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Biodistribution and Radiation Dosimetry for ^{68}Ga -DOTA-CCK-66, a Novel CCK₂R-Targeting Compound for Imaging of Medullary Thyroid Cancer

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Abstract: Cholecystokinin 2 receptor (CCK₂R) is a promising target for imaging and treatment of medullary thyroid cancer due to its overexpression in over 90% of tumor cells. ^{68}Ga -DOTA-CCK-66 is a recently introduced PET tracer selective for CCK₂R, which has shown favorable pharmacokinetics in vivo in preclinical experiments. In order to further investigate safety and suitability of this tracer in the human setting, whole-body distribution and radiation dosimetry were evaluated.

Patients and Methods: Six patients with a history of medullary thyroid cancer were injected intravenously with 169 ± 19 MBq of ^{68}Ga -DOTA-CCK-66. Whole-body PET/CT scans were acquired at 10 minutes, 1 hour, 2 hours, and 4 hours after tracer injection. Time-activity curves per organ were determined, and mean organ-absorbed doses and effective doses were calculated using OLINDA/EXM.

Results: Injection of a standard activity of 150 MBq of ^{68}Ga -DOTA-CCK-66 results in an effective dose of 4.5 ± 0.9 mSv. The highest absorbed organ doses were observed in the urinary bladder wall (40 mGy) and the stomach (15 mGy), followed by the kidneys (6 mGy), as well as the liver and the spleen (3 mGy each). CCK₂R-expressing tumor manifestations could be detected in 2 of the 6 patients, including lymph node, bone, and liver metastases.

Conclusions: ^{68}Ga -DOTA-CCK-66 exhibits a favorable dosimetry. Beyond physiologic receptor expression of the stomach, no other relevant tracer accumulation could be observed, rendering this organ at risk in case of subsequent radioligand therapy using ^{177}Lu -DOTA-CCK-66.

Key Words: medullary thyroid cancer, CCK₂R, theranostics, PET/CT imaging, dosimetry

Medullary thyroid cancer (MTC) is a rare neuroendocrine tumor arising from the parafollicular cells of the thyroid gland and accounts for approximately 1%–2% of all thyroid cancers. Since patients with MTC can only be cured by complete resection

of the primary tumor and any locoregional or distant metastases, accurate disease staging is mandatory.¹ In advanced disease, both non-selective multikinase and selective RET inhibitors are approved and have shown significant effects on disease response and progression-free survival.^{2,3} However, they may cause serious side effects and/or induce resistance,^{4,5} so other treatment options remain desirable.

Regarding imaging, standard imaging procedures like whole-body CT, MRI, or bone scintigraphy often fail to detect MTC metastases.^{1,6,7} The commonly used PET/CT tracers, ^{18}F -FDG and ^{18}F -DOPA, show sensitivities for detecting MTC lesions of around 59%–72%.⁸ Even if the detection rate for ^{18}F -DOPA increases to more than 85% in patients with calcitonin levels above 150 pg/mL and calcitonin doubling times shorter than 24 months,^{8,9} there is no therapeutic analog available for this compound for subsequent radioligand therapy (RLT).

Cholecystokinin 2 receptor (CCK₂R) is overexpressed in over 90% of MTC cases,¹⁰ making it a promising target for diagnostic imaging and targeted therapy. Various compounds designed to target this specific receptor have been developed over the past years,^{11–14} but there are just few data available for CCK₂R-targeting tracers suitable for PET/CT imaging.¹⁵ We recently reported on the development and initial translation of the new minigastrin analog, ^{68}Ga -DOTA-CCK-66, which revealed promising preclinical characteristics, particularly in terms of high in vivo stability and rapid activity clearance from off-target tissue,¹⁶ and thus, promising first preliminary clinical experience in 2 patients with advanced MTC.^{16,17} Since this vector can also be labeled with therapeutic nuclides like lutetium-177 or actinium-225, DOTA-CCK-66 can also serve as a therapeutic option.

To assess the safety of ^{68}Ga -DOTA-CCK-66 as well as its diagnostic potential, biodistribution, and dosimetry, we here report the first PET/CT imaging data with this new probe in a small cohort of patients with MTC in a pilot study.

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O.V., A.R., C.L., and C.H.P. contributed equally.

Conflicts of interest and sources of funding: A patent application on CCK₂R-targeted compounds including DOTA-CCK-66 with T.G., N.H., C.L., and H.J.W. as inventors has been filed. H.J.W. is founder and shareholder of Scintomics GmbH, Munich, Germany. No other potential conflicts of interest relevant to this article exist. This study has been funded by Deutsche Forschungsgemeinschaft (DFG, German Research Foundation—461577150).

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and A.R. The first draft of the manuscript was written by O.V., A.R., and C.L., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the local Ethics Committee of Ludwig-Maximilians-Universität München (Munich, Germany; Date: 18.08.2023; No.: 23-0627).

Consent to participate: Informed consent was obtained from all individual participants included in the study.

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PATIENTS AND METHODS

Research Design and Subjects

Six patients (man 4 female; mean age \pm SD, 54 ± 10 years) with a history of MTC underwent ^{68}Ga -DOTA-CCK-66 PET/CT for either restaging purposes or to evaluate a potential therapeutic option with CCK₂R-directed RLT. All patients showed elevated or rising tumor marker levels (mean calcitonin \pm SD, 131 ± 120 pg/mL; mean calcitonin doubling time \pm SD, 34 ± 26 months; mean CEA \pm SD, 2.5 ± 1.6 ng/mL) at the time of PET/CT imaging. All patients exhibited a normal kidney function. Safety was assessed by monitoring adverse events up to 4 hours after injection of ^{68}Ga -DOTA-CCK-66. Detailed patient characteristics are presented in Supplemental Table 1, <http://links.lww.com/CNM/A485>. Two patients of the current cohort have already been presented in Günther et al.¹⁶

Preparation of the CCK₂-Targeting Probe ^{68}Ga -DOTA-CCK-66

The synthesis of ^{68}Ga -DOTA-CCK-66 was completed as previously described.¹⁶

PET Imaging

All ^{68}Ga -DOTA-CCK-66 scans were obtained on a dedicated PET/CT scanner (Biograph mCT 40; Siemens Healthineers, Erlangen, Germany or GE Discovery MI, GE HealthCare, Milwaukee, WI). Four whole-body scans (from the skull to the proximal thighs) were acquired at 10 minutes, 1 hour, 2 hours, and 4 hours after IV tracer injection (6 to 8 bed positions with an emission time of 2 minutes per bed position). All data were decay-corrected to the starting time of each individual scan. PET data sets were reconstructed using a standard reconstruction protocol provided by the manufacturer (2 iterations, 21 subsets), corrected for randoms, scatter, decay, and attenuation (using whole-body auxiliary CT, 35 mAs, 120 keV, a 512×512 matrix, 5-mm slice thickness, increment of 30 mm/s, rotation time of 0.5 seconds, and pitch of 0.8).

The PET scanners are periodically checked for calibration accuracy as part of quality control according to published guidelines and are accredited by European Association of Nuclear Medicine Research Ltd.¹⁸

Imaging and Dosimetry

Whole-organ volumes of interest (VOIs) were drawn for heart, kidneys, liver, spleen, stomach, lumbar vertebrae 2–4, and

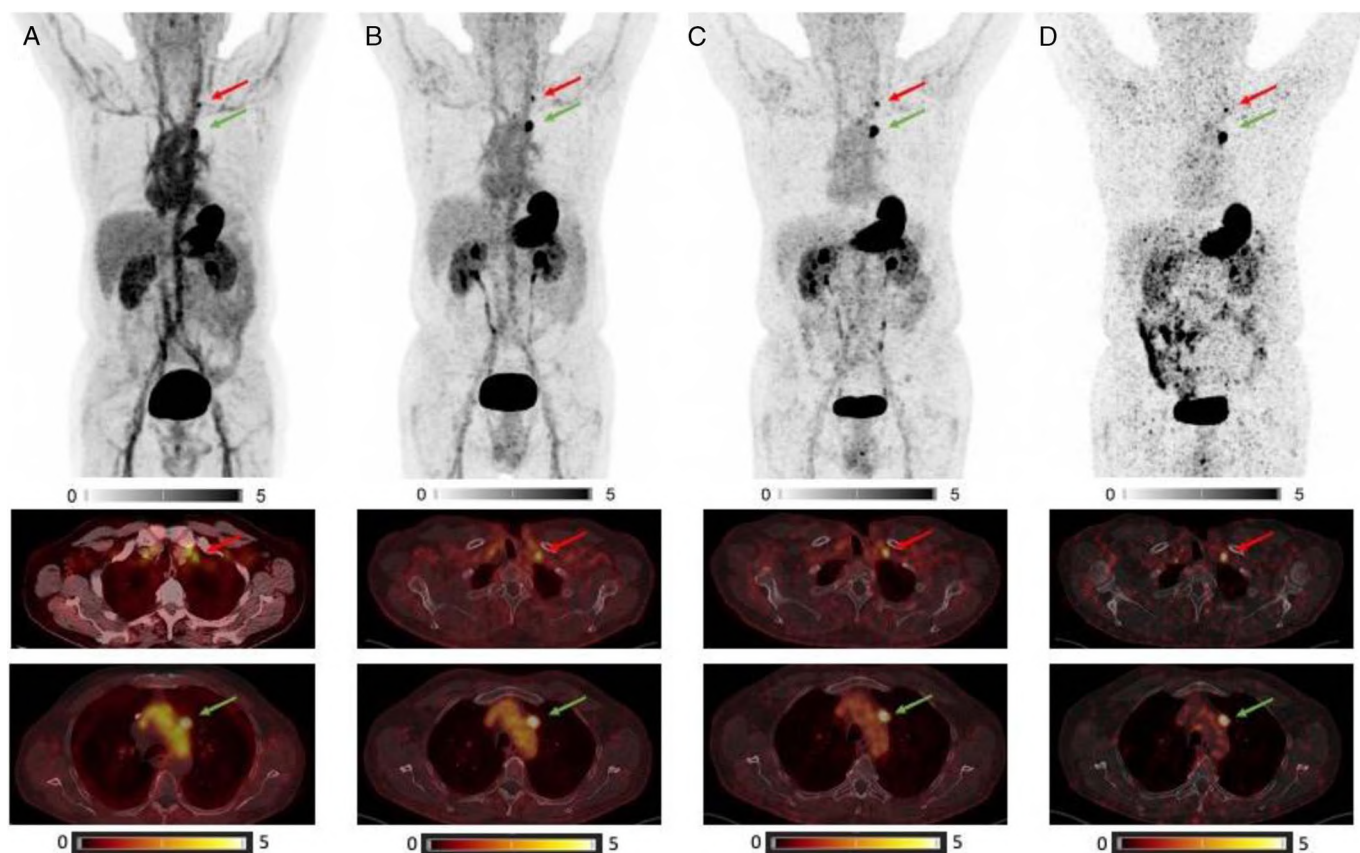


FIGURE 1. Sequential scans of a 64-year-old male patient who had initially undergone thyroidectomy and cervical lymph node dissection. After several local and lymphonodal recurrences, the patient presented with a rising calcitonin level of 110 pg/mL and a calcitonin doubling time of 16 months at the time of PET/CT imaging. MIPs (upper row) and fused transaxial PET/CT slices (lower rows) at (A) 10 minutes, (B) 1 hour, (C) 2 hours, and (D) 4 hours after tracer injection are displayed. Tracer uptake in CCK₂R-expressing lymph nodes could be observed already at 10 minutes and up to 4 hours after injection in the left retroclavicular region (10 minutes SUV_{max} 5.0; 4 hours SUV_{max} 8.0, red arrows) and in the upper mediastinum (10 minutes SUV_{max} 9.0; 4 hours SUV_{max} 23.5, green arrows).

the whole patient within the field of view on the first PET/CT scan using Simplicity^{90Y} (Mirada Medical and Boston Scientific). After coregistration, the VOIs were transferred to all quantified PET/CT images to determine the activity within each VOI for each time point. For the estimation of the activity of the red bone marrow, it was assumed that 6.7% of the red bone marrow is contained within lumbar vertebrae 2–4.¹⁹ Monoexponential and monoexponential functions plus a constant were fitted to each time-activity data set using NUKFIT software.²⁰ A systematic uncertainty of the activity values of 10% was assumed. Optimal fit function was selected considering visual inspection and the uncertainties of the fit parameters (less than 50% of the value). Time-integrated activity coefficients (TIACs) were analytically calculated by integration of the time-activity curves. For the cases in which both fit functions could be used, the higher TIAC was used to obtain an upper estimate of the absorbed dose. The maximal deviation between the TIACs using the 2 fit functions was below 10%. For the stomach, decay-corrected

activity within the VOIs was increasing for all time points. Thus, a trapezoidal integration from zero to the last time point with a following exponential decrease with the physical decay constant was used. The TIAC of the whole body was determined by using a scaling factor estimated from the administered activity and the decay-corrected activity within the field of view of the first PET/CT scan (before micturition). The TIAC of the urinary bladder was calculated by using the clearance rate of the remainder as filling rate and a bladder voiding interval. The following voiding interval was assumed: first voiding after 1 hour after injection and every 3.5 hours from then on, which reflects a realistic clinical setting. The TIACs for the urinary bladder were calculated by numerical integration from zero to 15 hours after injection using Excel (Microsoft Corporation).

Absorbed organ doses were calculated using OLINDA/EXM version 1.0.²¹ Individual organ weights for heart, kidneys, liver, spleen, and total body weight were considered. For red bone marrow, a mass of 1500 g was assumed.²²

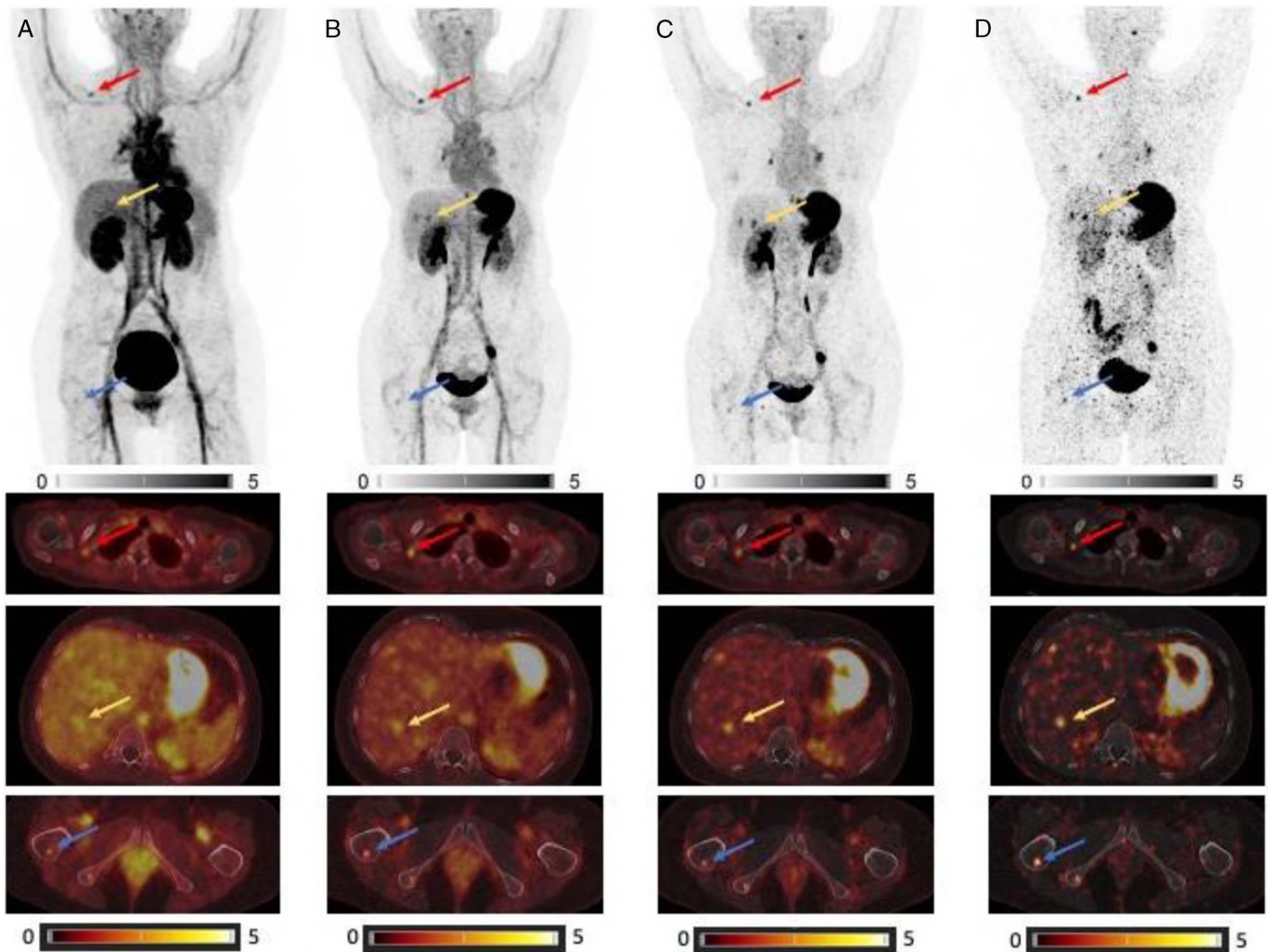


FIGURE 2. Sequential scans of a 46-year-old woman MTC patient who had undergone thyroidectomy and cervical lymph node dissection, as well as external beam radiation of the thyroid bed due to local tumor remnants. The patient showed a rising calcitonin level of 380 pg/mL and a calcitonin doubling time of 5 months at the time of PET/CT imaging. MIPs (upper row) and fused transaxial slices (lower rows) at (A) 10 minutes, (B) 1 hour, (C) 2 hours, and (D) 4 hours after tracer injection are displayed. ⁶⁸Ga-DOTA-CCK-66 PET detected several lymph node metastases (eg, right retroclavicular, 10 minutes SUV_{max} 3.2; 4 hours SUV_{max} 4.9, red arrows), liver metastases (ie, in the right liver lobe segment VI, 10 minutes SUV_{max} 3.8; 4 hours SUV_{max} 6.7, yellow arrows), and bone metastases (ie, right femur, 10 minutes SUV_{max} 2.1; 4 hours SUV_{max} 4.3, blue arrows).

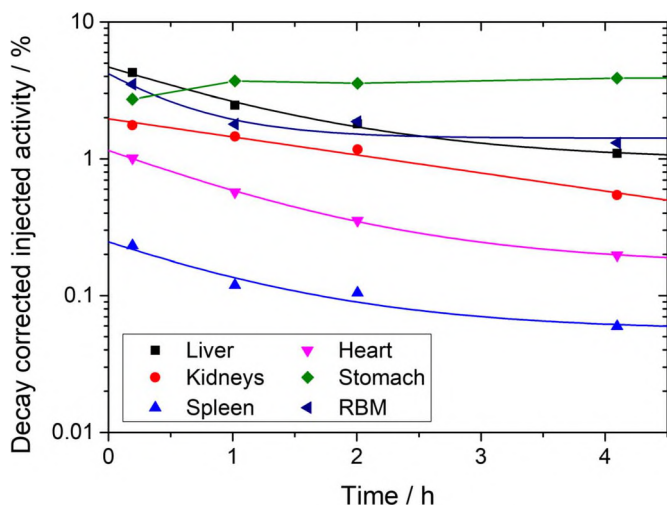


FIGURE 3. Time activity curves for patient 1 for major organs. An increasing decay-corrected tracer uptake over time was only observed in the stomach. In all other organs, decay-corrected activity uptake declined from early to late imaging.

For all other organs, the organ weights integrated in OLINDA/EXM were used. The effective dose was determined based on the current tissue weighting factors of ICRP 103.²³

Semiquantitative analysis of visually detectable lesions was also done by VOIs. Corresponding SUV_{max} was recorded for the various time points. For estimation of background activity, a sphere with a diameter of 2 cm was placed within normal liver tissue. For assessment of the optimal imaging time point, tumor-to-background ratios (TBRs) were calculated for each time point by dividing SUV_{max} of tumor lesions by background SUV_{mean} .

Quantitative data are presented as the mean \pm standard deviation (SD), as appropriate.

RESULTS

Radioligand and Patients

The administered amount of substance of ^{68}Ga -DOTA-CCK-66 was 18 μ g. The overall injected activity was 169 ± 19 MBq with a specific activity greater than 9 MBq/ μ g. Injection of ^{68}Ga -DOTA-CCK-66 was well tolerated by all subjects, and no side effects or changes in vital signs were observed during the tracer's slow IV injection (~2 minutes), or thereafter (with a follow-up period of up to 4 hours).

Biodistribution

The biodistribution of ^{68}Ga -DOTA-CCK-66 was determined for all major organs in all patients. Figure 1 and Figure 2 show whole-body MIPs and transaxial sections of the 2 patients with detectable tumor lesions (P1, P6) at different time points. Figure 3 shows the time-activity curves for major organs expressed as percentage injected activity (%ID) for the same patient as in Figure 1 (P1). Comparable time-activity curves were recorded in all other patients.

An increasing tracer accumulation over time was only observed for the stomach, which can be attributed to physiological CCK₂R expression. The highest decay-corrected tracer uptake in the stomach and also in any other organ was observed in patient 3 with 20.8 %ID at 4 hours after injection. For all patients, the mean uptake of the stomach increased from 4.5 ± 4.3 %ID at 10 minutes to 7.6 ± 6.8 %ID at 4 hours. The mean uptake in the kidneys varied between 1.8 ± 0.4 %ID and 1.0 ± 0.3 %ID at 10 minutes and 4 hours after administration, respectively. Significant tracer uptake was also observed in the liver, with a mean uptake of 4.3 ± 0.6 %ID after 10 minutes, declining to 1.5 ± 0.5 %ID after 4 hours. Only low tracer uptake was observed for the red bone marrow with 2.6 ± 0.6 %ID at 10 minutes declining to 1.3 ± 0.4 %ID at 4 hours.

The decay-corrected urinary bladder content at 10 minutes after injection was about 9.6 ± 2.1 %ID. All patients voided for the first time 40–60 minutes after administration of the radioligand.

Tumor Imaging and Tumor Marker Levels

Focal lesions consistent with malignancy were found in 2 patients (P1 and P6), whereas no suspicious tracer uptake could be detected in the other 4 individuals.

In brief, calcitonin levels were higher in the PET-positive patients with 110 pg/mL and 380 pg/mL, respectively, as compared with 73 ± 52 pg/mL in the PET-negative group. Also, a shorter calcitonin doubling time could be observed in the PET-positive patients with a calcitonin doubling time of 16 and 5 months as compared with 42 and 73 months in the PET-negative patients. CEA was only slightly elevated in 1 patient, who was CCK₂R negative.

In ^{68}Ga -DOTA-CCK-66 PET/CT, both PET-positive subjects presented with suspicious CCK₂R-expressing lymph nodes in the cervical and/or thoracic region. In patient 6, additional liver and bone metastases could be observed. A total of 12 lesions could be detected, including 5 CCK₂R-expressing lymph nodes, 3 liver lesions, and 4 bone lesions. Semiquantitative assessment of tumor SUV_{max} and TBR demonstrated an increase for lymph node, bone, and liver metastases over time, respectively. An overview of the SUV_{max} and TBR for the different tumor sites is given in Table 1, Table 2, and Supplemental Figure 1, <http://links.lww.com/CNM/A485>. Individual values for each CCK₂R-expressing lesion are presented in Supplemental Table 2, <http://links.lww.com/CNM/A485>.

TABLE 1. Tracer Uptake (SUV_{max}) in Visible Tumor Lesions and Background Uptake (SUV_{mean} in the Normal Liver Tissue) in Patient 1 and Patient 6 for Different Imaging Time Points.

	SUV_{max}			
	10 min Mean (Range)	1 h Mean (Range)	2 h Mean (Range)	4 h Mean (Range)
Lymph nodes (n = 5)	4.8 (3.2–9.0)	6.5 (3.3–14.1)	6.9 (4.0–13.2)	9.4 (3.5–23.5)
Hepatic lesions (n = 3)	3.8 (3.7–3.9)	3.6 (3.2–4.0)	3.9 (3.3–4.3)	5.4 (3.2–6.7)
Bone lesions (n = 4)	2.6 (1.6–4.3)	2.6 (1.9–3.8)	3.3 (2.4–5.2)	4.7 (4.2–6.2)
All lesions (n = 12)	3.8 (1.6–9.0)	4.5 (1.9–14.1)	4.9 (2.4–13.2)	6.8 (3.2–23.5)
SUV_{mean} background	2.2 (2.1–2.2)	1.5 (1.4–1.5)	1.1 (0.9–1.2)	0.5 (0.4–0.5)

TABLE 2. Comparison of TBR Determined by Dividing Average SUV_{max} of Tumor Lesions by Average SUV_{mean} of Background Tissue (as Measured in the Normal Liver Tissue) for Different Scanning Times

	TBR			
	10 min	1 h	2 h	4 h
Lymph nodes (n = 5)	2.2	4.5	6.5	20.9
Hepatic lesions (n = 3)	1.8	2.5	3.7	11.9
Bone lesions (n = 4)	1.2	1.8	3.1	10.5
All lesions (n = 12)	1.8	3.1	4.7	15.2

Dosimetry

Time-integrated activity coefficients of segmented organs were calculated for each patient individually. In addition, the mean values for all patients are given in Table 3. The highest number of disintegrations per organ occurred in the stomach and urinary bladder, with an average TIAC of 0.10 ± 0.09 hours (stomach) and 0.18 ± 0.06 hours (urinary bladder). The average absorbed dose/dose coefficients across all subjects are shown in Table 4. The highest absorbed dose per unit activity was observed in the urinary bladder wall (0.269 ± 0.103 mGy/MBq), followed by the stomach (0.098 ± 0.077 mGy/MBq), the kidneys (0.039 ± 0.019 mGy/MBq), as well as the liver and the spleen (both 0.018 ± 0.003 mGy/MBq).

The effective dose was individually determined for each patient using the current tissue-weighting factors from ICRP 103.²³

On average, the effective dose coefficient was 0.030 ± 0.006 mSv/MBq. Thus, the effective dose for a standard injection of 150 MBq of ⁶⁸Ga-DOTA-CCK-66 results in about 4.5 ± 0.9 mSv. For comparison, the effective dose coefficient using the outdated tissue-weighting factors from ICRP 60²⁴ as provided by OLINDA/EXM was 0.033 ± 0.006 mSv/MBq.

Table 5 provides an overview of absorbed doses for selected organs and effective doses for a typically injected activity for ⁶⁸Ga-DOTA-CCK-66 and other commonly used PET tracers.

Discussion

Given the clinical need for improved imaging and therapy modalities for staging and treatment of MTC patients, we recently reported on a new CCK₂R-targeting compound.¹⁶ Preclinical results suggested high in vivo stability and rapid activity clearance from off-target tissue,¹⁶ which could be also observed in preliminary proof-of-concept studies previously reported.^{16,17} In order to further examine the clinical value of ⁶⁸Ga-DOTA-CCK-66, we here investigated its biodistribution and dosimetry in 6 MTC patients.

TABLE 3. TIACs for Major Organs for Each Patient Individually and Mean TIACs for All Patients

Source Organs	TIACs (h)							
	P1	P2	P3	P4	P5	P6	MW	SD
Liver	0.042	0.047	0.042	0.045	0.061	0.039	0.046	0.008
Kidneys	0.021	0.020	0.022	0.021	0.028	0.026	0.023	0.003
Spleen	0.002	0.008	0.005	0.006	0.006	0.006	0.006	0.002
Heart	0.009	0.009	0.010	0.008	0.012	0.010	0.010	0.001
Stomach	0.054	0.075	0.269	0.095	0.039	0.040	0.095	0.088
Urinary bladder	0.209	0.176	0.081	0.187	0.178	0.267	0.183	0.060
Red bone marrow	0.035	0.035	0.023	0.028	0.028	0.026	0.029	0.005
Remainder	0.710	0.808	0.981	0.760	0.822	0.490	0.762	0.161

TABLE 4. Absorbed Organ Dose Coefficients and Absorbed Organ Doses (for a Typical Amount of 150 MBq of ⁶⁸Ga-DOTA-CCK-66)

Target Organ	β (mGy/MBq)	Photon (mGy/MBq)	Total (mGy/MBq)	Absorbed Dose (mGy/150 MBq)
Adrenals	0.004	0.005	0.009	1.3 ± 0.3
Brain	0.004	0.002	0.006	0.9 ± 0.2
Breasts	0.004	0.002	0.006	0.9 ± 0.2
Gallbladder wall	0.004	0.005	0.009	1.4 ± 0.2
LLI wall	0.004	0.008	0.012	1.8 ± 0.3
Small intestine	0.004	0.006	0.010	1.5 ± 0.2
Stomach	0.085	0.013	0.098	15 ± 12
ULI wall	0.004	0.006	0.010	1.4 ± 0.2
Heart wall	0.009	0.004	0.013	2.0 ± 0.3
Kidneys	0.033	0.007	0.039	5.9 ± 2.9
Liver	0.013	0.005	0.018	2.6 ± 0.5
Lungs	0.004	0.003	0.007	1.1 ± 0.2
Muscle	0.004	0.004	0.008	1.2 ± 0.2
Ovaries	0.004	0.008	0.013	1.9 ± 0.2
Pancreas	0.004	0.007	0.011	1.7 ± 0.4
Red marrow	0.006	0.004	0.010	1.4 ± 0.2
Osteogenic cells	0.011	0.004	0.014	2.1 ± 0.4
Skin	0.004	0.002	0.006	0.9 ± 0.2
Spleen	0.012	0.006	0.018	2.7 ± 0.5
Testes	0.004	0.004	0.008	1.2 ± 0.2
Thymus	0.004	0.003	0.007	1.1 ± 0.2
Thyroid	0.004	0.003	0.007	1.0 ± 0.2
Urinary bladder wall*	0.232	0.038	0.269	40 ± 15
Uterus	0.004	0.013	0.018	2.7 ± 0.2
Total body	0.005	0.003	0.008	1.2 ± 0.3
Effective dose coefficient (mSv/MBq)			0.030	
Effective dose (mSv)				4.5 ± 0.9

*Voiding at 1 hour and 3.5 hours.

LLI, lower large intestine; ULI, upper large intestine.

As expected and in line with other previous used CCK₂R-targeting tracers,^{12,14,15} ⁶⁸Ga-DOTA-CCK-66 was well tolerated by all patients. No acute or subacute adverse events were observed, and no significant changes in vital signs were noted. In line with preclinical data, a favorable biodistribution profile for ⁶⁸Ga-DOTA-CCK-66 was observed in all MTC patients, showing relevant uptake only in the CCK₂R-expressing stomach, whereas off-target accumulation was low or renally excreted within the first 4 hours. In 2 subjects with detectable MTC lesions, the highest lesion-to-background ratio was observed at 4 hours after administration of the radiopharmaceutical; however, for practical reasons and the fast decay of gallium-68, we recommend scanning the patients at 2 hours after administration of the compound, particularly because the lesion-to-background ratio is already well-suited for tumor detection.

In 2 of the 6 patients, pathologic tracer uptake consistent with MTC tumor manifestations was recorded. Although this finding might suggest a relatively low detection rate of ⁶⁸Ga-DOTA-CCK-66, it must be noted that the imaging was performed in a small and heterogeneous patient cohort. Therefore, the performance of ⁶⁸Ga-DOTA-CCK-66 needs to be verified in a larger group of

TABLE 5. Comparison of Absorbed Dose Coefficients and Effective Doses for ⁶⁸Ga-DOTA-CCK-66 and Commonly Used PET Tracers

Targeted Organs	Unit	⁶⁸ Ga-PSMA-I&T	¹⁸ F-FDG	⁶⁸ Ga-DOTATOC	¹⁸ F-DOPA	⁶⁸ Ga-DOTA-CCK-66
		Herrmann et al ²⁵	ICRP 106 ²⁶	Sandström et al ²⁷	ICRP 106 ²⁶	This work
Kidneys	mSV/MBq	0.220	0.017	0.082	0.031	0.039
Stomach	mSV/MBq	0.011	0.011	-	0.010	0.098
Urinary bladder wall	mSV/MBq	0.067	0.130	0.119	0.300	0.269
Liver	mSV/MBq	0.043	0.021	0.041	0.009	0.018
Spleen	mSV/MBq	0.063	0.011	0.108	0.010	0.018
Effective dose coefficient	mSV/MBq	0.020	0.019	0.021	0.025	0.030
Typical injected activity	MBq	150	370	150	300	150
Effective dose	mSV	3.0	7.0	3.2	7.5	4.5

patients, especially in comparison to the current gold standard ¹⁸F-DOPA. Since the CCK₂R PET-positive subjects exhibited higher calcitonin levels and shorter calcitonin doubling times than the CCK₂R PET-negative individuals, PET positivity and CCK₂R expression, respectively, could be linked to a more aggressive tumor biology, potentially rendering ⁶⁸Ga-DOTA-CCK-66 a noninvasive readout for tumor biology. Although no firm conclusions on this assumption can be drawn at this moment, further research especially in a larger number of patients is definitely warranted.

Since other PET tracers, such as ¹⁸F-DOPA, can achieve good detection rates in progressive disease as well, the potential strength of DOTA-CCK-66 is the possibility of receptor-directed RLT using its ¹⁷⁷Lu- or even ²²⁵Ac-labeled analog, a concept that has already been proven to be highly successful in the context of PSMA- or SSTR-directed RLT.^{28,29} ⁶⁸Ga-DOTA-CCK-66 demonstrated a favorable biodistribution and dosimetry and could be a meaningful addition to the theranostic approach for patients with advanced MTC. Although kidneys and bone marrow are not considered to be organs at risk in CCK₂R-directed therapeutic approaches, the highest absorbed organ dose and the only one that increased over time was observed in the stomach due to its high physiological CCK₂R expression.³⁰ Dosimetry data for the latest promising CCK₂R-targeting compounds like DOTA-MGS5 or PP-F11N are scarce, rendering a comparison with DOTA-CCK-66 difficult. However, high and increasing SUV_{max} values over time for the stomach (1 hour: 21.5, 2 hours: 23.6) have also been observed for ⁶⁸Ga-DOTA-MGS5 in a recent work,¹⁵ which corroborates our results. Dosimetry data for PP-F11N, which have already been investigated in a phase 0 and phase I study as a therapeutic agent, are only available for the ¹⁷⁷Lu-labeled agent. In a limited number of patients, it could be demonstrated that the maximum tolerable stomach dose (50 Gy) would not be exceeded with a cumulative activity of 50 GBq of ¹⁷⁷Lu-PP-F11N.^{14,31,32} Although we assume this threshold would also not be exceeded in the context of therapeutic application using DOTA-CCK-66 as well, dosimetry and subsequent therapy data for ¹⁷⁷Lu-labeled DOTA-CCK-66 are needed.

CONCLUSIONS

Application of ⁶⁸Ga-DOTA-CCK-66 was well tolerated and showed a favorable biodistribution and dosimetry with high accumulation observed only in tumor lesions and the CCK₂R-expressing stomach, thus offering promising imaging characteristics. Given the inherent theranostic option of this approach, its high in vivo stability, and favorable overall preclinical data, further studies with this novel vector and its ¹⁷⁷Lu/²²⁵Ac-labeled analog are highly warranted.

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