total amount of iodine dose

The total amount of iodine dose (gI) injected per patient was calculated knowing the injected volume and the contrast media concentration as collected from the DoseWatch software.

Statistical analysis

Patient characteristics were analyzed as per weight, height, BMI, age, and gender.

CEI_{NP} descriptive statistics (mean, minimum, maximum, and IQR) was performed, and histograms of each group were compared among each other and to a target range of 40–60HU, centered at the desired optimal level of 50HU.

The total amount of iodine dose injected was compared among the four contrast protocols by boxplots (median, minimum, maximum, and interquartile range (IQR)). Data were also stratified by gender.

The Kruskal-Wallis and Mann-Whitney *U* tests were used to assess significant differences ($p < 0.05$ was considered significant), as appropriate.

Results

Patient population

The study population consisted of 692 patients. Data distribution is reported in Table 2.

Iodine concentration and tube potential scaling factors

Regression analysis showed linear relation between HU and iodine concentration in the clinical range, for each of the kVps, scanner, and body size investigated, as shown in the example of Fig. 3.

From these equations, the iodine concentration scaling factors were estimated (Table 3). As an example of scaling factor estimation (GE Frontier, size L):

$$HU_{100kVp} = 20.124 \times C_0[mgI/mL]$$

with C_0 being the iodine concentration at 100kVp, and

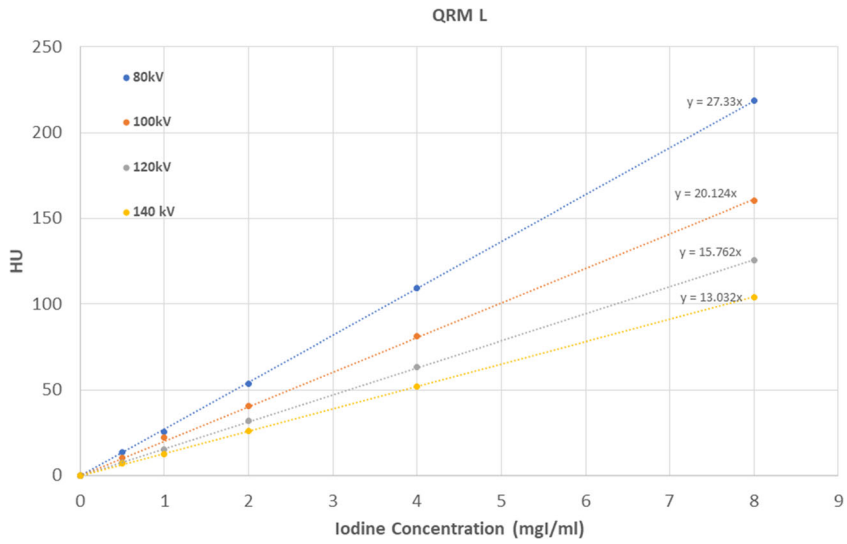

Fig. 3 Measurements at different kVps of syringes filled with different iodine concentrations inserted in the QRM phantom Large (L) for the CT Frontier scanner. Liner fits with intercept through the origin are shown

Table 3 Estimated iodine concentration scaling factors for all kVp settings, scanner models, and phantom size. For the GE Frontier, no standard deviation is available as we performed only one set of measurements. *SD*, standard deviation

kVp	Philips Ingenuity (average ± SD)		GE Optima 520 (average ± SD)		GE EVO (average ± SD)		GE Frontier (average)	
	M	L	M	L	M	L	M	L
80	0.749 ± 0.002	0.739 ± 0.005	0.741 ± 0.012	0.712 ± 0.036	0.766 ± 0.001	0.763 ± 0.024	0.741	0.736
100	1	1	1	1	1	1	1	1
120	1.240 ± 0.008	1.267 ± 0.017	1.242 ± 0.016	1.259 ± 0.024	1.232 ± 0.002	1.266 ± 0.026	1.245	1.277
140	1.515 ± 0.034	1.535 ± 0.016	1.501 ± 0.003	1.542 ± 0.025	1.500 ± 0.035	1.520 ± 0.006	1.534	1.544

$$HU_{120kVp} = 27.330 \times C[mgI/mL]$$

with C being the needed iodine concentration at 120 kVp to obtain the same enhancement (HU) at 100 kVp.

From $HU_{100kVp} = HU_{120kVp}$, we obtained

$$C[mgI/mL] = 20.12 \times C_0/15.762[mgI/mL]$$
$$= 1.277 \times C_0[mgI/mL]$$

For the scanner and phantom size under consideration, the scaling factor is 1.277, as also reported in Table 3.

Contrast enhancement index of normal parenchyma

Figure 4 (left) shows the CEI_{NP} boxplot for G1-G4. A statistically significant difference ($p < 0.001$) was found across the groups with the parenchymal liver enhancement decreasing from median over-enhanced values of 77.0 (G1), 71.3 (G2), and 65.1 (G3) to a target enhancement of 53.2 HU for G4. CEI_{NP} IQR was also reduced from 26.5 HU (G1), 26.0 HU (G2), and 17.8 HU (G3) to 14.5 HU (G4), indicating an improvement in liver enhancement uniformity across the four groups, with G4 having the lowest IQR.

A statistically significant difference ($p < 0.001$) between CEI_{NP} was also found for each pair of groups, except for G1 and G2 ($p = 1$). Figure 4 (right) shows the same data but stratified per gender. A significant difference ($p < 0.001$) between males and females was found only for G1.

Figure 5 reports the histograms of CEI_{NP} for G1–G4. The percent of patients with a CEI_{NP} within target enhancement increased from 20 (G1) to 63% (G4). The number of over-enhanced patients decreased from 79% (G1), 78% (G2), 65% (G3) to 32% (G4).

Total amount of iodine dose

G4 median iodine dose (26.0 gI) was significantly lower ($p < 0.001$) than G3 (33.9 gI), G2 (38.8 gI), and G1 (37 gI)

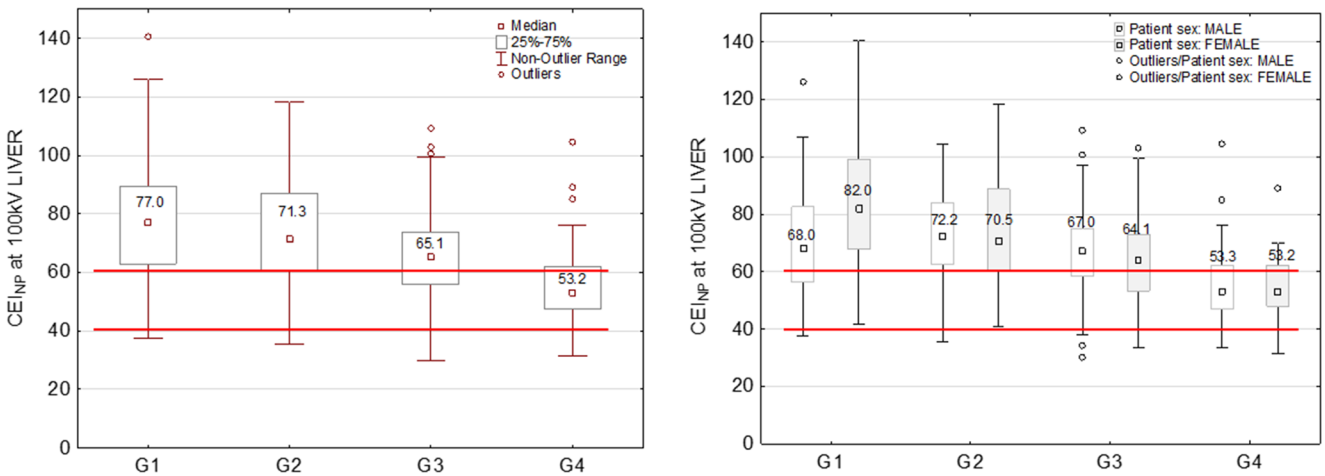

Fig. 4 Left: Box plot of the liver parenchymal enhancement stratified by group. Right: Box plot of the liver parenchymal enhancement stratified by group and gender. The red lines at 40 and 60 HU indicated the target range of liver enhancement for a diagnostically optimal image

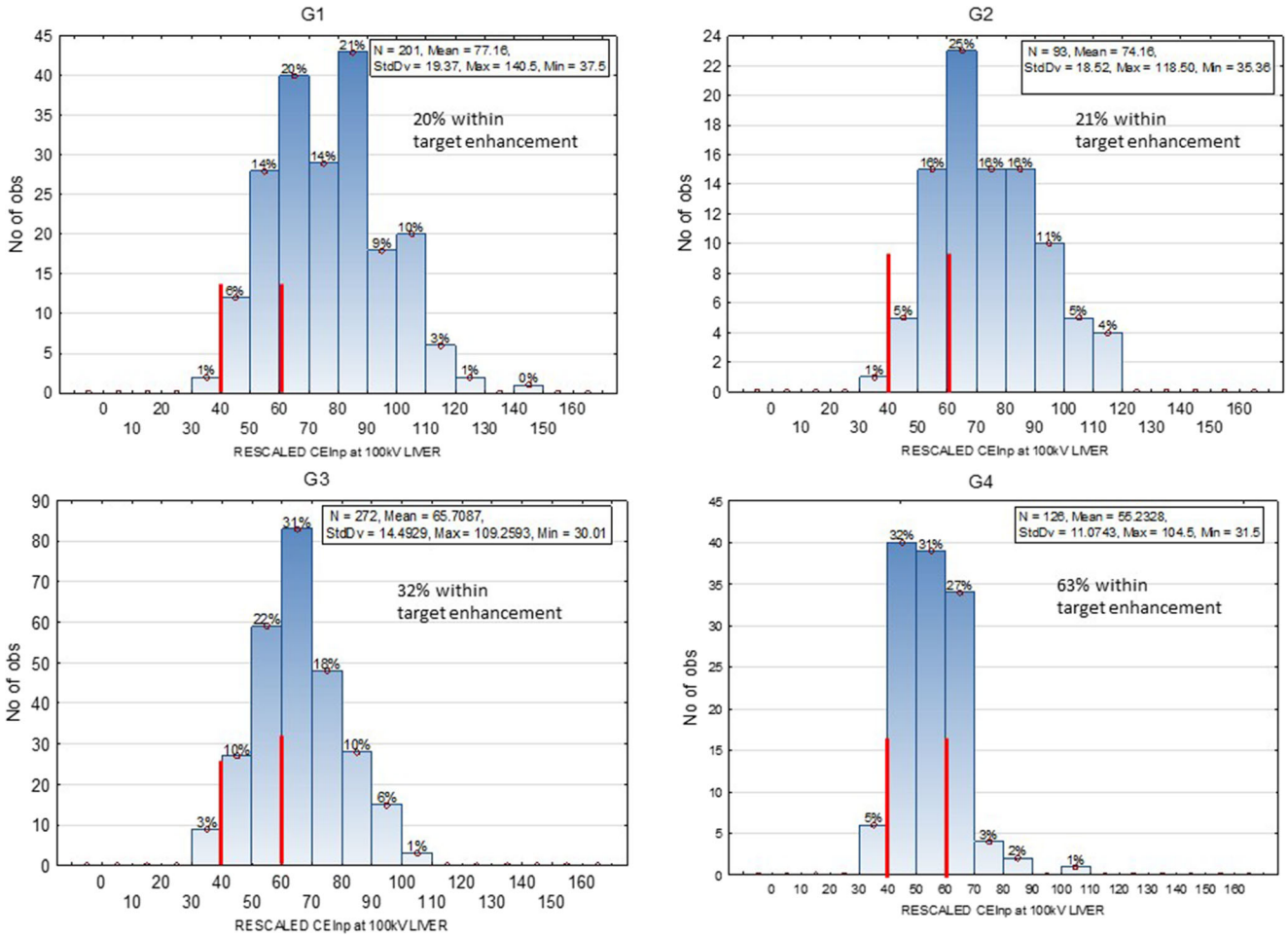

Fig. 5 Histograms of the CEI_{NP} distributions for the four groups. In red, the lines at 40 and 60 HU indicating the range of diagnostically optimal enhancement

(Fig. 6, left). When stratifying per gender, we observed that females got a significantly lower ($p < 0.01$) amount of iodine dose than males, for all groups except for G1 where the load injected was constant (Fig. 6, right).

Discussion

Patient-to-patient liver enhancement uniformity is essential for lesion assessment, accuracy, and reporting confidence in

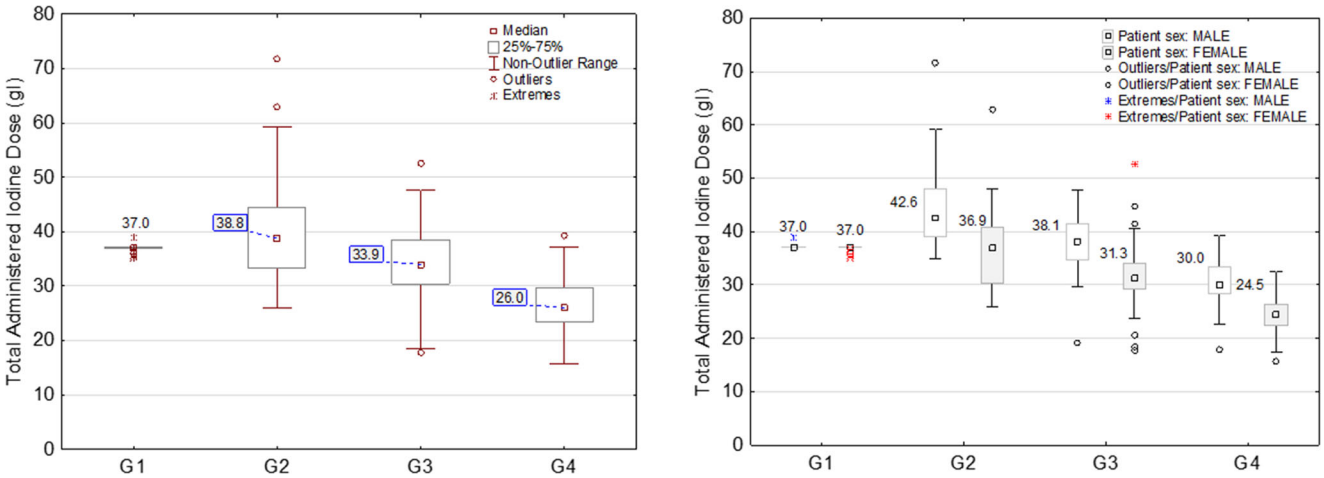

Fig. 6 Left: Box plot of the total administered iodine dose (gI) stratified by group. Right: Box plot of the total administered iodine dose (gI) stratified by group and gender

diagnostic and follow-up CT examinations. The aim of our prospective multicenter study was to identify a personalized and optimized MDCT contrast injection protocol resulting in a homogeneous and diagnostically appropriate portal phase liver parenchyma enhancement across patients.

Using a 600 mgI/kg of FFM contrast media injection protocol at 100 kVp enabled a net improvement towards 50 HU target liver enhancement (53.2 HU for G4) while narrowing the CEI_{NP} interquartile to 14.5 HU. This significantly improved patient-to-patient liver enhancement uniformity (Fig. 4).

Moreover, the number of patients within the target range of 40–60 HU reached 63%, compared to 32% in G3 (Fig. 5). Finally, CEI_{NP} was never lower than 30 HU which is considered the minimum diagnostically accepted level [2].

When stratifying our data based on gender, females got a significantly lower ($p < 0.01$) amount of iodine dose than males, for all group except for G1 where the load injected was constant (Fig. 6, right). Indeed, female patients' weight overall is less than in males and, for a given TBW, the percentage of body fat is greater in women than in men [27]. As expected, this difference in iodine load did not impact the CEI_{NP} (a significant difference ($p < 0.001$) between male and female is found only for G1 which used a fixed CM volume).

To the best of our knowledge, this is the first study using FFM as body habitus predictor for optimizing liver parenchymal enhancement and reduce variability. Earlier studies [11, 15, 17, 18, 28–32] used lean body weight (LBW) as an alternative metric to TBW. These studies show controversial results, with some reporting no difference in enhancement between TBW and LBW [29, 33]. Compared to FFM, LBW does not subtract the weight of the essential fat in our body (like fat in internal organs or bone marrow) which is about 3% in men and 12% in women. Besides, in several studies, LBW was calculated and not measured, resulting in significantly different LBW values [7, 30, 34]. Rengo et al [30] demonstrated that the use of the James formula underestimates LBW in obese patients, whereas the measurement of LBW with a bioimpedance measuring device, like in our case for FFM, is more accurate, though one study reported that FFM measurement can have systemic errors in estimating body compositions, particularly in the obese subjects [35]. The underestimation of LBW significantly influences the enhancement of liver parenchyma and might explain the controversial results discussed above.

If we compare the optimal iodine load of our study (600 mgI/kg of FFM) to obtain a liver parenchymal enhancement close to 50 HU with the iodine load based on LBW in the literature, we observe that the majority of the studies reported higher values (860/920 mgI/kg for men/women [11], 821 mgI/kg [15], or 750 mgI/kg of LBW [31]). This suggests that applying published CM protocols without accounting for tube potential or CM concentration differences may result in injecting inappropriate amounts of iodine dose and possibly over-enhancing a large proportion of the population.

Only [17, 29] reported values similar to ours (580/530 mgI/kg of LBW for female/male [29], 700 mgI/kg of LBW [17]), but with a wider distribution of enhancement, including cases below 30 HU.

Our study has limitations. First, all participating institutions were in Europe. Our findings might not be applicable to patients who are not European, as their body habitus may be different. Second, the number of patients for one group was relatively small and could have partially impacted some of the results. Third, we obtained the patient height and TBW directly from the patient at the time of examination. It might be that these data were less accurate than measuring at the time of the CT examination. Finally, in this study, we did not address the arterial phase; as the majority of our examinations are follow-up cancer staging, the portal phase is by far the most important. A dedicated study could be set up for the optimization of the arterial phase.

In conclusion, our study is, to the best of our knowledge, the first assessing the role of FFM as a metric for personalizing total iodine load while optimizing liver parenchymal enhancement and reduce variability. The clinical relevance of this patient-to-patient uniformity translates into the improvement of liver lesion assessment and reporting accuracy in diagnostic and follow-up CT examinations.

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Declarations

Guarantor The scientific guarantor of this publication is Federica Zanca.

Conflict of interest The authors of this manuscript declare relationships with the following companies:

P Pujadas is an employee of GE Healthcare.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent A written informed consent is submitted to every patient upon admission in Groupe 3r stating, among others, possible use of anonymized patient data for research purposes. The patient is free to oppose this use and listed as such. Specific written informed consent was therefore waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology

- prospective
- experimental
- multicenter study.

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