

# Radiation Exposure of Abdominal Cone Beam Computed Tomography

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## Abstract

**Purpose** To evaluate patients radiation exposure of abdominal C-arm cone beam computed tomography (CBCT).

**Methods** This prospective study was approved by the institutional review board; written, informed consent was waived. Radiation exposure of abdominal CBCT was evaluated in 40 patients who underwent CBCT during endovascular interventions. Dose area product (DAP) of CBCT was documented and effective dose (ED) was estimated based on organ doses using dedicated Monte Carlo

simulation software with consideration of X-ray field location and patients' individual body weight and height. Weight-dependent ED per DAP conversion factors were calculated. CBCT radiation dose was compared to radiation dose of procedural fluoroscopy. CBCT dose-related risk for cancer was assessed.

**Results** Mean ED of abdominal CBCT was 4.3 mSv (95 % confidence interval [CI] 3.9; 4.8 mSv, range 1.1–7.4 mSv). ED was significantly higher in the upper than in the lower abdomen ( $p = 0.003$ ) and increased with patients' weight ( $r = 0.55$ , slope = 0.045 mSv/kg,  $p < 0.001$ ). Radiation exposure of CBCT corresponded to the radiation exposure of on average 7.2 fluoroscopy minutes (95 % CI 5.5; 8.8 min) in the same region of interest. Lifetime risk of exposure related cancer death was 0.033 % or less depending on age and weight.

**Conclusions** Mean ED of abdominal CBCT was 4.3 mSv depending on X-ray field location and body weight.

**Keywords** Cone beam computed tomography · Radiation dosage · Fluoroscopy · Radiation-induced cancer

## Introduction

C-arm cone beam computed tomography (CBCT) is an advanced imaging technology that acquires volumetric “CT-like” images by flat panel detectors in state-of-the-art interventional angiography suites. Multiple viewing planes in three-dimensional (3D) datasets and enhanced soft-tissue contrast provide substantial improvement to conventional fluoroscopy and angiography [1]. In recent years, various clinical applications of CBCT have been evaluated for vascular and nonvascular interventional procedures and

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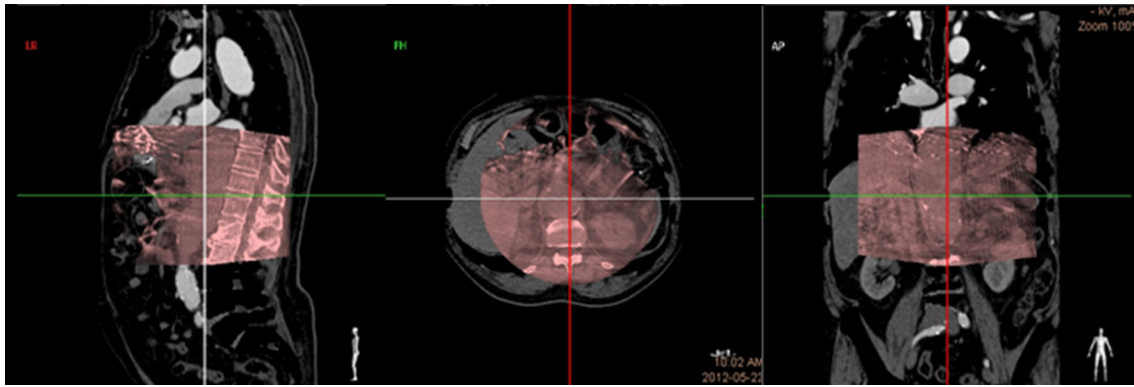
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**Fig. 1** Volumetric CBCT dataset (*pink*) coregistered to MDCT dataset (*grey*) in a patient with thoracoabdominal aortic aneurysm. CBCT was acquired in the patient's upper abdomen just before the intervention for image fusion guidance during BEVAR

reports of use emerge in medical literature. These include biopsy and ablation needle guidance [2–4], endovascular road-mapping and catheter guidance [5–9], immediate multiplanar posttreatment assessment [6, 10], and soft-tissue imaging [11, 12]. These features may enhance procedural efficacy and safety, but the body of data on radiation exposure is still limited.

CBCT should not result in additional radiation exposure for the medical staff, as all members are usually outside the interventional suite during acquisition. For patients, the application of CBCT may lead to an increase of procedural exposure to radiation, but a net reduction of fluoroscopy time and angiogram series due the availability of better spatial information also is possible [5, 13]. (Nonuniform) exposure to ionizing radiation can be assessed in terms of equivalent organ doses and effective dose (ED), which are expressed in units of Sievert, typically in the millisievert (mSv) range. The organ doses allow an estimation of the attributable risk to develop lethal malignancy later in life [14, 15]. The purpose of our study was to evaluate patients' radiation exposure of abdominal C-arm CBCT.

## Materials and Methods

This prospective study was approved by the institutional review board; informed consent was waived. CBCT radiation exposure was prospectively evaluated in patients with thoracoabdominal aneurysms and other complex vascular diseases who underwent fenestrated or branched endovascular aortic repair (FEVAR/BEVAR) or endovascular recanalization and stenting procedures between June 2012 and August 2013. In all patients, CBCT was performed before the intervention for image fusion guidance. Figure 1 shows an example of abdominal CBCT coregistered to multidetector computed tomography (MDCT) angiography.

## Acquisitions

Abdominal CBCT was acquired at our angiography suite through rotational movement of the C-arm covering a 180° circular under couch trajectory (Allura Xper FD20, Philips Healthcare, Best, The Netherlands). Volumetric datasets were automatically sent to a 3D workstation for multiplanar viewing and image coregistration. All technical parameters of the CBCT acquisition are summarized in Table 1. Standard parameters of fluoroscopic imaging were a total beam filtration of 0.4-mm copper and 3.5-mm aluminum, 15 frames per second, and automatic exposure control (AEC).

## Radiation Exposure Analysis

For all procedures, radiation exposure of the CBCT run and total procedure in terms of dose area product (DAP; in  $\text{Gycm}^2$ ) as well as total procedural fluoroscopy time were registered in the fluoroscopy unit's radiation dose report. For the last 17 procedures, standardized radiation dose structured reporting (RDSR) had become available wherein the DAP values of procedural fluoroscopy were also registered. Patients' individual body weight and height at the date of the intervention were documented. Precise CBCT X-ray field location was displayed on the scout image of each CBCT run. CBCT X-ray field was focused on the upper abdomen in 24 patients and on the lower abdomen in 16. Figure 2 demonstrates exemplary the X-ray field and included organs for upper and lower abdominal CBCT as drawn on the PCXMC phantom.

## Effective Dose Estimation

The ED was estimated by means of a dedicated Monte Carlo software program (PCXMC v2.0, STUK, Helsinki, Finland) in which a size adjustable mathematical

**Table 1** Technical parameters of abdominal CBCT acquisition with automatic exposure control

Parameter	Abdominal CBCT
Name	CT abdomen LD roll
Tube voltage	117–123 kV*
Tube current	142–325 mA*
mAs value	269–1027 mAs*
Pulse width	6–10 ms*
Speed	30 frames/s
Exposure/acquisition time	10.5 s
Angle of image acquisition	180°
Number of projections	316
Source–image distance	120 cm
Focus–isocenter distance	81 cm
Inherent filtration	2.5-mm aluminum equivalent
Added filtration	1-mm aluminum + 0.9-mm copper
Detector	Dynamic Flat Panel, Trixell, Pixium 4700
Image matrix	2480 × 1910 pixels
Pixel pitch	154 μm
Detector size	30 × 38 cm
Field of view CBCT (height × width × depth)	19 × 25 × 25 cm
Reconstructed slice thickness	0.98 mm

\* Values depend on body characteristics and vary during acquisition due to automatic exposure control

hermaphrodite phantom model is used (Fig. 2). The phantom incorporates 29 different organs and tissues for which organ doses can be calculated under consideration of patient size, exposure geometry, and beam quality. With PCXMC software, organ doses were calculated for every patient separately based on CBCT technical parameters (Table 1) and patients' individual DAP values and body characteristics. To this extent, the 180° rotation was divided into 19 projections with a 10° increment each. For each angle, we ensured that the center of the (hermaphrodite) software phantom remained in the isocenter of rotation, i.e., the focus-skin distance and entrance field size were adjusted according to the thickness of the phantom. The equivalent dose of all organs was estimated by the software for each projection using 1/19 of the total CBCT DAP value. The corresponding ED was calculated by means of ICRP 103 tissue weighting factors [14]. Total ED of CBCT represents the sum of the 19 projections. Calculations were separately repeated for each patient with adjustment of patient's individual body weight and height as well as precise CBCT X-ray field location and mean individual kV value. Weight-dependent ED per DAP conversion factors and their variation with projection angles were calculated.

## Comparison of CBCT with Fluoroscopy

The average fluoroscopy time corresponding to a radiation exposure equivalent to the radiation exposure of the CBCT was estimated for each patient individually by dividing the CBCT DAP by the fluoroscopy DAP rate. The fluoroscopy DAP rate is calculated as the total fluoroscopy DAP divided by the total fluoroscopy time.

## Assessment of Exposure Related Cancer Risk

Assessment of the cancer risk due to CBCT exposure was performed using the PCXMC software. The risk estimates are based on the organ doses, organ-specific risk factors, patient age, and risk models established by the Biological Effects of Ionizing Radiation (BEIR) VII committee [15] resulting in the risk of exposure induced death (REID).

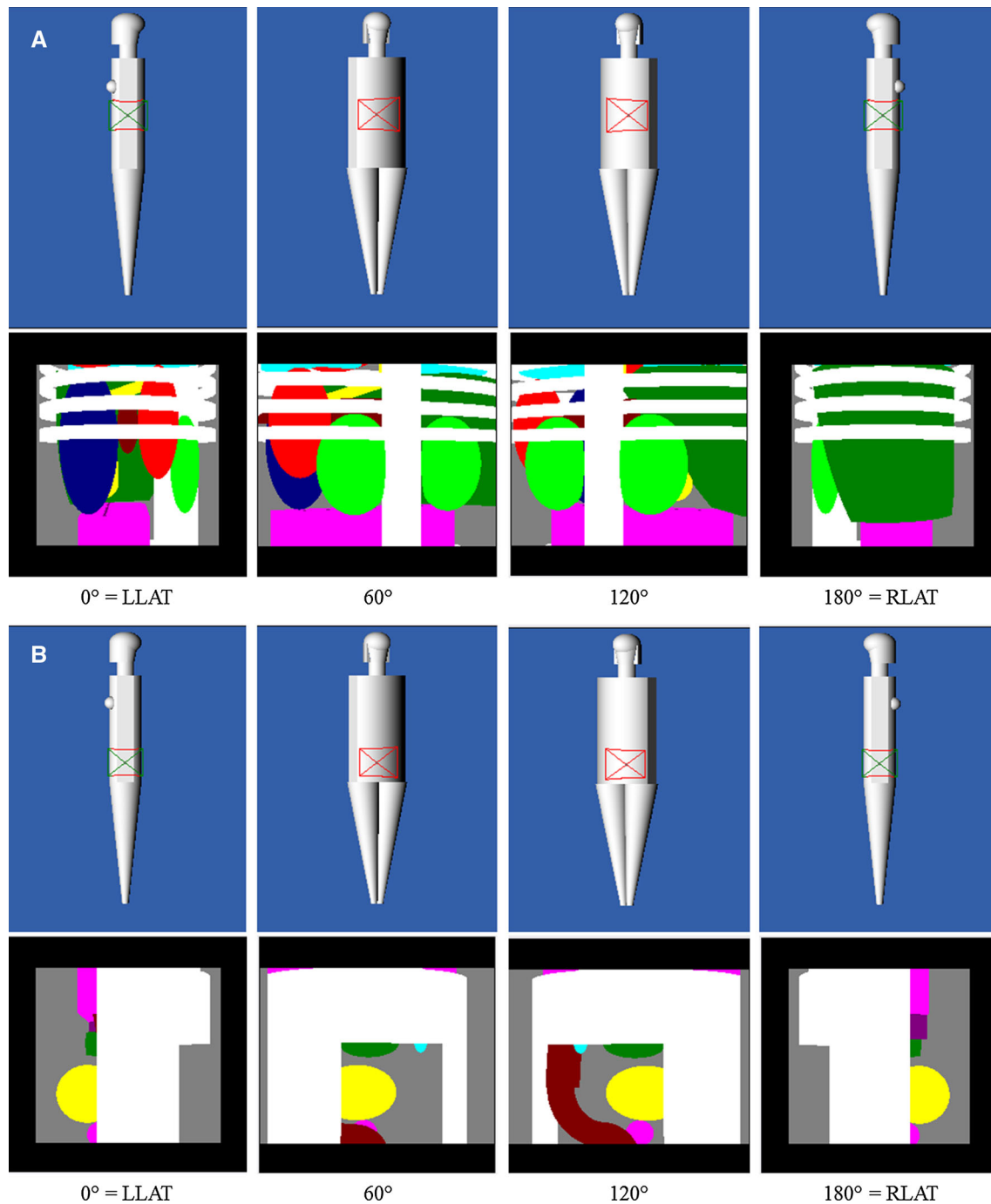
## Statistical Analysis

Differences in radiation exposure and patient characteristics between upper and lower abdominal CBCT were tested on statistical significance using the independent samples *t* test (SPSS statistics 20.0, Chicago, IL). Correlations between patients' body weight and height and CBCT radiation exposure and equivalent fluoroscopy time were examined using linear regression. Two-sided *p* values <0.05 were considered significant.

## Results

The study group consisted of 27 male and 13 female patients with a mean ± SD age of 68 ± 12 years and mean ± SD body mass index (BMI) of 26.7 ± 5.1 kg/m<sup>2</sup>. Table 2 gives an overview of the average organ doses for the CBCT run and standard error of the mean as well as associated tissue weighting factors [14]. The radiation dose was highest in the kidneys, spleen, adrenals, pancreas, and liver for upper abdominal CBCT and by ovaries, uterus, colon, small intestine, urinary bladder, and active bone marrow for lower abdominal CBCT. Table 3 provides summarized results of CBCT radiation exposure estimation. ED of the CBCT run was estimated to be in the range of 1.1–7.4 mSv. Mean ED for upper abdominal CBCT was 4.9 mSv (95 % confidence interval [CI] 4.3–5.4 mSv) and mean ED for lower abdominal CBCT was 3.5 mSv (95 % CI 3.0–4.1 mSv); differences between upper and lower abdominal X-ray field location were statistically significant (*p* = 0.003).

There was a significant positive correlation between DAP value and body weight (Fig. 3A; *r* = 0.76, slope



**Fig. 2** Upper rows Projection of the X-ray field on the PCXMC phantom exemplary shown for 4 of the 19 steps. Bottom rows schematic representation of the organs present in each projection. Organs included in upper abdominal CBCT X-ray field **A** lung base (light blue), heart (red), stomach (dark blue), distal esophagus (yellow), liver (dark green), spleen (red), pancreas (brown), kidneys

and adrenals (light green), colon (pink), small intestine (pink), gallbladder (yellow), and skeleton (white). Organs included in lower abdominal CBCT X-ray field **B** colon (brown), small intestine (pink), urinary bladder (yellow), female and male reproductive organs (red, green, and light blue), prostate (pink), and skeleton (white). LLAT left lateral detector position; RLAT right lateral detector position

0.238 Gy $\text{cm}^2/\text{kg}$ ,  $p < 0.001$ ) as well as ED and body weight (Fig. 3B;  $r = 0.55$ , slope = 0.045 mSv/kg,  $p < 0.001$ ). The conversion factor ED per DAP decreased with increasing body weight (Fig. 3C;  $r = 0.99$ , slope =  $-0.00279$  mSv/Gy $\text{cm}^2/\text{kg}$ ,  $p < 0.001$  for upper abdominal

CBCT and  $r = 0.99$  slope =  $-0.00197$  mSv/Gy $\text{cm}^2/\text{kg}$ ,  $p < 0.001$  for lower abdominal CBCT). Adding patients' body height as an independent variable into the regression models yielded no significant regression coefficients for height ( $p > 0.05$ ).

**Table 2** Mean equivalent organ doses and standard error of the mean for upper and lower abdominal CBCT and associated tissue weighting factors (IRCP 103) exemplary for mean patient size (170 cm, 78 kg) and associated DAP value (14.7 Gy $\text{cm}^2$ )

Organ	Upper abdominal CBCT mean dose $\pm$ SE (mGy)	Lower abdominal CBCT mean dose $\pm$ SE (mGy)	TWF IRCP 103
Active bone marrow	5.07 $\pm$ 0.71	8.92 $\pm$ 0.8	0.12
Adrenals	24.22 $\pm$ 1.56	0.34 $\pm$ 0.12	0.009
Brain	0 $\pm$ 0	0 $\pm$ 0	0.01
Breasts	0.64 $\pm$ 0.11	0.03 $\pm$ 0.02	0.12
Colon	4.68 $\pm$ 1.44	10.4 $\pm$ 1.38	0.12
Esophagus	4.8 $\pm$ 0.59	0.12 $\pm$ 0.05	0.05
Extrathoracic airways	0.03 $\pm$ 0.01	0 $\pm$ 0	0.009
Gallbladder	11.43 $\pm$ 2.16	1.68 $\pm$ 0.28	0.01
Heart	2.79 $\pm$ 0.39	0.09 $\pm$ 0.04	0.011
Kidneys	32.79 $\pm$ 1.57	1.38 $\pm$ 0.29	0.012
Liver	15.14 $\pm$ 2.18	0.59 $\pm$ 0.13	0.05
Lung	2.8 $\pm$ 0.32	0.07 $\pm$ 0.03	0.12
Lymph nodes	6.05 $\pm$ 1.12	3.11 $\pm$ 0.36	0.009
Muscle	3.21 $\pm$ 0.51	4.52 $\pm$ 0.7	0.009
Oral mucosa	0.02 $\pm$ 0	0 $\pm$ 0	0.009
Ovaries	1.55 $\pm$ 0.55	17.28 $\pm$ 1.99	0.04
Pancreas	15.52 $\pm$ 2.14	0.64 $\pm$ 0.17	0.009
Prostate	0.18 $\pm$ 0.09	8.78 $\pm$ 2.04	0.005
Salivary glands	0.02 $\pm$ 0.01	0 $\pm$ 0	0.01
Skeleton	4.14 $\pm$ 0.49	5.15 $\pm$ 0.81	0.00
Skin	2.27 $\pm$ 0.32	2.65 $\pm$ 0.41	0.01
Small intestine	6.16 $\pm$ 2.12	10.26 $\pm$ 1.15	0.009
Spleen	24.94 $\pm$ 2.77	0.56 $\pm$ 0.16	0.009
Stomach	11.45 $\pm$ 1.99	0.87 $\pm$ 0.17	0.12
Testicles	0.04 $\pm$ 0.02	1.9 $\pm$ 1.02	0.04
Thymus	0.55 $\pm$ 0.1	0.02 $\pm$ 0.01	0.009
Thyroid	0.07 $\pm$ 0.02	0 $\pm$ 0	0.05
Urinary bladder	0.39 $\pm$ 0.15	9.65 $\pm$ 1.71	0.05
Uterus	1.29 $\pm$ 0.48	14.6 $\pm$ 1.9	0.005

TWF tissue weighting factor

Radiation exposure of CBCT corresponded to the radiation exposure of on average 7.2 minutes (95 % CI 5.5–8.8 min) live fluoroscopy in the same region of interest. CBCT dose equivalent fluoroscopy time increased significantly with weight ( $r = 0.53$ , slope = 0.188 min/kg,  $p = 0.034$ ).

Calculated risk of CBCT exposure-induced death based on organ doses for various cancer types is shown in Fig. 4 as a function of age and body weight. For example, for a 60-year-old female patient with a body weight of 78 kg, the stochastic risk for exposure-related cancer death was

0.0182 % for upper abdominal CBCT and 0.0147 % for lower abdominal CBCT, respectively. Calculated maximum risk for lifetime exposure induced death was 0.033 %.

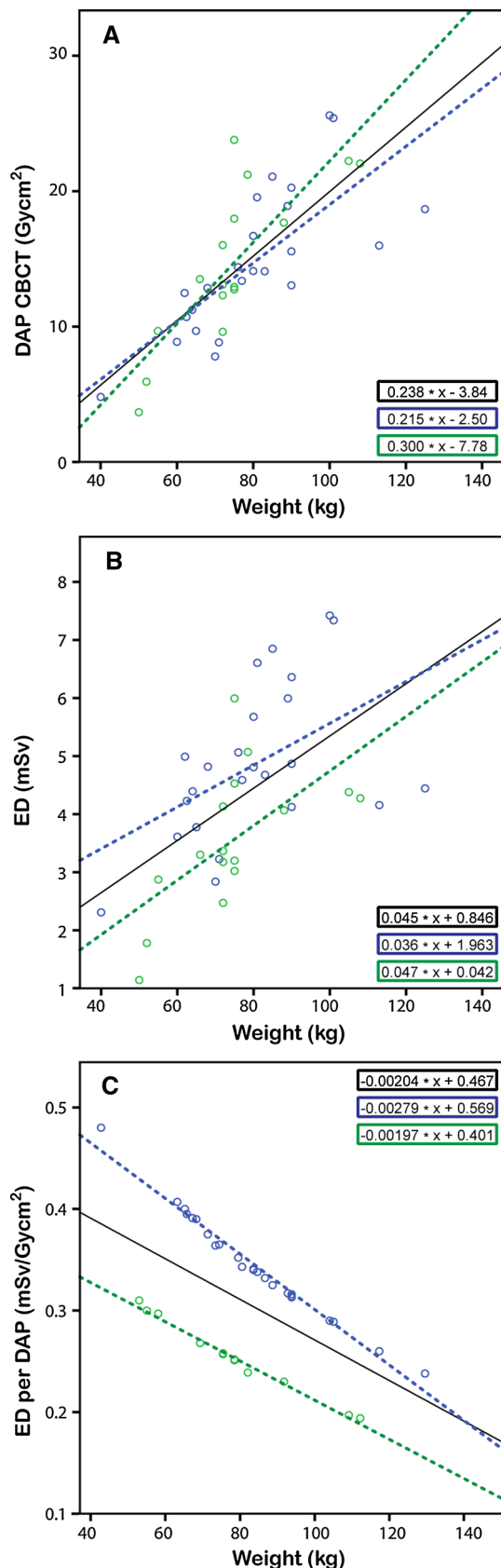
## Discussion

We prospectively evaluated the patient's radiation exposure in 40 abdominal CBCT runs by means of dedicated Monte Carlo modelling. Organs positioned in the X-ray field received the highest dose. Average ED of CBCT was 4.3 (range 1.1–7.4) mSv. Patient's radiation exposure of abdominal CBCT equals approximately 1.8–2.7 times the annual background radiation dose worldwide and the Netherlands (2.4 and 1.6 mSv respectively, excluding doses for medical purposes) [15, 16] and approximately half of the ED of abdominal MDCT (8 mSv, values reported between 3.5 and 25 mSv) [17, 18]. There was a significant relationship towards lower ED in CBCT with the X-ray field in the lower abdomen compared with upper abdomen ( $p = 0.003$ ) and a strong significant positive correlation between ED and body weight ( $p < 0.001$ ). For correct interpretation of the ED values, one must realize the uncertainties present in such estimations. Because ED and organ doses cannot be measured in vivo, different approaches are followed. In MDCT, dose estimations are often performed by means of CT dose index (CTDI). Due to the smaller in-plane field of view and larger scan range of CBCT compared with MDCT, the CTDI values are not applicable for CBCT [19, 20]. A more accurate method, in line with the definition of ED, is to estimate the organ doses and subsequently calculate the ED using tissue weighting factors [14]. The organ doses can be measured using an anthropomorphic phantom with integrated thermoluminescent dosimeters (TLDs), or using the DAP value (displayed by the angiography system) and Monte Carlo software. Main disadvantage of a dosimeter phantom is that the conversion factor ED per DAP does not account for differences in body characteristics, whereas our data show that there is a strong weight dependency for the conversion factor. Furthermore, the phantom might not be representative for the actual patient population as illustrated in the TLD phantom study from Tyan et al. [20] evaluating CBCT in liver embolization in the Taiwan population. They observed much higher DAP values in their patients compared to the phantoms.

To achieve the best possible estimation of the ED of CBCT runs, we performed separate PCXMC Monte Carlo calculations for each patient while precisely accounting for individual CBCT X-ray field location and body characteristics. Moreover, we divided the 180° CBCT run into 19 projection angles, thereby compensating for the varying

**Table 3** Results of CBCT radiation exposure estimation and impact on total procedure DAP as well as fluoroscopy time equivalence to CBCT

	All										<i>p</i> value					
	Upper abdominal CBCT					Lower abdominal CBCT										
	Mean	95 % CI	Min	Max	n	Mean	95 % CI	Min	Max	n						
<b>Patients</b>																
Number of patients (male/female)	40 (27/13)				24 (20/4)	16 (7/9)										
Body weight (kg)	72	83	40	125	80	73	87	40	125	74	67	82	50	108	0.32	
Body length (cm)	170	167	174	198	174	170	178	157	198	165	160	171	130	183	0.022	
BMI (kg/m <sup>2</sup> )	26.7	25.1	28.3	43.3	26.4	24.4	28.4	16.0	39.9	27.2	24.6	29.8	18.1	43.3	0.619	
<b>CBCT</b>																
DAP (Gycm <sup>2</sup> )	14.7	13.0	16.4	25.6	14.7	12.6	16.9	4.8	25.6	14.5	11.6	17.4	3.7	23.8	0.901	
ED per DAP (mSv per Gycm <sup>2</sup> )	0.31	0.29	0.33	0.48	0.34	0.32	0.37	0.24	0.48	0.25	0.24	0.27	0.19	0.31	<0.001	
Effective dose (mSv)	4.3	3.9	4.8	7.4	4.9	4.3	5.4	2.3	7.4	3.5	3.0	4.1	1.1	6.0	0.003	
<b>Total Procedure</b>																
Total DAP (Gycm <sup>2</sup> )	217	159	276	699	286	210	361	48	699	114	46	182	15	501	0.003	
Proportion CBCT on total procedure DAP	12.9 %	9.8 %	16.0 %	34.1 %	7.3 %	5.3 %	9.3 %	1.9 %	20.5 %	21.4 %	16.4 %	26.2 %	4.4 %	34.1 %	<0.001	
<b>Comparison CBCT – fluoroscopy</b>																
Number of patients (male/female)	17 (9/8)					12 (5/7)										
Cumulative fluoroscopy time	22 min 55 s	10 min 8 s	35 min 2 s	4 min 1 s	93 min 41 s	56 min 5 s	35 min 2 s	77 min 9 s	30 min 28 s	93 min 41 s	9 min 5 s	6 min 10 s	12 min 0 s	4 min 1 s	19 min 44 s	0.011
DAP fluoroscopy (Gycm <sup>2</sup> )	42.8	20.9	64.7	3.1	147.4	104.1	70.5	137.6	73.2	147.4	17.3	23.8	3.1	37.4	0.006	
DAP rate (mGycm <sup>2</sup> /s)	32.3	25.9	38.7	9.8	61.3	32.5	24.5	40.5	22.6	43.6	32.2	23.6	40.8	61.3	0.968	
Fluoroscopy time equivalent to CBCT dose	7 min 12 s	5 min 30 s	8 min 48 s	3 min 12 s	15 min 12 s	7 min 42 s	4 min 30 s	10 min 54 s	3 min 12 s	12 min 24 s	7 min 0 s	5 min 0 s	8 min 54 s	3 min 12 s	15 min 12 s	0.708

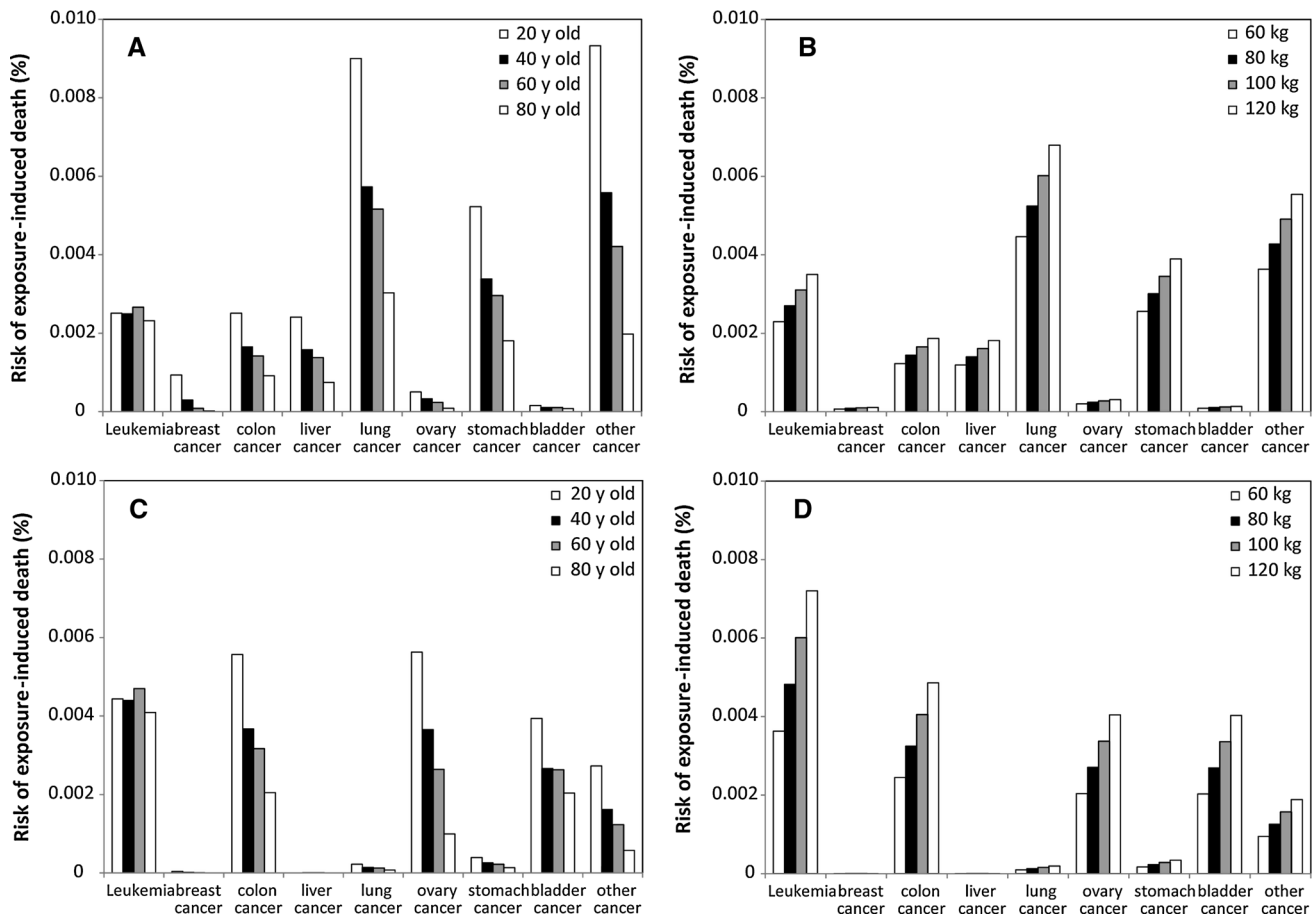


**Fig. 3** Correlation between **A** DAP value versus body weight **B** ED versus body weight and **C** ED per DAP versus body weight for upper and lower abdominal CBCT. *Blue symbols and lines* upper abdominal CBCT. *Green symbols and lines* lower abdominal CBCT. *Black lines* all CBCT

phantom thickness by adjusting the focus-skin distance and entrance field size. A limitation is that this method does not incorporate the dose and kV-modulation during the CBCT rotation by the AEC as a result of varying body geometry (i.e., the body is thicker in lateral projection compared to PA/AP). To estimate the error introduced, we assessed the angular dependence of DAP and high-voltage during CBCT acquisition by performing separate experiments on an Alderson Rando abdominal phantom, whereas DAP-rate and kV were dynamically recorded on video tape as displayed during rotation. ED was recalculated using the obtained nonuniform DAP and kV distribution showing that uniformly distributed DAP values and the fixed high-voltage overestimate the ED by 3.0 %.

Prior research has been performed on CBCT radiation exposure. Suzuki et al. performed a TLD phantom study and Monte Carlo simulations based on phantom DAP values to assess the radiation exposure of upper abdominal CBCT in three different angiography units (Siemens Artis dTA, Philips Allura Xper, GE Innova 4100). In the Monte Carlo simulations, they evaluated 13 projection angles and calculated ED per DAP conversion factors using the former ICRP 60 tissue weighting factors. Doses were estimated for three different phantom sizes. ED of upper abdominal CBCT in a medium size phantom (BMI 23.1 kg/m<sup>2</sup>) was reported to be in the range from 2.4 to 3.1 mSv, depending on the angiography unit's CBCT technical parameters. Largest dose difference between CBCT protocols from different angiography units was 0.8 mSv [21]. Analogously to our results, they found a decreasing conversion factor ED per DAP for increasing phantom size. Other studies reported the ED of abdominal CBCT to be in the range from 3.5 to 25.4 mSv; however, these results are based on phantom studies or lack detailed information on dose estimation method [6, 12, 22–25].

Exposure to ionizing radiation introduces risk of developing cancer. The ICRP has established the lifetime detriment adjusted risk coefficient for cancer in the whole population, i.e., comprised of all ages, to be 5.5 % per unit Sievert [14]. Such a risk estimation based on the ED exhibits inaccuracies as it does not account for age at exposure, current age, or body region exposed. We therefore performed accurate risk estimations using the PCXMC software that incorporates organ doses, age, and organ-specific risk factors [15], expressed in lifetime risk of exposure induced cancer death. The risk of overall cancer incidence is approximately a factor two higher, although



**Fig. 4** Risk for exposure-induced lethal cancer types for upper abdominal CBCT (A, B) and lower abdominal CBCT (C, D) based on individual organ doses as a function of age (A, C, weight = 80 kg) and weight (B, D, age = 60 years)

this varies for specific cancer types according to their lethality [15]. The stochastic model for cancer risks below 100 mSv has to be interpreted with caution. The BEIR VII committee reports 95 % confidence intervals for overall cancer mortality and incidence showing that the risks can be estimated within a factor of two [15]. This means that it is prudent to interpret the lifetime attributable risk (LAR) as an order of magnitude rather than an absolute number. Risk of cancer due to the CBCT radiation exposure is very low compared with natural cancer incidence, which is 37–46 %, and natural risk of lethal cancer, which is 18–22 % or one out of five for the U.S. population [15]. To put CBCT radiation in perspective, we performed PXXMC analysis for the whole procedures. In our patient population, mean radiation exposure for FEVAR/BEVAR procedures was 84.9 mSv (95 % CI 62.3–107.2 mSv) and 26.5 mSv (95 % CI 10.7–42.2 mSv) for pelvic procedures. Corresponding risk of cancer therefore was factor 17 and 8 higher respectively compared to the risk from only CBCT exposure. Furthermore, CBCT radiation has to be seen in the context of the vascular disease management as this patient population is expected to undergo further MDCT

during follow-up or may undergo reinterventions, which summarizes considerable lifetime dose.

As any new exposure, CBCT-related radiation has to be discussed in the context of the basic safety principle, i.e., to keep any radiation exposure As Low As Reasonably Achievable (ALARA). CBCT technology might contribute to enhance procedural efficacy and reduce procedural fluoroscopy time. The medical staff is normally in a protected area during CBCT. Therefore, any reduction in fluoroscopy due to the application of CBCT might lead to a welcome reduction of dose incurred by interventional radiologists.

In conclusion, ED of abdominal CBCT corresponds to approximately half of the dose of abdominal MDCT. Application of CBCT will result in a reduction of patients total procedural radiation exposure if a reduction of fluoroscopy time of approximately 7 min is achieved.

**Conflict of interest** Anna M. Sailer, Geert Willem H. Schurink, Joachim E. Wildberger, Rick de Graaf, Willem H. van Zwam, Michiel W. de Haan, Gerrit J. Kemerink and Cécile R. L. P. N. Jekens have no conflict of interest.



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