Potential of contrast agents based on high-Z elements for contrast-enhanced photon-counting computed tomography

Carlo Amato (a)
Division of X-Ray Imaging and Computed Tomography, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Laura Klein
Division of X-Ray Imaging and Computed Tomography, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Eckhard Wehrse
Medical Faculty, Ruprecht–Karls–University, Heidelberg 69120, Germany

Division of Radiology, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Lukas T. Rotkopf
Division of Radiology, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Stefan Sawall
Division of X-Ray Imaging and Computed Tomography, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Joscha Maier
Division of X-Ray Imaging and Computed Tomography, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Christian H. Ziener and Heinz-Peter Schlemmer
Division of Radiology, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

Marc Kachelrieß
Division of X-Ray Imaging and Computed Tomography, German Cancer Research Center (DKFZ), Heidelberg 69120, Germany

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Purpose: In clinics, only iodine- and barium-based contrast agents are currently used for contrast-enhanced x-ray computed tomography (CT). Recently, the introduction of new photon-counting (PC) detectors increased the interest in developing new contrast agents based on heavier elements. These elements may provide more contrast and spectral information compared to iodine and barium thanks to their k-edges at higher energies. In this paper, the potential of high-Z elements in contrast-enhanced CT was evaluated for different patient sizes and x-ray spectra using a PC detector.

Methods: An adult liver phantom with five high-Z element solutions (iodine, gadolinium, ytterbium, tungsten, and bismuth) was scanned with a whole-body photon-counting computed tomography (PCCT) prototype. For each element, the contrast-to-noise ratio at unit concentration and at unit dose (CNRCRD) was evaluated in low threshold images ($T_0 = 20\text{keV}$) as function of the tube voltage (80, 100, 120, and 140 kV) and in bin images (tube voltage = 120 kV) as function of the higher threshold ($T_0 = 20\text{keV}$ and $T_1 \in [50, 90]\text{keV}$). Simulations were performed for validation with measurements and to investigate more elements (cerium and gold), different patient sizes (infant, adult, and obese), and spectrum filtration (with and without 0.4-mm tin filter). The dose reductions associated with the CNRCRD improvements over iodine were quantified as well.

Results: CNRCRD improvements and dose reductions depend on the investigated scenario. For the infant phantom, dose reductions around 30% were reached using cerium or gadolinium in combination with the tin filter. For the adult and obese phantom, reductions around 50% were provided by gadolinium or ytterbium in combination with the tin filter. Independently of the high-Z element, the CNCRD of two optimally combined bin images was higher than the CNCRD of the low threshold image. Good agreement was found between measurements and simulations.

Conclusions: Between the investigated elements, gadolinium resulted to have the highest potential as novel contrast agent in PCCT, providing significant dose reductions for all patient sizes. Compared to the other elements, the implementation of gadolinium as CT contrast agent may be facilitated since it is already deployed as contrast agents for magnetic resonance imaging. © 2020 The Authors. Medical Physics published by Wiley Periodicals LLC on behalf of American Association of Physicists in Medicine [https://doi.org/10.1002/mp.14519]
1. INTRODUCTION

Contrast agents play an essential role in x-ray computed tomography (CT), allowing for the detection of perforations of organs, dysfunction of the esophageal sphincter, and imaging of the cardiovascular system. Approved contrast agents in CT are typically based on iodine, for intravenous injection, and on barium, for oral ingestion. During the past century, contrast agents based on these elements were thoroughly investigated and developed to increase their efficiency and biocompatibility. Despite this, the fundamental structures containing the high-Z element (tri-iodinated benzene rings and barium sulfate) remained unchanged. From a strictly physical point of view, iodine and barium may not be the best choice in all situations when considering x-ray attenuation properties. This is because their k-edges (33.2 keV for iodine and 37.4 keV for barium) are at relatively low energies if compared to a clinical x-ray spectrum used for adult patients. Poor attenuation may be provided as well by elements with k-edges at too high energy compared to the deployed spectrum. The importance of the relationship between k-edges and energy of the deployed spectrum is displayed in Fig. 1. For a 100 kV CT scan of an adult patient (approximated by 32 cm of water), the simulated transmitted spectrum and the attenuation coefficients of iodine, gadolinium, and bismuth are plotted. It is possible to see that in the energy interval from 50 to 90 keV (where 85% of the transmitted photons are contained), gadolinium is the element with the highest attenuation.

The possibility of using elements heavier than iodine for contrast-agent development has to face the challenge of the biocompatibility. In many cases, such elements are toxic or difficult to include in biocompatible molecules. Recently, nanostructures like liposomes or nanoparticles are being investigated in order to densely pack the desired element and to increase its biocompatibility. Liposomes and nanoparticles are of special interest for cardiovascular imaging, since they can be synthesized with a large diameter (up to hundreds of nanometers) and consequently reside in the vascular system for long periods (several hours, blood pool). Clinically approved iodinated contrast agents are instead based on small molecules (few nanometers) and are cleared from the vascular system within a few minutes. Furthermore, the coating of nanostructures can be engineered to create targeted contrast agents. The improvements related to high-Z elements in contrast-enhanced CT have been already investigated by Nowak et al. In this study, the authors quantified the contrast improvements and dose reductions related to the usage of elements from iodine to bismuth, for different patient sizes and x-ray spectra.

The introduction of novel photon-counting (PC) detectors is another recent innovation in CT. PC detectors are based on semiconductor technology, which allows for single PC and assigns an equal weight to detected photons. Conversely, the energy integrating (EI) detectors deployed in nowadays CT scanners are based on scintillators and weight the photons proportionally to their energy. The advantages of PC detectors over EI detectors have been already partially investigated and improvements have been shown regarding spatial resolution, image noise, and iodine contrast enhancement. Another feature of PC detectors is the presence of multiple and adjustable energy thresholds which can be used to differentiate incoming photons according to their energy and therefore provide spectral information. EI detectors are also capable of spectral imaging, but techniques like dual-source, kV-switching or sandwich detector have to be used. Despite the promising results, PC detectors have to face many challenges before replacing EI detectors, first of all the limited photon count rate.

In this study, we investigated the potential of different high-Z elements as contrast agents for contrast-enhanced photon-counting computed tomography (PCCT). The performance of each element was compared to iodine (gold standard) for different patient sizes, tube voltages, prefiltration settings, and energy thresholds. In the end, the results obtained with a PC detector were compared to the results previously achieved with an EI detector.

2. MATERIALS AND METHODS

2.A. Contrast in PCCT

To assess the improvements related to different high-Z contrast agents, the contrast-to-noise ratio (CNR) was used as figure of merit. The CNR is defined as:

\[
\text{CNR} = \frac{\Delta \mu}{\sqrt{V}} = \frac{|\mu_A - \mu_B|}{\sqrt{V}},
\]

where \( \mu_A / \mu_B \) are the mean CT-values measured in two regions of interest (ROIs) and \( V \) is the variance of pixel values measured in a homogeneous region.
In order to compare measurements acquired with different tube voltages, prefiltration settings, and concentration of the contrast agent, the CNR at unit concentration and at unit dose (CNRCD) will be used in this study. The CNRCD is defined as:

\[
\text{CNRCD} = \frac{\text{CNR}}{C \cdot \sqrt{D}},
\]

(2)

where \(D\) is the patient radiation dose (CTDIvol 32 cm) and \(C\) is the mass concentration of the high-Z elements in the contrast agent solution.

When more than one energy threshold is used with a PC system, multiple bin images are acquired simultaneously. The bin images can be linearly combined to obtain a composed image. In case of two energy thresholds, the final image \(f_{PC2}\) is calculated as:

\[
f_{PC2} = w_1 f_1 + w_2 f_2,
\]

(3)

where \(f_1\) and \(f_2\) are the bin images and \(w_1\) and \(w_2\) are the weighting coefficients with \(w_1 + w_2 = 1\). The CNR of the final image can be directly computed as:

\[
\text{CNR}_{PC2} = \frac{(w_1 \Delta \mu_1 + w_2 \Delta \mu_2)^2}{w_1^2 V_1 + w_2^2 V_2},
\]

(4)

If the weights are chosen to maximize the \(\text{CNR}_{PC2}\) (i.e., \(w_j \propto \Delta \mu_j / V_j\)), the CNRCD of the final image can be directly calculated as:

\[
\text{CNRCD}_{\text{max}} = \sqrt{\text{CNRCD}_1^2 + \text{CNRCD}_2^2},
\]

(5)

where \(\text{CNRCD}_i\) is the CNRCD of the \(i\)-th bin image.

### 2.B. Measurements

All measurements performed in this study were conducted using the SOMATOM CountT scanner, a whole-body PCCT prototype by Siemens Healthineers, Forchheim, Germany. The prototype is based on the SOMATOM Definition Flash, a two source scanner where one of the two EI detectors was replaced by a PC detector.\(^{15,16}\) For this study, only the PC detector was used. This detector has a 1.6-mm CdTe-sensitive layer with a pixel size of 225 μm and a bias voltage of 1000 V. The detector has up to four energy thresholds, depending on which of the available modes is used. In this study, all measurements were acquired using the MACRO mode, wherein the pixels are binned in a 4 × 4 pattern, resulting in a pixel size of 900 μm. The PC detector has a field of view of 27.5 cm. When scanning objects larger than 27.5 cm, an additional data completion scan with the wider EI detector is required to avoid truncation artifacts.\(^{17}\)

The PCCT prototype was used to scan a semi-anthropomorphic liver phantom (QRM, Möhrendorf, Germany) (Fig. 2). The phantom was equipped with a 2.5-cm fat ring in order to simulate an adult patient with a size of 35 cm × 25 cm. The liver insert can host up to seven vials. Five of them were filled with solutions of commercially available contrast agents or solutions of high-Z elements in an acid matrix. Table I lists the deployed solutions. The final concentrations of the solutions were chosen to reproduce realistic values which can be expected in clinical scenarios. The iodine solution was obtained by diluting an iodine-based contrast agent used in clinical CT practice (Optiray™ 300, Covidien, Neustadt/Donau, Germany) with water to achieve a final iodine concentration of 14.2 mg/mL. A gadolinium-based contrast agent used in magnetic resonance imaging (Multihance® 0.5 M, Bracco, Milan, Italy) was diluted to achieve a gadolinium concentration of 15.8 mg/mL. The 10 mg/mL acid solutions of ytterbium, tungsten, and bismuth were purchased from different vendors and no further dilutions were required. The described elements were chosen to have a broad range of k-edges. At the lower limit, there is iodine, which is the gold standard in CT imaging and has an energy k-edge at 33.2 keV. For an adult scan at 100 kV, there are almost no transmitted photons below 33.2 keV (see Fig. 1), therefore elements with lower k-edges were neglected. At the upper limit, bismuth is the stable element with the highest k-edge (90.5 keV). In Fig. 2, a reconstructed slice of the liver phantom with the high-Z solutions is shown. Two sets of measurements were performed and compared to simulations for validation. The first set was acquired to evaluate how the CNRCD of the different high-Z solution varies with the tube voltage. Low threshold images were acquired at a tube voltage of 80, 100, 120, and 140 kV with a single energy threshold \(T_0\) at 20 keV. The second set of measurements was performed to evaluate how the CNRCD of the different elements depends on the relationship between the k-edge and two energy thresholds. The lower threshold \(T_0\) was fixed at 20 keV, whereas the higher threshold \(T_1\) varied between 50 and 90 keV (maximum values that can be set on the scanner). For this scenario, a fixed tube voltage of 120 kV was chosen.

![Fig. 2. Slice of the adult liver phantom with inserts of high-Z solutions. The phantom is cropped in a circular shape because of the limited FOV of the PC detector. [Color figure can be viewed at wileyonlinelibrary.com]](image-url)
in order to avoid photon starvation in the high energy bin image when $T_1$ is at 90 keV. The CNRCD was evaluated for each of the bin images and CNRCD\textsubscript{max} was evaluated for the optimally combined image [Eq. (5)].

2.C. Simulations

Polychromatic simulations of the PCCT system were performed for comparison with measurements and to investigate a broader range of scenarios. The geometry of the scanner and the parameters of the detector were simulated according to the SOMATOM CountT prototype and are listed in Table II. The spectral response of the detector was simulated using the semirealistic detector model described in Faby et al.\textsuperscript{18} which analytically describes the semiconductor detector physics. The spectral response $R(E',E)$ is defined as the ration between the amount of photons $N(E',E)$ detected at energy $E'$ when $N(E)$ photons at energy $E$ impinge on the detector:

$$R(E',E) = \frac{N(E',E)}{N(E)}.$$ (6)

The spectral responses were then used to calculate the bin sensitivity $s_b(E)$ according to the chosen energy thresholds:

$$s_b(E) = \int_{E_{b-1}}^{E_{b+1}} R(E',E)dE',$$ (7)

where $E_{b-1}$ and $E_b$ are the upper and lower threshold of the $b$-th energy bin, respectively. In Fig. 3 an example of bin sensitivity is displayed for $T_0 = 20$ keV and $T_1 = 50$ keV. It can be noticed that the bin sensitivity includes the detection efficiency since the sum of the two bin sensitivities (solid black line in Fig. 3) decreases at energies higher than 80 keV. Furthermore, the bin sensitivity accounts also for multiple counts due to the charge sharing. This results in a bin sensitivity which exceeds 1 at certain energies. Other effects as the pulse pile-up and the noise correlation between different bin images were neglected. A point source was modeled using the semiempirical spectrum model by Tucker et al.\textsuperscript{19} and prefilterings (see Table II) were applied to harden the spectrum. A simulated spectrum at 120 kV is shown in Fig. 3. A circular trajectory and 1024 projections were used to simulate scan of a mathematical model of the liver phantom, which is represented by surface meshes provided by the vendor (QRM, Möhrendorf, Germany). As described in the following, the phantom was also scaled to simulate different patient sizes. The number of pixels in the detector rows was scaled accordingly, such that the FOV could host the whole phantom without the need of a data completion scan. For each detector element and each angle, the number of photons $n_b$ through the phantom detected in the $b$-th energy bin was calculated as:

$$n_b = \int_0^{E_{max}} \Phi(E) \cdot s_b(E) \cdot e^{-\sum_{m=1}^{M} \mu_{m}(E) \cdot L_m \cdot dE},$$ (8)

where $\Phi(E)$ is the Tucker spectrum in air, $s_b(E)$ is the bin sensitivity, $L_m$ is the intersection length through the different materials $m$ of the phantom and $\mu_{m}(E)$ is the photon attenuation coefficient of such materials. Poisson noise was added to the photons number and then the projection values were calculated and water precorrected. A 4 × 4 pixel binning was applied as in the measurements. The FDK cone-beam algorithm\textsuperscript{20} was used to reconstruct the volume with isotropic voxels. For each scan, the CTDI\textsubscript{vol} 32 cm was estimated using Monte Carlo simulations. The Monte Carlo simulations were performed using our in house MC code which was verified against Geant4. Further details can be found in Baer et al.\textsuperscript{21}

As stated before, two sets of simulations were performed. The first one is for direct comparison with measurements and validation of simulations. The adult sized liver phantom was simulated with tube voltages form 70 kV to 150 kV in steps of 5 kV using the described prefiltration and a fixed energy threshold at 20 keV. The five high-Z element solutions were simulated according to the composition listed in Table I. The concentration of the solvent was adjusted within 5% to roughly match the measured attenuation of each solution. Then, the phantom was simulated with a fixed tube voltage of 120 kV and two energy thresholds: $T_0$ fixed at 20 keV and $T_1$ varying between 50 and 90 keV in steps of 5 keV.

The second set of simulations was performed in order to investigate a range of scenarios broader than in measurements, including different patient sizes and different prefiltration of the x-ray beam. Starting from the adult size (35 cm × 25 cm) an infant patient (15 cm × 10 cm) was

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**Table I.** List of the contrast agents and high-Z solutions used in measurements. The same formulations were used in the simulations.

| High-Z element | k-edge | Material and concentration | Composition | Concentration of the solution |
|----------------|--------|---------------------------|-------------|-----------------------------|
| I              | 33.2 keV | Optiray 300 300 mg/mL | C\textsubscript{18}H\textsubscript{24}I\textsubscript{3}N\textsubscript{3}O\textsubscript{9} | 14.2 mg/mL |
| Gd            | 50.2 keV | Multihance 0.5 M 78 mg Gd/mL | C\textsubscript{36}H\textsubscript{65}GdN\textsubscript{5}O\textsubscript{21} | 15.8 mg Gd/mL |
| Yb            | 61.3 keV | Ytterbium Oxide 10 mg Yb/mL | Yb\textsubscript{2}O\textsubscript{3} in 5% HNO\textsubscript{3} | 10.0 mg Yb/mL |
| W             | 69.5 keV | Tungsten 10 mg W/mL | W in 10% NH\textsubscript{3} | 10.0 mg W/mL |
| Bi            | 90.5 keV | Bismuth 10 mg Bi/mL | Bi in 10% HNO\textsubscript{3} | 10.0 mg Bi/mL |
simulated by scaling the liver phantom and an obese patient (50 cm × 40 cm) was simulated by increasing the thickness of the fat ring. For these three patient sizes, two set of pre-filters were used: the one already used in the first set of simulations (see Table II) and another one with an additional 0.4-mm Sn filter. The thickness of the Sn filter was chosen in accordance to the Sn filter present in the Siemens Flash and Siemens Count scanners. Seven ideal water solutions of iodine, cerium, gadolinium, ytterbium, tungsten, gold, and bismuth were used (Table III). The concentration of the high-Z elements was fixed to 10 mg/mL. For each patient size and prefiltration set, simulations were performed for tube voltages from 70 to 150 kV in steps of 5 kV. The energy threshold $T_0$ was fixed at 20 keV.

2.D. Image quality assessment

The CNRCD [Eq. (2)] was evaluated both in measurements and simulations to compare the contrast provided by the high-Z element solutions in the different scenarios. The contrast of each solution was measured with respect to water, therefore $\mu_B = 0$ HU in Eq. (2). Noise was measured as the variance of pixel values in a homogeneous ROI placed in a soft tissue region of the liver phantom (ROI 0 in Fig. 2). When dealing with two thresholds and therefore two bin images, the CNRCD$_{max}$ [Eq. (5)] was evaluated as well. The error was evaluated as the standard deviation over different slices. Since iodine is the gold standard in CT, in each of the investigated scenarios the CNRCD of the potential contrast agent was normalized to the value of iodine ($I$) at a reference tube voltage ($U_{ref}$) without Sn filter. Therefore, the relative CNRCD of each contrast agent $X$ was calculated as:

$$\text{Relative CNRCD}_X(U) = \frac{\text{CNRCD}_X(U)}{\text{CNRCD}_I(U_{ref}, 0 \text{ mm Sn})}.$$  \(\text{(9)}\)

The reference tube voltage $U_{ref}$ was set to 80 kV for the infant phantom, 100 kV for the adult phantom, and 120 kV for the obese phantom.

From the relative CNRCD, it is possible to evaluate the potential dose reduction as:

$$\text{Dose Reduction}_X(U) = 1 - \left(\frac{\text{CNRCD}_I(U_{ref}, 0 \text{ mm Sn})}{\text{CNRCD}_X(U)}\right)^2.$$  \(\text{(10)}\)

When evaluating the relative CNRCD and dose reductions in the different scenarios, only values obtained for a tube voltage higher than $U_{ref}$ were considered. This is because the usage of lower tube voltages could be limited by the power of the x-ray tube. Especially for obese patients, this limitation could lead to undesired long scan time.22

3. RESULTS

In the following, the achieved results are described. In Section 3.A, the measurements are presented together with the simulations of the realistic high-Z solutions. Then, in Section 3.B, the simulations with ideal high-Z solutions, different patient sizes and prefiltrations are presented.

3.A. Measurements

The first measurement with the adult liver phantom was performed with the five high-Z solutions listed in Table I. In Fig. 4, the CNRCDs measured in the low threshold image ($T_0 = 20$ keV) are plotted (dots) as a function of the tube

![Image](https://example.com/image.png)

**Table II.** List of the parameters used to simulate the PCCT

| Parameter                          | Value          |
|-----------------------------------|----------------|
| Source to isocenter distance       | 595 mm         |
| Detector to isocenter distance     | 490 mm         |
| Detector pixel size               | 225 Åμm        |
| Pixel binning                     | 4 × 4          |
| Detector material                 | CdTe, 6.3 g/cm³|
| Detector thickness                | 1.6 mm         |
| Bias voltage                      | 1000 V         |
| Prefilters                        | 6.8 mm Al, 1.0 mm C, 0.7 mm Ti, 0.008 mm W |
| Voxel size                        | 0.78 mm        |

**Table III.** List of the ideal high-Z solutions used in simulations. The contrast enhancement refers to the simulation of the adult size phantom at 100 kV without Sn filter. The contrast enhancement with respect to water was measured in each vial in the low threshold image ($T_0 = 20$ keV)

| High-Z element | K-edge (keV) | Concentration of the solution | Contrast enhancement at 100 kV (HU) |
|----------------|-------------|------------------------------|-----------------------------------|
| I              | 33.2        | 10.0 mg I/mL                 | 305                               |
| Ce             | 40.4        | 10.0 mg Ce/mL                | 370                               |
| Gd             | 50.2        | 10.0 mg Gd/mL                | 422                               |
| Yb             | 61.3        | 10.0 mg Yb/mL                | 357                               |
| W              | 69.5        | 10.0 mg W/mL                 | 287                               |
| Au             | 80.7        | 10.0 mg Au/mL                | 246                               |
| Bi             | 90.5        | 10.0 mg Bi/mL                | 232                               |
voltage $U$. The values were normalized for the CNRCD of iodine at 100 kV. Simulations of the realistic solutions are shown as continuous lines for comparison and validation. The CNRCD of iodine decreases as the tube voltage increases, accordingly with the fact that its k-edge is at too low energy compared to the used spectra. The other high-Z solutions have a maximum which can be found at increasing tube voltages as the energy of the k-edge increases. For gadolinium, the maximum is at approximately 80 kV, whereas for tungsten, it is at 110 kV. Gadolinium outperforms the other high-Z solutions for all tube voltages, with a measured maximum of 1.75 at 80 kV. Good agreement with simulations is found. The relative deviations between the measured and simulated points were evaluated: a mean deviation of 4% is found, with a maximum deviation of 9% for gadolinium at 80 kV.

The second measurement aimed to evaluate how a set of two energy thresholds can be used to maximize the CNRCD. At a fixed tube voltage of 120 kV and with a variable $T_1$, the CNRCD of the solutions was measured in the low and high energy bin. These values were also combined to calculate the CNRCD$_{max}$ [Eq. (5)]. In Fig. 5 left, the measured and simulated CNRCDs of the tungsten solution are shown as a function of $T_1$. As $T_1$ increases, the CNRCD of the low and high energy bin image exhibits an increasing and decreasing behavior, respectively. The measured CNRCD$_{max}$ is instead almost constant for $T_1$ between 50 and 70 keV. For higher values of $T_1$, the CNRCD$_{max}$ decreases up to 10%, probably because of photon starvation in the high energy bin image. In Fig. 5 right, the CNRCD$_{max}$ is plotted for each solution. The values were normalized to the CNRCD$_{max}$ of iodine at $T_1 = 50$ keV. The behavior of the measured CNRCD$_{max}$ is the same of the previously described for tungsten. Good agreement is found between simulations and measurements, with a mean deviation of 5.6% and a maximum deviation of 14% for ytterbium at $T_1 = 85$ keV.

For each solution, the maximum measured CNRCD$_{max}$ can be compared to the CNRCD previously measured in low threshold images at 120 kV. Despite the relative position of the contrast agents remains the same, an improvement could be measured when using two optimally combined bin images. For each solution, the improvement is listed in Table IV together with the value of $T_1$ which maximized CNRCD$_{max}$.

3.B. Simulations

The first set of simulations (described in Section 2.C) was performed with five realistic high-Z element solutions and has been already presented together with measurements in Section 3.A. The second set of simulations was performed with seven ideal high-Z element water solutions and is presented in the following for the three different patient sizes and the two sets of prefiltrations.

**FIG. 4.** For the adult liver phantom, the CNRCD in the low threshold image ($T_0 = 20$ keV) of high-Z element solutions as function of the tube voltage. Measurements are displayed with discrete markers, whereas simulations are displayed with continuous lines. Values are normalized for the value of iodine at 100 kV. [Color figure can be viewed at wileyonlinelibrary.com]
3.B.1. Infant patient phantom

In Fig. 6, the CNRCD of the seven solutions is shown for the infant size phantom with and without additional Sn filtration. The CNRCD values were normalized to the value of iodine at $U_{\text{ref}} = 80$ kV without Sn filter. The dose reduction was also calculated [Eq. (10)] and plotted.

When using no Sn filtration, gadolinium and cerium outperform iodine at all tube voltages, except for gadolinium at 70 kV. The highest dose reduction for $U \geq U_{\text{ref}}$ is $27 \pm 2\%$ with cerium at 80 kV, followed by gadolinium ($17 \pm 4\%$) at a tube voltage between 80 and 90 kV.

When using the additional Sn prefiltration, the CNRCD of iodine and cerium decreases. The heavier element (with exception of bismuth and gold), increase their maximum CNRCD. The highest dose reduction ($30 \pm 4\%$) is seen for gadolinium at 80 kV.

3.B.2. Adult patient phantom

In Fig. 7, the results for the adult phantom scanned with and without Sn prefiltration are shown. For this phantom size, the reference value is iodine at $U_{\text{ref}} = 100$ kV without Sn filter.

Without Sn filtration, iodine is outperformed by cerium, gadolinium, and ytterbium for tube voltages higher than $U_{\text{ref}}$. Gadolinium at 100 kV provides the highest dose reduction ($48 \pm 1\%$). Cerium and ytterbium provide approximately the same dose reduction of $30 \pm 2\%$ at 100 kV.

With the Sn filter, the CRND of iodine and cerium decreases. Also the CNRCD of gadolinium decreases for tube voltages $\geq U_{\text{ref}}$, reaching a maximum dose reduction of

| Element | Improvement | $T_0$ (keV) |
|---------|-------------|-------------|
| I       | $(5.8 \pm 7.7)\%$ | 50          |
| Gd      | $(8.3 \pm 7.2)\%$ | 52          |
| Yb      | $(9.4 \pm 8.2)\%$ | 52          |
| W       | $(8.4 \pm 7.6)\%$ | 52          |
| Bi      | $(6.6 \pm 7.8)\%$ | 50          |

TABLE IV. For each high-Z element, the CNRCD improvement obtained by using two optimally combined bin images compared to one low threshold image. In both cases, $T_0$ was 20 keV and the tube voltage was 120 kV.

Fig. 6. For the simulations of an infant patient (15 cm × 10 cm), the relative CNRCD (top row) and the dose reduction (bottom row) of the different high-Z solutions are shown as function of the tube voltage. In the left column, the additional Sn filter was deployed. Results are normalized to the value of iodine at 80 kV with no Sn filter. [Color figure can be viewed at wileyonlinelibrary.com]
44 ± 1% at 100 kV. The maximum dose reduction is provided by ytterbium (49 ± 1%) at 100 kV. When using the Sn filter, also heavier elements provide a positive dose reduction: tungsten at 100 kV has a maximum of 33 ± 1% and the gold at 115 kV has a maximum of 5 ± 2%.

### 3.B.3. Obese patient phantom

In Fig. 8, the results of simulations are shown for an obese-sized phantom, with and without additional Sn prefiltration. The CNRCD values of the different high-Z solutions were normalized to the value of iodine at 120 kV with no Sn filter. When using no additional Sn filter, iodine is outperformed by all the heavier elements for tube voltages higher than $U_{\text{ref}}$. The highest dose reduction (53 ± 2%) is provided by gadolinium (closely followed by ytterbium) at 120 kV.

With the Sn filtration, the CNRCD of elements lighter than ytterbium decreases, whereas ytterbium and tungsten provide the best performance and a dose reduction of approximately 52 ± 3% with a tube voltage of 120 kV. Also maximum CNRCD of gold and bismuth increase.

### 4. SUMMARY AND DISCUSSION

In this study, high-Z elements were investigated as potential contrast agents in contrast-enhanced PCCT. The CNRCDs were compared to the gold standard iodine for different patient sizes (infant, adult, and obese), tube voltages (from 70 to 150 kV), filtration settings (with and without 0.4-mm Sn filter), and energy threshold values.

The measurements of the adult liver phantom with a fixed low energy threshold have shown how elements with k-edges at different energies have a different behavior as function of the tube voltage. In this scenario, gadolinium outperformed all the other elements for all the tube voltages. In the measurements with a fixed tube voltage (120 kV) and two energy thresholds ($T_0$ fixed at 20 keV and $T_1$ varied between 50 and 90 keV), the two bin images were combined to maximize the CNRCD. For each element, the CNRCD$_{\text{max}}$ exhibited a wide flat maximum for $T_1$ between 50 and 70 keV, proving that the CNRCD can not be significantly increased by fine threshold optimization. As rule of thumb, $T_1$ could be fixed to 50 keV independently of the high-Z element. This effect was already described by Sawall et al. for iodine. For each
element, the CNRCD$_{\text{max}}$ measured with two energy thresholds was higher than the one measure with only one energy threshold for the same tube voltage. This effect has been investigated for iodine in a recent publication.\textsuperscript{12} For the same phantom size and tube voltage, the values herein found are compatible with the one of the publication. For all high-Z elements, the simulations were in good agreement with the measurements. The maximum measured deviations were found for the two bins experiment for $T_1 > 70$ keV, probably because the simulated spectral response does not reproduce accurately the real spectral response in the whole interval of investigated energies.

After the validation, the simulations were used to investigate CNRCDs and dose reductions in different scenarios. A set of ideal high-Z solutions (I, Ce, Gd, Yb, W, Au, and Bi) in water was used to avoid contrast enhancement due to the solvent or molecular structure of the contrast agent. For the different high-Z elements in the different scenarios, the maximum CNRCDs relative to iodine are listed in Table V. For each patient size and filtration setting, the elements providing the highest CNRCD are highlighted in Table V and the corresponding dose reductions are summarized in Table VI. A result common to all the patient sizes is that the maximum CNRCD is achieved at a tube voltage equal to $U_{\text{ref}}$. For the adult and obese patient size, the usage of gadolinium instead of iodine at the same concentration can lead to dose reductions around 50%. For the infant patient size, a $27 \pm 2\%$ dose reduction was achieved using cerium. As it can be seen in Figures 6–8, further dose reductions can be achieved in all scenarios if tube voltages below $U_{\text{ref}}$ are considered. The examination of obese patients is the most challenging concerning an adequate tube current time product. However for these patients, the maximum dose reduction with $U < U_{\text{ref}}$ is $65 \pm 1\%$ (gadolinium at 90 kV without Sn filter), which is only slightly better that the $53 \pm 2\%$ dose reduction already found for gadolinium at 120 kV without a Sn filter.

As shown in Table IV, further increases of the CNRCD and consequent dose reductions can be achieved by using two optimally combined bin images instead of only one threshold image. Despite improvements are measured for all the considered elements, some specific elements benefit more than other of this effect. From Table IV, it can be seen how the ytterbium CNRCD increases by 9.5%, whereas for iodine the improvement is only of 5.8%.

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Fig. 8. For the simulations of an obese patient (50 cm × 40 cm), the relative CNRCD (top row) and the dose reductions (bottom row) of the different high-Z solutions are shown as function of the tube voltage. In the left column, an additional Sn filter was deployed. Results are normalized to the value of iodine at 120 kV without Sn filter. [Color figure can be viewed at wileyonlinelibrary.com]
Among all the investigated elements, gadolinium resulted to be the most promising high-Z element for contrast-enhanced CT: it could provide dose reduction values of around 50% for adult and obese patients scans and up to 30% for infant patients in combination with a 0.4-mm Sn filter. Compared to the other elements, gadolinium has also the advantage that it is a well-established contrast agent for magnetic resonance imaging. Therefore, its implementation as a CT contrast agent should be facilitated. However, it has to be stressed that...
the gadolinium-based contrast agents which are currently available in clinic have a concentration significantly lower than the iodine-based contrast agents (see Table I). A simplistic increase of the gadolinium concentration is not the solution since gadolinium-based contrast agents are being investigated for their potential toxicity for the human neurons. Nonetheless, nanoparticle contrast agents based on gadolinium have been already studied for applications in magnetic resonance and micro-CT.

Besides contrast enhancement and biocompatibility, also k-edge imaging and material decomposition performance must be taken into account when evaluating high-Z elements as potential CT contrast agents. Unlike iodine, the heavier elements have k-edges at energies where photons are still transmitted through the patient. This can be nicely exploited in combination with the adjustable thresholds of PC detectors to generate better contrast agent maps or to decompose multiple contrast agents at the same time. In the future, we plan to investigate which is the best performing high-Z element for k-edge imaging.

The findings of this work partially differ from what found by Nowak et al. for a similar investigation with an EI detector. The authors quantified via simulations the potential dose reduction achievable for four different patient sizes (16, 32, 48, and 64 cm diameter) with high-Z contrast agents (I, Gd, Ho, Yb, Hf, W, Os, Au, and Bi) and tube voltages between 70 and 180 kV.

One of the main differences is that, as the tube voltage increases, the CNRCD of the different elements decreases more rapidly for the EI detector than for the PC detector. For example, when increasing the tube voltage from 80 to 140 kV for the adult phantom size, the iodine CNRCD decreases by 31% for the PC detector, whereas for the EI detector the decrease is 44%. A possible explanation is that as the tube voltage increases, the spectrum detected by the EI detector becomes harder than the one detected by the PC detector because the EI spectrum is weighted by the photon energy. In Fig. 9 left, the detected spectra (through a 32 cm water phantom) are plotted for both detectors. The EI detector was simulated as a Gd$_2$O$_2$S layer 1.4 mm thick. The PC detector was simulated as described in Section II.C at 80 and 140 kV. It can be seen how for a tube voltage of 80 kV the centers of mass of the two spectra are approximately the same, whereas at 140 kV the center of mass of the EI spectrum is 9% higher than the PC’s one. In the interval of energies relevant for CT imaging, the attenuation coefficient of matter without k-edge decreases with increasing energies. Therefore the contrast measured by the EI detector will be lower than for the PC detector.

Another difference between the two investigations is that in each scenario the maximum dose reduction for the EI detector is achieved by an element slightly heavier than for the PC detector. For each scenario and detector, the atomic number of the element providing the highest dose reduction is shown in Fig. 9 right. As discussed before, the spectrum detected by an EI detector has a higher center of mass than that of a PC detector and therefore the maximum CNRCD for an EI detector is reached by elements with a k-edge at a slightly higher energy compared to PC detector.

A common finding between the two works is that the best performance are always reached for a tube voltage equal to $U_{ref}$.

5. CONCLUSIONS

The investigation carried out in this work highlighted the potential of contrast agents based on elements heavier than iodine for contrast-enhanced PCCT. Between the investigated elements, gadolinium provided the highest contrast enhancement in most scenarios. Compared to iodine, the usage of gadolinium lead to dose reductions up to 50% for adult and obese patients and up to 30% for infant patient in combination with a 0.4-mm Sn filter. Also, ytterbium in combination with the Sn filtration resulted to be a good candidate adult and obese patients. Further dose reductions can be achieved by using a tube voltage lower than $U_{ref}$ or two optimally combined bin images. For the latter option, the maximum achievable CNRCD was not significantly dependent on the value of the higher energy threshold, which can therefore be used to optimize other processes like k-edge imaging.

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CONFLICT OF INTEREST

The authors have no conflict to disclose.

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