Journal of Nuclear Medicine, published on January 19, 2023 as doi:10.2967/jnumed.122.264977

Preliminary clinical experience of cholecystokinin-2 receptor PET/CT imaging using the ^{68}Ga-labeled minigastrin analog DOTA-MGS5 in patients with medullary thyroid cancer

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Short running title: ^{68}Ga-DOTA-MGS5 PET/CT imaging of MTC

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Word count: 2495

Abstract

PET/CT imaging was performed in patients with advanced medullary thyroid cancer (MTC) with the new ^{68}Ga-labeled minigastrin analog DOTA-DGlu-Ala-Tyr-Gly-Trp-(N-Me)Nle-Asp-1-Nal-NH_2 (^{68}Ga-DOTA-MGS5) to evaluate the cholecystokinin-2 receptor expression status.

Methods: Six patients with advanced MTC underwent PET/CT imaging with ^{68}Ga-DOTA-MGS5. From the images acquired one and two hours post injection (p.i.) preliminary data on the biodistribution and tumor targeting properties were evaluated in a retrospective analysis.

Results: A total of 87 lesions with increased radiotracer uptake considered malignant (two local recurrence, eight lymph nodes, 27 liver and 50 bone lesions) was detected. In general, radiotracer accumulation in lesions was found higher two hours as compared to one hour p.i. (mean SUV_{max}/SUV_{mean} of 7.2/4.4 versus 6.0/3.6).

Conclusion: The preliminary results clearly demonstrate the potential of ^{68}Ga-DOTA-MGS5 PET/CT in detecting local recurrence and metastases in patients with advanced MTC.

Key words: cholecystokin-2 receptor, minigastrin, gallium-68, positron emission tomography, medullary thyroid cancer

INTRODUCTION

Medullary thyroid cancer (MTC) is a rare disease arising from the parafollicular C-cells of the thyroid and accounts for 1-2% of thyroid cancers. Calcitonin is routinely used as tumor marker for MTC. After primary treatment, additional imaging procedures are recommended when calcitonin levels raise above 150 pg/mL *(1)*. Besides conventional radiologic imaging procedures (ultrasound, computed tomography (CT), magnetic resonance imaging), positron emission tomography (PET) with different radiotracers is performed to detect and localize persistent/recurrent disease. In patients with suspected MTC recurrence [^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET/CT has a reported detection rate of 59-69%, whereas 6-[^{18}F]fluoro-L-3,4-dihydroxyphenylalanine (^{18}F-DOPA) PET/CT shows a detection rate of 66-72%, which increases to 86% in patients with higher calcitonin levels and calcitionin doubling time <24 months. PET/CT imaging using ^{68}Ga-labeled somatostatin analogs (^{68}Ga-SSTR PET/CT) has demonstrated variable sensitivity with an overall detection rate of 63.5% and allows to select patients for peptide receptor radionuclide therapy *(2)*.

Cholecystokinin-2 receptors (CCK2R) are over-expressed in >90% of MTC *(3)*. We have recently reported on the development of the new minigastrin analog DOTA-DGlu-Ala-Tyr-Gly-Trp-(N-Me)Nle-Asp-1-Nal-NH_2 (DOTA-MGS5) with improved stability *in vivo* and enhanced tumor targeting *(4)*. CCK2R targeting with DOTA-MGS5, therefore, offers a promising new diagnostic and therapeutic approach for patients with advanced MTC.

We here report on our initial clinical experience with ^{68}Ga-labeled DOTA-MGS5 for PET/CT imaging with the primary goal to evaluate the potential of the new radiotracer to detect tumor lesions in patients with proven recurrent or residual metastatic disease.

MATERIALS AND METHODS

Six patients with histologically proven MTC and confirmed metastatic disease from previously performed diagnostic contrast-enhanced CT (ceCT) and PET imaging with ^{18}F-DOPA or ^{68}Ga-labeled DOTA-TOC underwent PET/CT imaging with ^{68}Ga-labeled DOTA-MGS5. For patient characteristics see Supplemental Table 1. All patients were without tumor-specific treatment at the timepoint of imaging and selected individually to evaluate a potential therapeutic option with radionuclide therapy targeting CCK2R. The examination was performed within a "named patient use" and written informed consent was obtained from all patients as part of the standard practice in all nuclear medicine examinations. All procedures performed in this study were in accordance with the principles of the 1964 Declaration of Helsinki and its subsequent amendments. The retrospective analysis of the data was approved by the Ethics Committee of the Medical University of Innsbruck (approval n. 1162/2022).

Radiopharmaceutical

^{68}Ga-labelled DOTA-MGS5 (^{68}Ga-DOTA-MGS5) used in this study was prepared according to the Austrian Medicines Act (AMG §8 and §62) as described elsewhere (*5*) and was administered as a slow intravenous injection (~2 min) with a mean administered mass of DOTA-MGS5 of 16 ± 6 µg (range, 12-28 µg) and a mean administered activity of 177 ± 16 µg (range, 163-208 MBq).

Imaging Protocol

PET/CT scans were conducted using a dedicated PET/CT system in time of flight mode (Discovery; GE Healthcare, Milwaukee, WI). A whole-body PET scan (skull vertex to upper thighs) in three-dimensional mode was acquired one and two hours after tracer injection (emission time: two min per bed position with an axial field-of-view of 20 cm). Five patients received a diagnostic ceCT scan one hour after injecton. A CT scan of the thorax, abdomen and pelvis

(shallow breathing) was acquired 40 – 70 sec after injection of contrast agent (60 to 120 ml of Iomeron 400 mg/l, depending on patient body weight), followed by a CT scan of the thorax in deep inhalation. In one patient, with ceCT available from another PET/CT examination, only a low-dose CT was performed one hour after injection. All patients received a low-dose CT two hours after injection. Low-dose CT was used for attenuation correction of the PET emission data. Images were corrected for randoms, scatter and decay. Reconstruction was performed on the GE acquisition workstation with the iterative reconstruction method VUEPOINT FX (GE®), no z-axis filter and the software package Q.Clear (beta=1000), a fully convergent iterative reconstruction method with noise control (GE®).

Image Analysis

All PET/CT images were analyzed with dedicated commercially available software (GE Advance Workstation SW Version AW4.5 02), which allowed the review of PET, CT and fused imaging data in axial, coronal and sagittal slices. Intensity of tracer accumulation in organs and tissues with physiologic tracer uptake was measured using mean and maximum standardized uptake values (SUV_{mean}, SUV_{max}). For SUV-calculations volumes of interest were generated automatically with the default isocontour threshold of 42% centered on organs and tissues of interest. SUV-calculations one and two hours p.i. were performed in: blood pool (aortic arch), gluteal muscle, brain, bone (thoracic vertebra), lung, liver, gallbladder, pancreas, stomach, adrenal gland, spleen, small bowel, large bowel, kidney, renal pelvis, urinary bladder. For bowel activity the area with the highest uptake was selected. In addition, PET images were analyzed visually and lesions with increased radiotracer uptake judged as pathologic were counted with respect to their localization. SUVs of these lesions were measured on images one and two hours after injection. Furthermore, tumor-to-background (T/B) ratio was determined, dividing SUV_{max} of tumor lesions

by SUV_{mean} of the surrounding tissue (SUV_{mean} blood pool for local recurrence and lymph nodes; SUV_{mean} of normal tissue for liver and bone lesions).

RESULTS

The administration of ^{68}Ga-DOTA-MGS5 was well tolerated with no adverse effects. In all six patients with metastatic MTC, as confirmed by diagnostic ceCT and PET imaging with ^{18}F-DOPA or ^{68}Ga-labeled DOTA-TOC (see Supplemental Table S1), metastatic spread was also shown with ^{68}Ga-DOTA-MGS5. CCK2R-positive local recurrence was detected in two patients. A total of eight CCK2R-positive lymph nodes with pathologic uptake were found in five patients, 27 liver lesions with increased uptake suggestive of metastases were present in three patients, whereas in two patients 50 bone lesions were tracer-avid. Semiquantitative assessment of tumor lesions showed a slight increase of radiotracer accumulation between scans one hour and two hour p.i. in lymph nodes, in liver and bone metastases, remaining stable in local recurrences. An overview of SUV values and TB ratios of lesions judged as malignant is given in Table 1 and Supplemental Table S2 and S3.

With regard to physiological biodistribution of ^{68}Ga-DOTA-MGS5, physiological tracer uptake and detailed information on SUV values in normal tissue and organs is presented in Table 2 and Supplemental Table S4 and Figure S1. An increase of median SUV_{max} values two hours p.i. compared with images acquired one hour p.i. was observed in the following organs: brain, gallbladder, urinary bladder, renal pelvis, small bowel, large bowel and stomach. In contrast, a decrease of median SUV_{max} between one and two hours p.i. was detected in blood pool, bone, adrenal gland, lung, spleen, liver, kidney and pancreas, whereas median SUV_{max} of background activity (gluteal muscle) remained stable. Apart from one bone lesion T/B ratio was higher two hours p.i. than one hour p.i. in all lesions, irrespective of tumor site. When comparing T/B ratios

of the different tumor sites, mean T/B ratios of 3.3 at one hour p.i. and of 4.1at two hours p.i. were found for local recurrence, whereas for lymph nodes values of 2.4 and 3.3 were found, respectively. In comparison, higher mean T/B ratios were observed in liver lesions, with values of 5.1 and 7.1 at one and two hours after injection, as well as in bone lesions with values of 5.4 and 7.6 at one and two hours p.i. (see also Supplemental Table S3). Exemplary images of a patient with different sites of metastasis are shown in Figure 1.

DISCUSSION

The potential of CCK2R targeting peptide analogs for imaging and therapy was highlighted already in the late nineties. However, the first ^{111}In-labeled minigastrin analogs suffered from low diagnostic performance and PET/CT imaging with ^{68}Ga-labeled minigastrin analogs was reported only in two patients so far *(6)*. New clinical trials have been initiated evaluating the diagnostic performance and dosimetry of alternative peptide derivatives by scintigraphic imaging *(7,8)*. Based on DOTA-MGS5, with increased *in vivo* stability and enhanced tumor targeting in preclinical investigations, we have performed PET/CT imaging with ^{68}Ga-DOTA-MGS5. All six patients examined revealed at least one CCK2R-positive lesion consistent with malignancy. Lesions rated positive for local recurrence as well as local and distant metastases (lymph nodes, liver and bone) could be visualized, as demonstrated in Figure 1. In the majority of lesions (87.4%) a trend towards higher SUV_{max} values was found for two versus one hour after injection. Higher tumor-to-background ratios were present two hours p.i. in 98.9% of the lesions. The low radiotracer uptake in normal tissue resulted in high contrast especially in hepatic and skeletal lesions.

However, the preliminary data have to be interpreted with caution, due to the small number of patients and the selection bias, as all patients presented with tumor lesions known from previously performed imaging. In addition, the data do not allow a statement on the diagnostic

accuracy of the new radiotracer, as a systematic direct comparison with standard imaging procedures such as ^{18}F-DOPA, ^{68}Ga-DOTATOC and ceCT was not performed. Therefore, further studies are needed to confirm the preliminary results in a higher number of patients.

CONCLUSION

The preliminary results of this small series of patients clearly demonstrate that ^{68}Ga-DOTA-MGS5 PET/CT has the potential to detect local recurrence and metastases in advanced MTC. ^{68}Ga-DOTA-MGS5 PET/CT further allows to evaluate the feasibility of peptide receptor radionuclide therapy targeting CCK2R. In order to provide data on the diagnostic performance of ^{68}Ga-DOTA-MGS5 PET/CT in patients with locally advanced or metastatic MTC we have recently initiated a prospective study (EudraCT:2020-003932-26; approval n. 1336/2020) at our center, comparing also PET/CT imaging with ^{68}Ga-DOTA-MGS5 also to ^{18}F-DOPA, ^{68}Ga-DOTATOC and ceCT as reference standard.

Acknowledgements:

We thank all staff members for their help in performing the PET imaging studies.

Financial disclosure:

Elisabeth von Guggenberg and Maximilian Klingler were named in a patent application (EP3412303) for peptide analogues with improved pharmacokinetics and cholecystokinin-2 receptor (CCK2R) targeting for diagnosis and therapy. No other potential conflict of interest relevant to this article was reported.

Key Points

Question: Has PET/CT imaging with ^{68}Ga-DOTA-MGS5 targeting the expression of the cholecystokinin-2-receptor (CCK2R) a potential role in the diagnostic follow-up of patients with advanced medullary thyroid cancer (MTC)?

Pertinent Findings:

In a small series of six patients with advanced MTC, PET/CT imaging with ^{68}Ga-DOTA-MGS5 was able to visualize local recurrence as well as lymph node, liver and bone metastases. The low physiological liver uptake of the radiotracer allows for a high contrast of hepatic lesions.

Implications for Patient Care:

^{68}Ga-DOTA-MGS5 PET/CT is an interesting new tool in the diagnostic follow-up of patients with advanced MTC. In addition to localization of tumor lesions the feasibility of peptide receptor radionuclide therapy targeting CCK2R can be evaluated.

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Table 1. Comparison of intensity of ^{68}Ga-DOTA-MGS5 uptake one and two hours after radiotracer injection in lesions considered malignant, expressed in maximum standardized uptake value (SUV_{max}).

SUV_{max}		**1 h p.i.** **mean; median (range)**	**2 h p.i.** **mean; median (range)**
Local recurrence	(n=2)	6.2; 6.2 (4.6-7.8)	6.2; 6.2 (3.9-8.5)
Lymph nodes	(n=8)	4.3; 3.8 (2.1-7.1)	4.5; 3.9 (2.2-8.1)
Liver lesions	(n=27)	9.6; 5.0 (2.4-53.2)	11.0; 5.3 (4.0-62.6)
Bone lesions	(n=50)	4.3; 4.0 (1.9-8.0)	5.3; 4.6 (1.9-12.4)

Table 2. Comparison of intensity of ^{68}Ga-DOTA-MGS5 uptake one and two hours after radiotracer injection in organs and tissues with physiologic tracer uptake, expressed in maximum standardized uptake value (SUV_{max}).

SUV_{max}, median (range)	**1 h p.i.** **mean; median (range)**	**2 h p.i.** **mean; median (range)**
Blood pool	3.3; 3.3 (2.4-4.0)	2.9; 2.7 (2.2-4.0)
Gluteal muscle	1.0; 1.0 (0.8-1.3)	0.9; 1.0 (0.7-1.1)
Bone	1.3; 1.4 (0.9-1.6)	1.3; 1.3 (1.0-1.4)
Adrenal gland	2.4; 2.3 (2.0-2.9)	1.8; 1.7 (1.2-2.4)
Brain	0.7; 0.6 (0.3-1.1)	0.7; 0.7 (0.4-0.8)
Lung	1.1; 1.2 (0.8-1.4)	1.0; 1.1 (0.6-1.2)
Spleen	2.0; 1.7 (1.3-3.7)	1.6; 1.3 (1.1-2.9)
Liver	2.4; 2.5 (2.2-2.6)	2.2; 2.1 (1.3-3.1)
Gallbladder	6.7; 5.8 (4.3-10.7)	6.2; 6.5 (4.7-7.1)
Urinary bladder	89.5; 101.9 (30.1-123.8)	132.2; 118.6 (70.1-213.1)
Kidney	6.3; 5.9 (4.0-11.2)	5.1; 4.9 (3.8-6.8)
Renal pelvis	28.8; 27.3 (8.8-48.0)	50.6; 35.3 (12.9-150.3)
Small bowel	3.1; 2.5 (1.9-6.1)	4.1; 3.4 (1.4-10.0)
Large bowel	1.9; 1.9 (1.6-2.6)	2.7; 2.0 (1.6-5.9)
Stomach	21.5; 20.4 (10.4-38.9)	23.6; 26.2 (11.5-31.3)
Pancreas	2.9; 3.0 (2.2-3.2)	1.7; 2.8 (2.1-3.4)

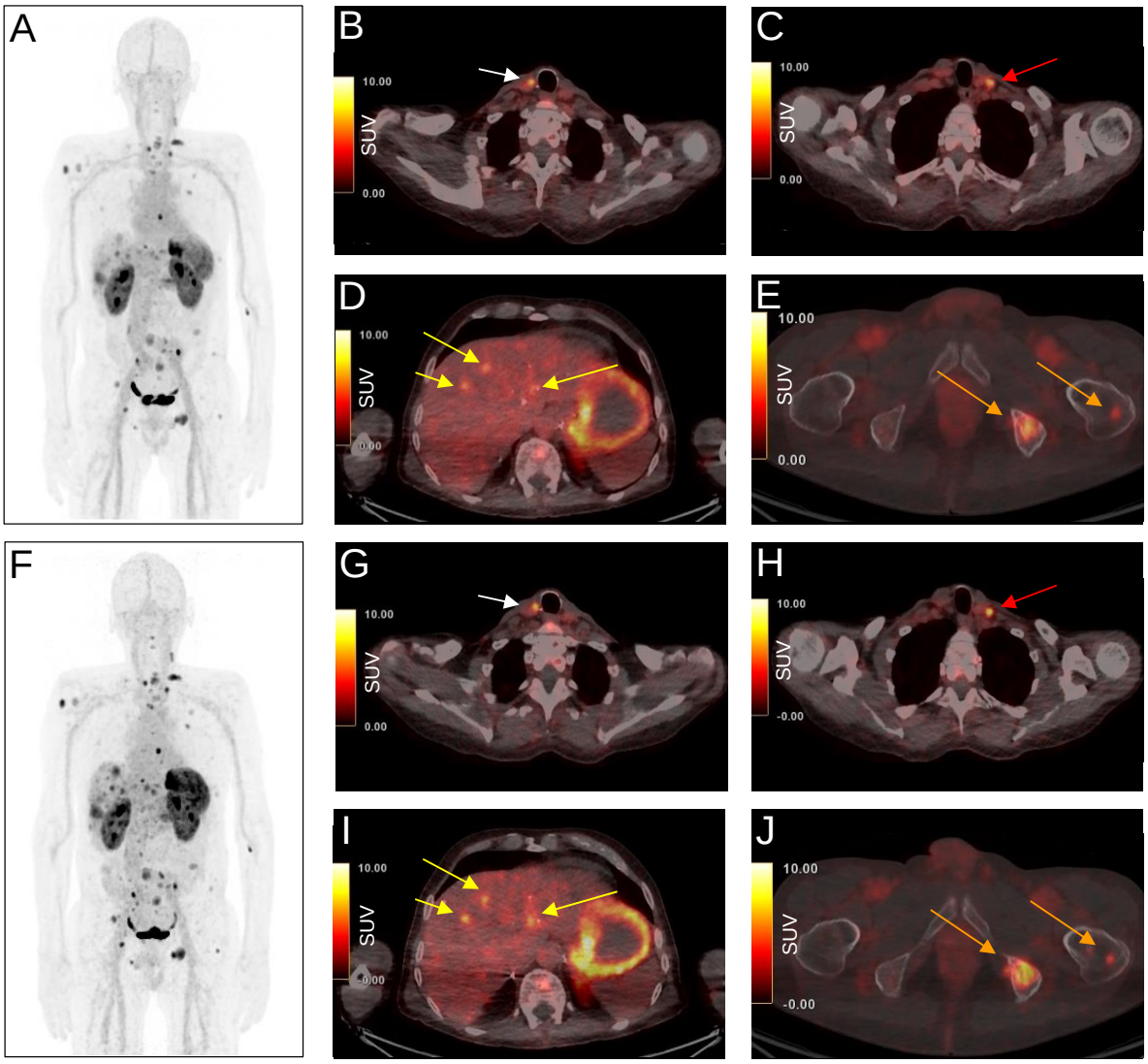
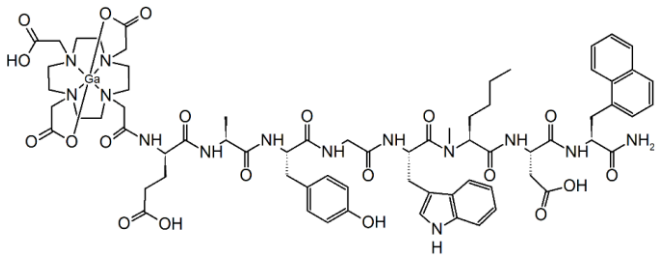


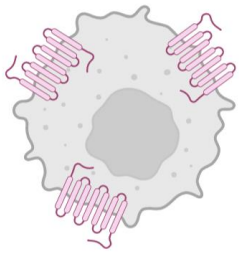
Figure 1. Maximum intensity projection and axial fused ^{68}Ga-DOTA-MGS5 PET/CT images one hour (a-e) and two hours p.i. (f-j) of a metastatic MTC patient (calcitonin: >2000 ng/L), showing local recurrence on the right paratracheal region with SUV_{max} of 7.8 vs. 8.5 at 1 and 2 h p.i. (b, g; white arrow), cervical lymph node metastasis with SUV_{max} of 7.1 vs. 8.1 (as depicted on the left cervical region in c and h; red arrow), several liver metastases with SUV_{max} of 5.5, 6.3, 5.3 vs 6.7, 7.1, 6.7 (d and i; marked with yellow arrows) and multiple bone metastases with SUV_{max} in two lesions of 7.6, 3.6 vs 9.7, 5.1 (as demonstrated, in the left iliac bone and left femur on e and j; orange arrows).

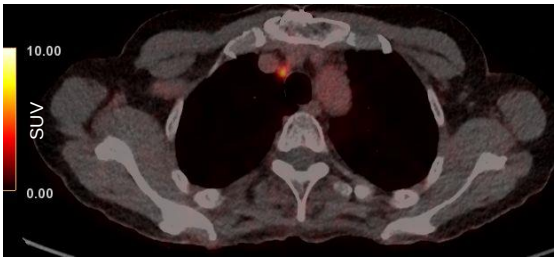
Graphical abstract

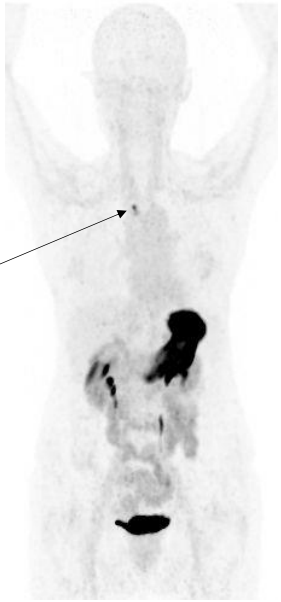


^{68}Ga-DOTA-MGS5

Lymph node metastasis
SUV_{max}: 7.4 (2 h p.i.)







Preliminary clinical experience of cholecystokinin-2 receptor PET/CT imaging using the ^{68}Ga-labeled minigastrin analog DOTA-MGS5 in patients with medullary thyroid cancer

The Journal of Nuclear Medicine

Supplemental Data

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Supplemental Table S1. Patient characteristics of the six patients with advanced MTC who underwent ^{68}Ga-DOTA-MGS5 PET/CT, including previously performed imaging procedures.

Patient no.	Sex	Age (years)	CT level (ng/L)	Time after diagnosis (years)	TTE + neck dissection	ceCT	^{18}F-DOPA PET	^{68}Ga-SSTR PET
1	F	75	>2000	34	y	y	y	n
2	M	60	>2000	14	y	y	n	y
3	M	57	>2000	23	y	y	n	y
4	F	65	516	10	y	y	y	n
5	M	49	69	8	y	y	y	n
6	F	40	812	10	y	y	y	n

CT: calcitonin; TTE: total thyroidectomy; ceCT=contrast-enhanced CT; y: yes; n: no

Supplemental Table S2. Comparison of intensity of ^{68}Ga-DOTA-MGS5 uptake one and two hours after radiotracer injection in lesions considered malignant, expressed in maximum standardized uptake value (SUV_{max}) and mean standardized uptake value (SUV_{mean}).

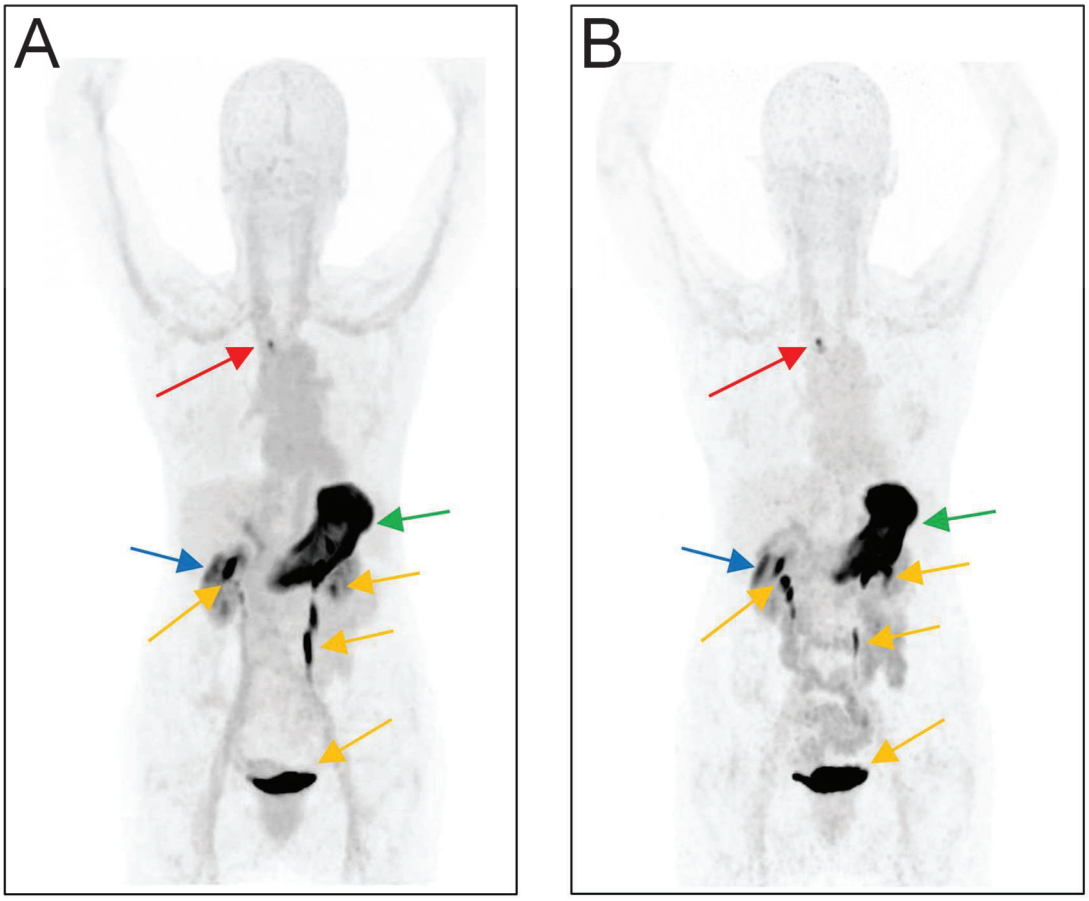
Uptake values		1 h p.i. mean; median (range)	2 h p.i. mean / median (range)
Local recurrence	SUV_{max}	6.2; 6.2 (4.6-7.8)	6.2; 6.2 (3.9-8.5)
(n=2)	SUV_{mean}	3.7; 3.7 (2.5-4.8)	3.9; 3.9 (2.4-5.4)
Lymph nodes	SUV_{max}	4.3; 3.8 (2.1-7.1)	4.5; 3.9 (2.2-8.1)
(n=8)	SUV_{mean}	2.4; 2.1 (1.3-4.4)	2.7; 2.4 (1.2-5.3)
Liver lesions	SUV_{max}	9.6; 5.0 (2.4-53.2)	11.5; 5.3 (4.0-62.6)
(n=27)	SUV_{mean}	6.0; 2.7 (1.4-35.1)	7.0; 3.2 (2.1-39.9)
Bone lesions	SUV_{max}	4.3; 4.0 (1.9-8.0)	5.3; 4.6 (1.9-12.4)
(n=50)	SUV_{mean}	2.6; 2.4 (1.0-5.1)	3.2; 2.7 (1.1-8.2)

Supplemental Table S3. Comparison of tumor-to-background ratio, determined by dividing SUV_{max} of tumor lesions by SUV_{mean} of blood pool for local recurrence and lymph nodes, SUV_{mean} of liver for liver lesions and SUV_{mean} of bone for bone lesions, for the time points of one and two hours after radiotracer injection.

Tumor-to-background ratio	1 h p.i. mean / median (range)	2 h p.i. mean / median (range)
Local recurrence (n=2)	3.3; 3.3 (3.1-3.5)	4.1; 4.1 (3.5-4.7)
Lymph nodes (n=8)	2.4; 2.6 (0.9-3.5)	3.3; 3.2 (1.4-5.7) 1.4
Liver lesions (n=27)	5.1; 2.5 (1.2-28)	7.1; 3.5 (2.1-39.1)
Bone lesions (n=50)	5.4; 4.9 (2.5-10)	7.6; 6.5 (2.7-17.7)

Supplemental Table S4. Comparison of intensity of ^{68}Ga-DOTA-MGS5 uptake one and two hours after radiotracer injection in organs and tissues with physiologic tracer uptake, expressed in maximum standardized uptake value (SUV_{max}) and in mean standardized uptake value (SUV_{mean}).

Uptake values		1 h p.i. mean; median (range)	2 h p.i. mean; median (range)
Blood pool	SUV_{max}	3.3; 3.3 (2.4-4.0)	2.9; 2.7 (2.2-4.0)
	SUV_{mean}	2.2; 2.2 (1.5-2.4)	1.6; 1.6 (1.1-2.0)
Gluteal muscle	SUV_{max}	1.0; 1.0 (0.8-1.3)	0.9; 1.0 (0.7-1.1)
	SUV_{mean}	0.5; 0.5 (0.5-0.7)	0.5; 0.5 (0.4-0.6)
Bone	SUV_{max}	1.3; 1.4 (0.9-1.6)	1.3; 1.3 (1.0-1.4)
	SUV_{mean}	0.7; 0.7 (0.5-0.9)	0.6; 0.7 (0.5-0.7)
Adrenal gland	SUV_{max}	2.4; 2.3 (2.0-2.9)	1.8; 1.7 (1.2-2.4)
	SUV_{mean}	1.6; 1.5 (1.3-2.1)	1.1; 1.1 (0.7-1.5)
Brain	SUV_{max}	0.7; 0.6 (0.3-1.1)	0.7; 0.7 (0.4-0.8)
	SUV_{mean}	0.3; 0.3 (0.1-0.6)	0.4; 0.4 (0.2-0.5)
Lung	SUV_{max}	1.1; 1.2 (0.8-1.4)	1.0; 1.1 (0.6-1.2)
	SUV_{mean}	0.6; 0.6 (0.4-0.7)	0.5; 0.5 (0.3-0.6)
Spleen	SUV_{max}	2.0; 1.7 (1.3-3.7)	1.6; 1.3 (1.1-2.9)
	SUV_{mean}	1.3; 1.3 (1.0-1.7)	0.9; 0.8 (0.6-1.4)
Liver	SUV_{max}	2.4; 2.5 (2.2-2.6)	2.2; 2.1 (1.3-3.1)
	SUV_{mean}	1.6; 1.5 (1.3-2.0)	1.2; 1.1 (0.8-1.9)
Gallbladder	SUV_{max}	6.7; 5.8 (4.3-10.7)	6.2; 6.5 (4.7-7.1)
	SUV_{mean}	3.9; 3.3 (2.5-6.4)	3.1; 3.4 (1.7-3.9)
Urinary bladder	SUV_{max}	89.5; 101.9 (30.1-123.8)	132.2; 118.6 (70.1-213.1)
	SUV_{mean}	62.1; 69.2 (22.9-88.3)	86.2; 73.6 (44.2-145.0)
Kidney	SUV_{max}	6.3; 5.9 (4.0-11.2)	5.1; 4.9 (3.8-6.8)
	SUV_{mean}	3.9; 3.7 (2.4-6.2)	3.4; 3.2 (2.4-5.2)
Renal pelvis	SUV_{max}	28.8; 27.3 (8.8-48.0)	50.6; 35.3 (12.9-150.3)
	SUV_{mean}	17.0; 15.7 (4.8-28.5)	29.7; 22.0 (6.3-84.7)
Small bowel	SUV_{max}	3.1; 2.5 (1.9-6.1)	4.1; 3.4 (1.4-10.0)
	SUV_{mean}	1.8; 1.5 (1.1-3.6)	2.4; 1.7 (0.8-6.4)
Large bowel	SUV_{max}	1.9; 1.9 (1.6-2.6)	2.7; 2.0 (1.6-5.9)
	SUV_{mean}	1.1; 1.0 (0.8-1.6)	1.5; 1.3 (0.8-3.1)
Stomach	SUV_{max}	21.5; 20.4 (10.4-38.9)	23.6; 26.2 (11.5-31.3)
	SUV_{mean}	12.6; 12.4 (6.7-21.1)	14.2; 15.9 (7.3-18.1)
Pancreas	SUV_{max}	2.9; 3.0 (2.2-3.2)	2.8; 2.8 (2.1-3.4)
	SUV_{mean}	2.0; 2.0 (1.8-2.1)	1.7; 1.7 (1.4-2.0)



Supplemental Figure S1. Maximum intensity projection of ^{68}Ga-DOTA-MGS5 PET/CT one hour (A) and two hours p.i. (B) of a metastatic MTC patient (calcitonin: 516 ng/L), showing a mediastinal lymph node metastasis (red arrow) with SUV_{max} of 6.6 vs. 7.4 at 1 and 2 h p.i., demonstrating also physiological radiotracer distribution with the highest uptake in stomach (green arrow), gallbladder (blue arrow) and the urinary system (yellow arrows).