Feasibility of iodine-123-mIBG SPECT/CT quantification in neuroblastoma using CZT and NaI detectors

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Abstract

Background In [^{123}I]mIBG SPECT/CT for neuroblastoma, lesion uptake quantification could improve therapy monitoring. This study compared quantitative accuracy of a CZT (WEHR45) and NaI (LEHR) system (GE Discovery 670). **Methods** Volume sensitivity VS hom was estimated from a homogenous cylindrical phantom (811 ml) acquired with body contour or fixed 27 cm detector radius. Relative accuracy of VS hom to retrieve true background activity concentration (AC) in an IEC body phantom was calculated. Maximum/peak contrast recovery (CR) of the sphere inserts used VS IEC estimated from the IEC phantom. In 16 children with 37 [^{123}I]mIBG SPECT/CTs (range, 1-6 per patient; CZT, 12; NaI, 25), normal organ SUVmean (liver r/l, spleen, myocardium, blood pool, spine, muscles) were calculated using VS hom and VS IEC. Iterative reconstruction (Q.Metrix) used resolution recovery with/without scatter correction (SC) by dual energy window (DEW; $159 \pm 10\%$ and $130 \pm 10\%$ keV). In 20 exams, metabolic tumor volume (MTV)*SUVmax changes of primary tumors were correlated with changes of MRI tumor volume in serial scans (Pearson). **Results** VS hom ($\text{cts} \cdot \text{MBq}^{-1} \cdot \text{s}^{-1}$) using SC was slightly lower for 27 cm radius vs. body contour with CZT (48 vs. 50, $p < 0.001$) but comparable with NaI (59 vs. 61, $p = 0.18$). Relative error in IEC phantom AC based on VS hom for CZT vs. NaI was -1.3% vs. $+4.1\%$ with SC ($p = 0.22$). Acquisition time reduction by 50% (CZT) showed similar VS hom and relative error. CRmax/peak overestimated true AC in largest spheres (diameter, 22-37 mm) with SC and underestimated it without SC. Average SUVmean in liver and myocardium of CZT vs. NaI patients were similar. In the remaining organs (high estimated scatter proportions of $>60\%$ [CZT] or $>40\%$ [NaI]), average SUVmean differed between CZT and NaI, and coefficient of variation was significantly higher in SC vs. non-SC with CZT. MTV*SUVmax changes correlated with MRI volume changes with $r = 0.62$ (non-SC) or $r = 0.59$ (SC). **Conclusions** In principle, both CZT and NaI allow quantification in [^{123}I]mIBG SPECT/CT, but quantitative accuracy remains limited if using DEW for SC due to effects from source geometry (e.g. phantoms and organs) on scatter. Detector radius and acquisition time showed minor effects. MTV*SUVmax changes might be surrogate of response to therapy.

Background

Children with neuroblastoma (NB) are commonly treated in multinational treatment optimization trials to ensure standardized and progressively improving diagnostic workup and therapy. In the largest international trials by the SIOPEN group (*clinicaltrials.gov* identifier NCT01704716) and the Children's Oncology Group (e.g., NCT03794349, NCT02176967), [^{123}I]metaiodobenzylguanidine (mIBG) scintigraphy remains the essential diagnostic tool besides magnetic resonance imaging (MRI) for initial tumor staging and restaging. Recent guidelines on [^{123}I]mIBG scintigraphy recommend single photon emission computed tomography / computed tomography (SPECT/CT) in addition to planar images to improve lesion detection (1, 2). However, while treatment options in NB multiplied with the aim of individualized therapy (3–5), image assessment in clinical routine and trials remains visual (6, 7) and thus subjective and poorly differentiated. Quantitative image assessment could support advances in treatment optimization by offering parameters of response to therapy as well as – generally speaking –

comparability between examinations, patients, cameras and study centers. However, attempts to derive additional prognostic or predictive information from (semi-)quantitative parameters in [^{123}I]mIBG SPECT/CT have been scarce (8).

The accuracy of quantification in SPECT/CT is not only influenced by patient-specific factors (patient geometry, attenuation, scatter within the patient) and system-specific factors (e.g., intrinsic resolution, collimator-detector response [CDR], reconstruction algorithms) (9–16). Detection properties for different radionuclides also differ between detector materials, which are commonly sodium iodide (NaI) or – more recently – cadmium zinc telluride (CZT). Brady *et al.* recently showed that quantification of [^{123}I]mIBG SPECT/CT in patients with neuroblastoma is feasible with two different NaI cameras and can provide comparable standardized uptake values (SUV) for normal organs between a low energy high resolution (LEHR) and a medium energy (ME) collimator (17).

The current study investigated a NaI and CZT camera to evaluate if quantification of clinical [^{123}I]mIBG SPECT/CT data using phantom-based volume sensitivity estimates is equally feasible with both cameras using standard reconstruction algorithms provided by the manufacturer. In addition to different detectors, major influencing factors (detector positioning, acquisition time, object geometry and scatter correction) were evaluated to determine if their variation in clinical routine would substantially affect the reproducibility of quantitative data. Finally, an exemplifying analysis using quantitative [^{123}I]mIBG SPECT/CT data of NB patients examined the correlation of changes in metabolic tumor volume (MTV)*SUVmax with changes of the tumor volume in MRI during therapy as surrogates for response.

Methods

Phantom measurements: Image acquisition

Two phantoms, (1.) a homogeneously filled cylindrical phantom (inner diameter, 10 cm; volume, 811 ml; 33 kBq/ml iodine-123) and (2.) a NEMA IEC Body phantom without the lung insert (background volume, 9.65 liters; background, 17 kBq/ml iodine-123; spheres, 137 kBq/ml; sphere diameters, 10, 13, 17, 22, 28 and 37 mm) were scanned alternately with a GE Discovery 670 CZT (WEHR45 collimator; GE Healthcare, Milwaukee, WI, USA) and GE Discovery 670 DR Pro (NaI detector; LEHR collimator) camera. Each acquisition was performed using a) body contour mode and b) a fixed detector radius of 27 cm (360° scan, 6°/step, 40 s/step; matrix size, 128 × 128). The fixed detector radius simulated a scan setup where an automated body contouring is inappropriate (e.g., anxious/claustrophobic patient or equipment for anesthesia). Energy windows were 159 ± 10% keV (photopeak) and 130 ± 10% keV (scatter) with both cameras (dual energy window; DEW).

Phantom measurements: Image reconstruction

All data were reconstructed using standard settings defined by a manufacturer-specific workflow (GE “preparation for Q.Metrix” tool) using 3D-ordered subset expectation maximization (OSEM; voxel size, 4.42 × 4.42 × 4.42 mm³; matrix size, 128 × 128; iterations, 4; subsets, 10; postprocessing filter, none). All

data were reconstructed with CT-based attenuation correction, resolution recovery (by a 3D point spread function) and either with scatter correction (SC; DEW method; weighting factor k , 1.0) or without scatter correction (non-SC).

For both the homogenous and the IEC phantom, data with the CZT camera was acquired in list mode, and all data were retrospectively rebinned to reconstruct further datasets representing an acquisition time of 50% (i.e, 20 s/step).

Phantom measurements: Volume sensitivity (homogenous phantom)

To estimate volume sensitivity for the homogeneously filled phantom, a cylindrical volume of interest (VOI) with 11 cm diameter (volume, 1.34 liters) was created covering the whole phantom in each dataset (ROVER software, version 3.0.34, ABX advanced biochemical compounds GmbH, Radeberg, Germany). Volume sensitivity ($\text{cts} \cdot \text{MBq}^{-1} \cdot \text{s}^{-1}$) was calculated by dividing the overall counts in the VOI by the total acquisition time in s, the decay-corrected applied activity in MBq and the voxel size in mm^3 . The mean (and standard deviation; SD) of 4 separate acquisitions with identical acquisition and reconstruction settings at different time points after initial phantom filling was used (with correction for decay).

Estimated volume sensitivity was validated with the IEC phantom data. The analysis was performed using a cylindrical VOI (volume, 644 ml) placed in the background of the IEC phantom with adequate distance from the sphere inserts and the outer phantom wall. The mean volume sensitivity estimated from measurements of the homogeneously filled phantom for the specific camera and reconstruction (SC vs. non-SC) was used to determine background activity concentration (AC) in the IEC phantom in kBq/ml and its relative accuracy compared to the true AC (mean $\pm$ SD of 3 separate acquisitions each).

Phantom measurements: Contrast recovery (IEC phantom)

To calculate maximum and peak contrast recovery (CR) for the IEC phantom spheres, volume sensitivity for the IEC phantom was estimated using a cuboid VOI (volume, 25.3 liters) for each dataset that covered the entire IEC phantom. Volume sensitivity was calculated analogously to the homogenous phantom (mean of 3 serial acquisitions). Using the ACCURATE tool (version v23102018, Ronald Boellaard, Amsterdam UMC, Amsterdam, The Netherlands), the maximum counts of each of the six spheres was estimated. Furthermore, the peak counts of each sphere were determined as the average counts in a spherical VOI of 1.2 cm in diameter that was automatically positioned to calculate the highest peak counts of the corresponding sphere. Sphere AC in kBq/ml was derived from sphere counts using the mean IEC phantom volume sensitivity obtained from the three serial measurements. CR_{max} / CR_{peak} were then calculated as the ratio of maximum/peak sphere AC to true AC.

Phantoms and patients: Estimation of scatter proportions

The estimated proportion of scatter relative to all reconstructed counts was calculated as $(1 - \text{SC data counts} / \text{non-SC data counts})$.

Patients: Characteristics

The patient analysis included 16 children (female, 4; male, 12; median age, 2 years; range, 0.3 to 17 years; 2 children > 5 years of age) who underwent [^{123}I]mIBG SPECT/CT for NB ($n = 13$; mIBG positive, 12; mIBG negative, 1) or suspicion for NB with a different final diagnosis ($n = 3$; mIBG positive, 0). A total of 37 [^{123}I]mIBG SPECT/CT examinations were performed with > 1 examination in 8 of 16 children (range, 2 to 6). In 7 of these 8 children, the camera (GE Discovery 670 CZT or DR Pro) varied between examinations.

Patients: [^{123}I]mIBG SPECT/CT acquisition

[^{123}I]mIBG was administered based on patient weight (median, 7.2 MBq/kg; interquartile range [IQR], 6.9 to 8.8 MBq/kg) according to recommendations by the European Association of Nuclear Medicine (EANM) (18). [^{123}I]mIBG SPECT/CT was performed 23.8 h (IQR, 22.8 to 25.2 h) after injection. SPECT imaging was performed under clinical conditions in body contour mode using a GE Discovery 670 CZT ($n = 22$ examinations) or DR Pro ($n = 14$) over 1 to 2 bed positions (total angular range, 360°; degrees per step, 6°; duration per step, 50 s [$n = 1$] or 40 s [$n = 7$] or 35 s [$n = 18$] or 30 s [$n = 9$] or 20 s [$n = 1$]) including low-dose CT for attenuation correction (automated X-ray tube current modulation; max. tube current, 25 mA; voltage, 120 kV; slice thickness, 3.75 mm). All reconstruction parameters, including energy windows (DEW) for SC, were identical to phantom measurements.

Patients: [^{123}I]mIBG SPECT quantification

Quantification of SPECT data was performed with the ROVER software. Mean counts of normal organs (right and left liver lobe, spleen, left ventricular myocardium, mediastinal blood pool [MBPS], spine, gluteal muscles) were derived with adequately small spherical VOI (unless the location was affected by metastases). In 6 patients with serial examinations (20 examinations; CZT, 13; NaI, 7), maximum and mean counts of the NB primary tumors were measured at each examination (38 measured values overall) after delineation of the metabolic tumor volume (MTV) with a threshold-based, background-adapted algorithm (8, 19). SUVmax and SUVmean were calculated using volume sensitivity for the respective camera and reconstruction setting (non-SC, SC), voxel volume (ml) and injected activity per kg (decay-corrected). SUV in normal organs and primary tumor lesions primarily used volume sensitivity obtained from the homogenous phantom as recommended by the manufacturer (20). To account for higher scatter proportions (e.g., in larger patients or in organs with higher scatter proportions), normal organ SUV were also calculated based on volume sensitivity from the larger IEC phantom for comparison. No partial volume correction was applied. The product MTV*SUVmax was calculated for primary tumor lesions.

MRI

The primary tumor MRI volume was calculated by $0.5 * (\text{transversal} * \text{coronal} * \text{sagittal diameter})$ in MRI examinations corresponding to each [^{123}I]mIBG SPECT/CT examination in the 6 patients with serial

examinations.

Statistical analysis

Statistical analysis was performed using SPSS 22 (IBM Corporation, Armonk, NY, USA) and R 3.6.1 (Foundation for Statistical Computing, Vienna, Austria, 2019, <http://www.R-project.org>). Descriptive parameters were expressed as mean and SD (phantom data) or median, IQR and range (patient data). The t test was used for comparison of volume sensitivities or CR between paired data (50% vs. 100% acquisition time or non-SC vs. SC) or independent data (27 cm detector distance vs. body contour). SUV from patient data were compared with the Wilcoxon test (non-SC vs. SC data) or Mann-Whitney *U* test (CZT vs. Nal). Coefficients of variation (CV) were compared using the R package *cvequality* based on the asymptotic test by Feltz and Miller (21). Correlation of relative changes in MRI volume with relative changes in MTV*SUVmax on serial scans was analyzed with Pearson's correlation coefficient. Interpretation of correlation coefficients was performed as previously proposed (22). Statistical significance was assumed at $p < 0.05$.

Results

Volume sensitivity: Homogenous phantom

Volume sensitivity ($\text{cts} * \text{MBq}^{-1} * \text{s}^{-1}$) for the homogeneously filled cylindrical phantom using the CZT was 104.9 ± 1.2 for non-SC data or 50.3 ± 0.4 for SC data, respectively. Volume sensitivity ($\text{cts} * \text{MBq}^{-1} * \text{s}^{-1}$) with the Nal for non-SC and SC data was 87.2 ± 0.4 and 60.7 ± 0.2 .

Volume sensitivity ($\text{cts} * \text{MBq}^{-1} * \text{s}^{-1}$) with the CZT was slightly different between 50% vs. 100% acquisition time for non-SC data (50% vs. 100% time, 104.3 ± 1.0 vs. 104.9 ± 1.2 , $p = 0.02$) and SC data (50% vs. 100% time, 51.8 ± 1.3 vs. 50.3 ± 0.4 , $p = 0.044$).

Volume sensitivity ($\text{cts} * \text{MBq}^{-1} * \text{s}^{-1}$) was lower with the fixed 27 cm detector radius vs. body contour with CZT (non-SC, 97.9 ± 0.5 vs. 104.9 ± 1.2 , $p < 0.01$; SC, 48.4 ± 0.7 vs. 50.3 ± 0.4 , $p < 0.001$). Nal showed similar volume sensitivity with the fixed 27 cm detector radius vs. body contour (non-SC, 83.7 ± 0.4 vs. 87.2 ± 0.4 , $p = 0.16$; SC, 58.9 ± 0.4 vs. 60.7 ± 0.2 , $p = 0.18$).

Accuracy in IEC phantom activity concentration (AC) recovery

Relative error in calculating AC in the IEC phantom background based on volume sensitivity from the homogenous phantom with the CZT vs. Nal was $+73.1 \pm 3.2\%$ vs. $+49.3 \pm 9.1\%$ for non-SC ($p = 0.03$) or $-1.3 \pm 2.5\%$ vs. $+4.1 \pm 5.5\%$ for SC ($p = 0.22$), respectively.

Acquisition time reduction for the CZT resulted in similar relative error at 50% compared to 100% for non-SC data (50% vs. 100% time, $+74.4 \pm 3.5\%$ vs. $+73.1 \pm 3.2\%$, $p = 0.03$) and for SC data (50% vs. 100% time, $-0.2 \pm 5.2\%$ vs. $-1.3 \pm 2.5\%$, $p = 0.57$).

CRmax and CRpeak

In the three smallest spheres, CRmax and CRpeak for each sphere were similar for SC vs. non-SC data with CZT and NaI (each $p > 0.05$; Table 1). In the three largest spheres, CRmax and CRpeak were each significantly higher with SC vs. non-SC for both CZT and NaI (each $p < 0.05$; Table 1).

Table 1
CRmax

	CRmax (CZT)		CRmax (NaI)	
Sphere	non-SC	SC	non-SC	SC
37 mm	0.76 (0.04)	1.81 (0.08)	0.87 (0.1)	1.51 (0.2)
28 mm	0.74 (0.05)	1.58 (0.19)	0.9 (0.14)	1.53 (0.22)
22 mm	0.58 (0.05)	0.88 (0.06)	0.67 (0.03)	0.98 (0.09)
17 mm	0.38 (0.03)	0.5 (0.07)	0.45 (0.01)	0.58 (0.05)
13 mm	0.22 (0.05)	0.28 (0.08)	0.27 (0.04)	0.3 (0.06)
10 mm	0.22 (0.01)	0.25 (0.05)	0.22 (0.02)	0.23 (0.04)
50% reduction				
Sphere	non-SC	SC		
37 mm	0.84 (0.08)	2.0 (0.19)		
28 mm	0.74 (0.04)	1.57 (0.11)		
22 mm	0.57 (0.08)	0.81 (0.12)		
17 mm	0.36 (0.06)	0.38 (0.02)		
13 mm	0.25 (0.09)	0.35 (0.15)		
10 mm	0.26 (0.04)	0.33 (0.1)		
Mean (SD) CRmax for each sphere are displayed for CZT and NaI separated by non-SC and SC data. For the CZT, CRmax for data rebinned to a reduced acquisition time of 50% is shown additionally.				

In the four smallest spheres, both CRmax and CRpeak consistently underestimated true AC in non-SC and SC data (Fig. 1). In the two largest spheres, CRmax and CRpeak in SC data overestimated sphere AC while both CRmax and CRpeak in non-SC data underestimated AC.

Acquisition time reduction by 50% for the CZT affected neither mean CRmax nor CRpeak of any sphere in non-SC or SC data, respectively (50% vs. 100%, each $p > 0.05$; Table 1).

Estimates in scatter proportions (phantoms and normal organs)

With both CZT and NaI, mean scatter proportions estimated by the DEW method in the homogenous phantom (CZT, $52.0 \pm 0.7\%$; NaI, $30.4 \pm 0.4\%$) were comparable to scatter proportions estimated for the right and left liver lobe and the myocardium (range of median proportions, CZT, 49.5 to 59.9%; NaI, 23.2 to 35.2%; Table 2). In contrast, mean scatter proportions in the IEC phantom (CZT, $72.3 \pm 0.3\%$; NaI, $50.3 \pm 1.0\%$) were similar to proportions estimated for the spleen, MBPS, spine and gluteal muscles (range of median proportions, CZT, 75.6 to 80.0%; NaI, 41.3 to 55.5%).

Table 2
Estimated scatter proportions

	CZT	NaI
Phantom		
Homogenous	52.0 ± 0.7	30.4 ± 0.4
IEC	72.3 ± 0.3	50.3 ± 1.0
Organ		
Liver, right lobe	59.0 (56.2 to 62.5)	35.2 (33.6 to 38.0)
Liver, left lobe	59.9 (54.7 to 63.9)	30.5 (25.9 to 34.1)
Spleen	75.6 (55.0 to 85.0)	41.3 (33.2 to 50.6)
Myocardium	49.5 (42.7 to 61.1)	23.2 (16.6 to 29.0)
MPBS	80.0 (72.4 to 85.0)	51.0 (29.0 to 56.9)
Spine	79.6 (72.2 to 86.8)	55.5 (50.3 to 65.4)
Gluteal muscles	76.9 (68.4 to 82.8)	44.6 (32.4 to 55.2)
Scatter proportions estimated by the DEW method ($k = 1.0$ for both cameras) are given for both phantoms (mean $\pm$ SD) and for each organ (median, IQR). For both cameras, estimated scatter proportion in the homogeneously filled phantom were similar to estimated proportions in the liver and myocardium while scatter proportions in the IEC phantom were more comparable to spleen, MBPS, spine and gluteal muscles.		

Normal organ SUVmean: Effect of different scatter proportions

Based on volume sensitivity obtained with the homogenous phantom (i.e., at scatter proportions that matched liver and myocardium), SUVmean for each normal organ were significantly higher for non-SC vs. SC data with both CZT and NaI (each $p < 0.05$; except for myocardium with CZT and left liver lobe with NaI; Fig. 2A).

Based on volume sensitivity from the IEC phantom (i.e., at scatter proportions that matched spleen, MBPS, spine and muscles), SUVmean were similar between non-SC and SC data in the spleen with the CZT ($p = 0.64$), in MBPS ($p = 0.68$) and spine ($p = 0.07$) with the NaI and in the gluteal muscles with both CZT and NaI (each $p > 0.1$). In contrast, normal organ SUVmean in right/left liver lobe and myocardium were significantly higher for SC data than non-SC data (both cameras, each $p < 0.01$; Fig. 2B).

Normal organ SUVmean: Comparison of CZT and NaI

Normal organ SUVmean were similar in CZT examinations vs. NaI examinations for non-SC data (each $p > 0.1$; Fig. 3A).

In SC data based on volume sensitivity obtained from the homogenous phantom, normal organ SUVmean were comparable between CZT vs. NaI examinations for right/left liver lobe, spleen and myocardium (each $p > 0.05$) but different for MBPS, spine and gluteal muscles (each $p < 0.05$; Fig. 3B). In SC data based on volume sensitivity from the IEC phantom, normal organ SUVmean were also comparable between CZT vs. NaI examinations for right/left liver lobe, spleen and myocardium (each $p > 0.05$) but different for MBPS, spine and gluteal muscles (each $p < 0.05$).

Coefficient of variation (CV) in normal organ SUVmean

CV of SUVmean in organs with high scatter proportion (spleen, MBPS, spine and gluteal muscles) were significantly higher in SC vs. non-SC data with the CZT (each $p < 0.05$) but comparable between non-SC vs. SC data with the NaI (each $p > 0.05$; Table 3). CV of SUVmean in the liver and myocardium were similar between non-SC vs. SC data with both cameras (each $p > 0.05$).

Table 3
CV for normal organ SUVmean

CZT	CV of SUVmean (%)			p value
Organ	non-SC	SC (homogenous)	SC (IEC)	(non-SC vs. SC)
Liver, right lobe	28	37	37	0.31
Liver, left lobe	31	41	41	0.31
Spleen	51	96	96	< 0.01
Myocardium	57	68	68	0.34
MBPS	49	86	86	< 0.05
Spine	29	50	50	< 0.01
Gluteal muscles	32	57	57	< 0.01
NaI	CV of SUVmean (%)			p value
Organ	non-SC	SC (homogenous)	SC (IEC)	(non-SC vs. SC)
Liver, right lobe	49	49	49	0.31
Liver, left lobe	63	70	70	0.31
Spleen	71	77	77	0.84
Myocardium	47	51	51	0.74
MBPS	40	38	38	0.34
Spine	50	50	50	0.79
Gluteal muscles	61	57	57	0.81
CV of SUVmean (%) are listed for non-SC and SC data separated by CZT (upper table) and NaI (lower table). Differences in CV between non-SC and SC are compared, and significant p values are printed in bold. Please note that CV for SC data based on the homogenous and IEC phantom are identical (each p = 1.0), and comparison with non-SC data therefore gives identical p values.				

CV with both cameras were identical between SC data obtained with either volume sensitivity from the homogenous phantom or IEC phantom, respectively (each p = 1.0).

Correlation of MRI volume changes with MTV*SUVmax changes

In 6 patients with serial examinations (n = 20; CZT and NaI mixed), Pearson correlation coefficient of changes in MRI volume with changes in MTV*SUVmax was similar for non-SC data (r = 0.62; p = 0.014) vs. SC data (r = 0.59; p = 0.021; Fig. 4).

Discussion

This study examined the feasibility of quantification in [^{123}I]mIBG SPECT/CT data in phantom measurements and NB patients as a basis for potential application of quantitative image parameters for predictive or prognostic purposes.

Numerous factors influence quantitative accuracy in SPECT/CT. While attenuation is routinely addressed with CT-based attenuation correction, correction for scatter, e.g. within the patient, is not necessarily an integral part of iodine-123 SPECT/CT reconstruction in clinical routine (i.e., for visual interpretation). As highlighted by the current data, the scatter proportion estimated by the DEW method for iodine-123 in an IEC phantom geometry can account for up to half (NaI; LEHR collimator) (23) or even > 70% of the acquired counts (CZT; WEHR45 collimator). This implicates that in [^{123}I]mIBG imaging for children, which is in principle characterized by low count statistics and unfavorable noise properties, the additionally available counts in non-SC data could be beneficial for image quality and resulting confidence for visual reading in clinical care.

However, if quantitative accuracy is intended, high trueness (i.e., low systematic deviations from the true value) and precision (i.e., high reproducibility of measurements) are required. In phantom measurements, trueness of non-SC data in recovering the background activity concentration in the IEC phantom based on volume sensitivity of the smaller, homogeneously filled phantom was poor (average relative error > 70%). In contrast, SC data showed high trueness (low average relative error < 5%) and high precision (low variability between serial scans) suggesting that the DEW method with a low-energy scatter window could be sufficient for SC in iodine-123 SPECT/CT if only the accurate depiction of homogeneous activity concentrations in a sufficiently large volume is required. However, SC data considerably overestimated CR of the larger sphere inserts. This is, among other effects, due to the inability of the DEW method to account for the spatial distribution of scattered photons that originate from the sphere inward but are detected in the background and therefore systematically increase sphere-to-background ratios (24). This overestimation increases with an increase of the weighting factor k for the scatter window ($k = 1.0$ in the current study for both cameras) (25). In contrast, without SC, CRpeak underestimated the AC of larger sphere inserts by about 30% (NaI) or 40% (CZT) which is in accordance with Lagerburg *et al.* (25). The consistent results for CRmax and CRpeak show that this observation is not merely due to the chosen delineation method (CRpeak) or statistical outliers (CRmax). The general observation that CRpeak better represents sphere AC in larger spheres compared CRmax, which usually overestimates it, has been previously demonstrated for positron emission tomography (PET) (26).

In patient data, trueness usually cannot be determined unless the standard of truth is known from activity concentrations determined *in vivo* (e.g., in the urine (27)). However, one should aim at achieving comparability between camera systems. Similarity in average normal organ SUV between both cameras served as a surrogate assuming that normal organ SUV should be similar on average – even in different patient samples. Under this premise, SUV in non-SC data were similar between both cameras for all normal organs. Intuitively, the similarity of estimated scatter proportions between the homogeneous

phantom and organs such as liver and myocardium as well as between the IEC phantom and organs such as MBPS and spine would suggest that the DEW method could overall account for varying scatter geometries in different organs. Consequently, normal organ SUV in SC data should also be similar between both cameras – irrespective of the examined organ and its estimated scatter proportion. In contrast, in specific organ geometries with high estimated scatter proportions (spleen, MBPS, spine, gluteal muscles), SUV in SC data were different between CZT and NaI patients. It must be hypothesized that the use of a unique k value for both systems accentuates these effects of SC. Furthermore, SC could not reduce the imprecision in patient data when the variation of normal organ SUV_{mean} (CV) between different examinations was used as a surrogate.

In summary, surrogates for both trueness and precision in the current patient data imply that SC based on the DEW method with a low-energy scatter window is insufficient for quantitative accuracy in clinical iodine-123 SPECT/CT with both CZT (WEHR45) and NaI cameras (LEHR collimator). In both detectors, the DEW method is limited by the inability to account for spatial distribution of scattered photons (see above). Moreover, it relies on calibration of the k factor which is then applied indiscriminately to the acquired dataset, and DEW cannot account for downscatter from the 529 keV iodine-123 peak (28, 29); both adaptations would require a third energy window above the photopeak window. In CZT detectors, overestimation of scatter using the DEW method will result from the detector-specific low-energy tail which is caused by contamination from photons that are unscattered but detected with lower energy (28, 30).

Considering these spatially variant and invariant sources of error in SC for iodine-123 with the simplified DEW method, Monte Carlo based SC in combination with CDR modelling may be superior in achieving accurate quantitative data in the complex and variable geometry of the patient body (13, 31); however, these algorithms are resource consuming and not commonly integrated in clinical SPECT/CT systems. Brady *et al.* recently investigated SUV in [¹²³I]mIBG SPECT/CT acquired with two NaI cameras (LEHR and ME collimator) in 43 patients with NB. Using Monte Carlo based SC and volume sensitivity from a homogeneously filled cylindrical phantom, normal organ SUV (salivary glands, heart, liver, adrenal glands, urinary bladder) were – on average – similar between both cameras. However, considerable variation in SUV of all organs remained between examinations. IQR of liver SUV was 1 to 2 and therefore comparable to CZT examinations in the current study but lower than in NaI examinations in the present analysis (IQR, 1 to 3). It may be noted that even with optimal image acquisition and processing, physiological variability of normal organ SUV will occur, which will itself vary between organs (e.g., due to varying sympathetic innervation of the left ventricular myocardium (32)). If normal organ SUV variation remains high, it could ultimately limit the potential of normal organ SUV in [¹²³I]mIBG imaging to serve as physiological intraindividual reference as has been commonly proposed for the liver or MBPS SUV in [¹⁸F]fluorodeoxyglucose (FDG) PET (33, 34).

Independent of the SC method used for quantifying patient data, an appropriate calibration procedure (e.g., scan protocol, phantom geometry) must be chosen to estimate volume sensitivity for SPECT data. If the employed SC method is accurate, it would be sufficient to obtain volume sensitivity from a

homogenously filled cylindrical phantom (20). Appropriateness of the volume sensitivity could be examined under varying scatter properties using a body phantom. However, the current results suggest that further steps will be required to ensure that the SC method is appropriate for normal organ and lesion quantification in patients. This may ultimately require *in vivo* measurements of activity concentrations, e.g. in the urine (27).

Further influencing factors were examined in the current study (detector radius, acquisition time reduction with the CZT). Differences in volume sensitivity for the homogenous phantom between acquisition with body contour or fixed 27 cm detector radius were < 5% in SC data. This is facilitated by resolution recovery as part of image reconstruction which aims at compensation for CDR including its variation at different detector radii along the angular range (35, 36). Although relative differences were small, volume sensitivity with the CZT at 27 cm radius was significantly lower than with body contouring. This may be due to higher dependency of effective spatial resolution from source-to-collimator distance compared to NaI detectors (37–39). Consequently, variation in detector distance among patients could add system-specific variance in quantitative accuracy. However, the currently chosen differences in detector radii were comparably large, especially considering the context of a pediatric population, with the aim of identifying the consequential deviations under extreme conditions – while (considerably) smaller deviations can usually be expected in clinical routine. Furthermore, volume sensitivity for both phantoms as well as CR_{max} and CR_{peak} of the sphere inserts did not differ relevantly between 100% or 50% acquisition time (CZT).

This underlines that the appropriateness of SC remains the most relevant factor in determining the accuracy in quantification of [¹²³I]mIBG SPECT/CT data and that SC optimization should be prioritized. The current approach and results could serve as a blueprint for a convenient clinical workflow towards quantitative [¹²³I]mIBG SPECT/CT data. Volume sensitivity for the in-house acquisition protocol can be obtained with a homogenously filled cylindrical phantom. Body contour acquisition is recommended for optimized CDR.

In the light of these results, MTV*SUV_{max} of NB lesions in patients with serial examinations were examined as a measure of lesional metabolic tumor load. It was hypothesized that this could be a surrogate for response to therapy, and correlation of changes in MRI volume with MTV*SUV_{max} changes was moderate for non-SC and SC data. The prognostic value of [¹²³I]mIBG scintigraphy in NB beyond definition of the tumor stage is currently limited to visual scores of whole-body lesion counts in planar scintigraphy (Curie score and SIOPEN score) which have shown prognostic value at initial staging and after chemotherapy (40, 41). A quantifiable parameter of lesional metabolic activity could serve as a supplementary prognostic or predictive measure. However, the current explorative analysis on MTV*SUV_{max} in patient data is only exemplifying. Systematic investigation of the reproducibility and clinical implications of quantitative parameters in NB in a multicenter setting with international cooperative group trials is needed.

Conclusions

The proposed approach for quantification of [^{123}I]mIBG SPECT/CT data based on volume sensitivity estimated from a homogeneously filled cylindrical phantom may be, in principle, used for both CZT and NaI cameras. However, appropriate SC is crucial for accurate quantification of normal organ and lesion SUV, and the DEW method, although simple for clinical use, may introduce substantial inaccuracies. In contrast, detector radius and acquisition time reduction by 50% had comparably little or insignificant influence on quantitative data and may therefore be chosen as optimized for clinical routine (preferably body contour acquisition with sufficiently high acquisition time as recommended for visual reading). In this small patient series, therapy-associated changes in MTV*SUVmax of NB primary tumors correlated with MRI volume changes. The clinical value of quantitative [^{123}I]mIBG SPECT/CT data for prognostication or response assessment in NB warrants further investigation in larger samples from multicenter NB trials. This should also address SC optimization and potential limitations from considerable variability of normal organ SUV.

Abbreviations

AC activity concentration

CDR collimator-detector response

CR contrast recovery

CV coefficient of variation

CZT cadmium zinc telluride

DEW dual energy window

EANM European Association of Nuclear Medicine

FDG fluorodeoxyglucose

IQR interquartile range

LEHR low energy high resolution

MBPS mediastinal blood pool

ME medium energy

mIBG metaiodobenzylguanidine

MRI magnetic resonance imaging

MTV metabolic tumor volume

NaI sodium iodide

NB neuroblastoma

OSEM ordered subset expectation maximization

PET positron emission tomography

SC scatter correction

SD standard deviation

SPECT/CT single photon emission computed tomography / computed tomography

SUV standardized uptake value

VOI volume of interest

VS_{hom} volume sensitivity obtained from the homogenously filled phantom

VS_{IEC} volume sensitivity obtained from the IEC phantom

Declarations

Ethics approval and consent to participate

All procedures were in accordance with the ethical standards of the Charité ethics commission (vote, EA2/150/16), and all patients or their legal guardian gave their informed consent to participate.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JMMR participated in data analysis and interpretation as well as preparation of the manuscript. SB and JA contributed to obtaining and interpreting data. OG, IS and SS participated in data interpretation as well as preparation of the manuscript. AE and HA participated in data interpretation and review of the manuscript.

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Figures

Figure 1

CRmax and CRpeak for non-SC and SC data CRmax (A) and CRpeak (B) for non-SC data and SC data separated by CZT and NaI (error bars: 1 SD). True sphere activity concentration (i.e., CR of 1.0) is given by a dotted line. With both detectors CRmax and CRpeak for non-SC data substantially underestimate true activity concentrations whereas SC considerably overestimates activity concentrations in the larger spheres.

Figure 2

Normal organ SUVmean (non-SC vs. SC) Boxplots of SUVmean either based on volume sensitivity obtained from the homogenous phantom (A) or IEC phantom (B) are separated by organs and for non-SC vs. SC data. Outliers are displayed as circles or asterisks. In organs with high scatter proportion (spleen, MBPS, spine and muscles), SUVmean in non-SC data and SC data are similar if based on volume sensitivity from the IEC phantom (matching high scatter proportion). In contrast, non-SC and SC data are more similar in liver and myocardium (low scatter proportion) if volume sensitivity is obtained with the homogenous phantom (matching low scatter).

Figure 3

Normal organ SUVmean (CZT vs. NaI) Boxplots of SUVmean from non-SC (A) or SC data (B) for CZT vs. NaI, both based on volume sensitivity obtained from the homogenous phantom. Outliers are displayed as circles or asterisks. SUVmean in non-SC data show lower differences between CZT and NaI than SC data. Results for SC data based on volume sensitivity obtained from the IEC phantom are not displayed as they are almost identical to data in (B).

Figure 4

MRI volume changes and MTV*SUVmax changes Lesion-wise changes (6 neuroblastoma primary tumors) in MRI volume and MTV*SUVmax are displayed (each line = one lesion/patient). Changes in MTV*SUVmax are mostly comparable for non-SC and SC data (based on volume sensitivity from the homogenous phantom).