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Intraindividual Comparison of Selective Arterial versus Venous ^{68}Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors

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Abstract

Purpose: Therapy with the somatostatin analogue DOTA-(0)-Phe(1)-Tyr(3)-octreotide (DOTATOC) labeled with a β-(DOTA-Phe-Tyr-Octreotide) emitter such as ^{90}Y or ^{177}Lu is accepted for the palliative treatment of unresectable neuroendocrine cancer. However, the optimal route of administration has not been determined. Using positron-emission tomography (PET)-labeled ^{68}Ga-DOTATOC, we compared selective tumoral uptake on PET/computed tomography (CT) after arterial or venous administration of the agent in patients with gastroenteropancreatic neuroendocrine tumor.

Experimental Design: Fifteen patients with neuroendocrine cancer were examined with ^{68}Ga-DOTATOC PET/CT after intravenous (i.v.) and intraarterial (i.a.) administration within 4 weeks of each other and without any intervening therapy. Eleven patients had multifocal metastases, six were considered to have unresectable primary tumor. The intraarterial catheter was placed in the vessel supplying the main tumor burden. The standard uptake value (SUV) was used to compare intratumoral concentrations of ^{68}Ga-DOTATOC.

Results: Compared with i.v. infusion, the i.a. infusion resulted in an increased SUV in 117 of 122 (96%) liver metastases. The average increase in SUV was 3.75-fold higher with i.a. administration. The increase in uptake for the primary tumors was dependent on the selectivity of the catheter placement, resulting in variable increases in SUV after i.a. injection (1.44- to 7.8-fold higher).

Conclusions: This study showed that uptake of DOTATOC is commonly several fold higher after selective i.a. administration in comparison with i.v. injection in both the primary tumor as well as in liver metastases of neuroendocrine cancer. Therefore, intraarterial DOTATOC is a promising drug for regionally intensified radiopeptide therapy. *Clin Cancer Res; 16(10); 2899–905. ©2010 AACR.*

There are few effective treatments for unresectable, well differentiated, disseminated gastroenteropancreatic neuroendocrine tumor (GEP-NET). Although the progression rate was slower than with many solid tumors, NETs also showed poor response to conventional chemotherapy with objective response rates in the range of 10% to 36% (1, 2). Antiproliferative therapy with octreotide or IFN could stabilize disease for ~8 months (mean), as recently shown in the PROMID study (3). However, tumor shrinkage occurs in <10%. NETs commonly metastasize to the liver, and regional treatments such as radiofrequency ablation, transarterial chemoembolization, and selective internal radiation therapy have been used in this setting. However, radiofrequency ablation suffers from high recurrence rates (4); whereas transarterial chemoembolization and selective internal radiation therapy are contraindicated in cases of complete portal vein thrombosis or hepatic insufficiency. Additionally, postembolization syndrome is often observed and the effect on survival has yet to be proven in larger clinical trials (5). These treatments are also not generally suitable for metastases outside the liver (2).

Although selective internal radiation therapy provides regional untargeted radiation therapy to the liver, peptides targeting the somatostatin receptor, which is frequently overexpressed in GEP-NET but not in normal liver, can be radiolabeled to deliver targeted radiation therapy (6). A large series with 310 patients treated with ^{177}Lu-[DOTA0,Tyr3] octreotate showed the effectiveness of this technique in providing symptomatic relief and prolonging survival (7). However, complete and partial remission rates are still limited to 10% to 30% (1, 8–10).

Thus, there is a medical need for therapeutic options, which potentially address both primary and secondary GEP-NETs

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Translational Relevance

To show that intraarterial administration of DOTATOC results in regionally intensified radiopeptide therapy of neuroendocrine cancer. The treatment is a promising and more selective alternative to transarterial chemoembolization or selective internal radiation therapy for liver metastases. Furthermore, it might convert unresectable neuroendocrine primary tumors to resectable ones.

that are otherwise unresectable. Selective intraarterial (i.a.) application of DOTA(0)-Phe(1)-Tyr(3)-octreotide (DOTATOC) provides a method of intensifying therapy by delivering more concentrated doses of the agent to the lesion. When combined with a therapeutic radioisotope, such a conjugate could focally and specifically treat GEP-NETs.

However, it is important to document that i.a. administration would result in higher concentrations of the agent within the tumor. Using a PET-labeled version of DOTATOC, ^{68}Ga-DOTATOC, it is possible to quantify the tumor uptake *in vivo*. We determined the potential improvement in tumor uptake using i.a. administration over intravenous (i.v.) administration in the same patients serially imaged with positron emission tomography (PET)/computed tomography (CT).

Materials and Methods

Experimental design. We carried out an intraindividual comparison of tumor uptake after intravenous and selective arterial application of ^{68}Ga-DOTATOC. In each patient, the two examinations were obtained within 4 weeks of each other. No intervening therapy was permitted on this protocol. The examinations were conducted in accordance with the Helsinki Declaration and our national regulations, written informed consent was obtained from all patients.

Patients. We evaluated 15 patients (6 men, 9 women, ages 40-65 years) with histologically confirmed GEP-NET. The origins of the tumors were pancreatic (10), gastric (3), and enteral (2). Eleven patients had one or more hepatic metastases, nine of these patients had already undergone resection of the primary lesion; however, in two patients (one with G-NET and one with P-NET), it was still present. We evaluated up to 12 liver metastases per patient (total $n = 122$). In four patients, the focus was exclusively on the primary tumor due to local symptoms.

Radiopharmaceuticals. DOTA0-D-Phe1-Tyr3-octreotide was synthesized as described in the literature (11). ^{68}Ga [half-life, 68.3 minutes; β+ (β plus), 88%; Eβ+ maximum, 1.900 keV] was obtained from a ^{68}Ge/^{68}Ga radionuclide generator developed by the Radiochemistry Department of the German Cancer Research Center, Heidelberg. Twenty-four micrograms of peptide (16.8 nmol of aqueous DOTATOC solution) were used per synthesis. Chromatography revealed <2% of unchelated ^{68}Ga. Pyrogenicity and sterility were also evaluated.

PET/CT imaging. All PET studies were done on a Biograph 6 PET/CT (Siemens/CTI). Based on experience from a previous investigation by our group, imaging was started 40 ± 10 minutes after either i.v. injection of 84 to 196 MBq or i.a. injection of 64 to 172 MBq of ^{68}Ga-DOTATOC (12). For attenuation correction of the PET scan, a low-dose CT (130 keV, 30 mAs; CareDose) without contrast medium was done. Static emission scans, corrected for dead time, scatter, and decay, were acquired from the vertex to the proximal legs—requiring eight bed positions, 4 minutes each. The images were iteratively reconstructed with the OSEM algorithm using four iterations with eight subsets and Gauss filtering to an in-plane spatial resolution of 5 mm at full-width half-maximum.

For calculation of the standardized uptake value (SUV), circular regions of interest were drawn around the area with focally increased uptake in transaxial slices and automatically adapted to a three-dimensional volume of interest with e.soft software (Siemens) at a 70% isocontour.

Catheter placement. In general, a 4-Fr catheter (Sidewinder-S1) was placed in the celiac artery via a transfemoral access in Seldinger technique using local anesthetic. Then a microcatheter (Progreat) was inserted coaxially and advanced to the common hepatic artery, proper hepatic artery, or gastroduodenal artery. In cases of anatomic variation, the most appropriate arterial feeder was cannulated.

Data analysis. The raw data of all analyzed paired SUVs (after i.a. and i.v. administration) were summarized in a box plot with mean, median, range, and SD. We independently analyzed the possible improvement of SUV(max) in liver metastases, primary tumor, and with regard to radiation burden of normal tissue (kidney, pituitary gland, hepatic background). Differences were considered significant at $P < 0.05$, highly significant at $P < 0.01$ in paired sample t test.

Results

All 15 patients were examined twice without complications and were analyzed successfully.

Liver metastases. The average SUV(max) of 122 analyzed tumor sites in the 11 patients with liver metastases was 17.7 (median, 14.9; SD, 11.0; range, 4.8-51.7) and the average SUV(mean) was 14.1 (median, 12.1; SD, 9.1; range, 2.5-42.2) after i.v. injection of ^{68}Ga-DOTATOC. The average SUV(max) after i.a. administration was 60.8 (median, 40.8; SD, 56.4; range, 9.4-267.7) and the average SUV(mean) was 51.8 (median, 34.5; SD, 46.6; range, 9.4-196.7). In 117 of 122 liver metastases, the intraarterial uptake of ^{68}Ga-DOTATOC was increased in comparison with intravenous uptake, respectively, and the differences of the SUV(mean) and SUV(max) were also significantly higher (paired t test; $P < 0.001$; Fig. 1). The average enhancement of SUV(max) was 3.75-fold higher using the intraarterial

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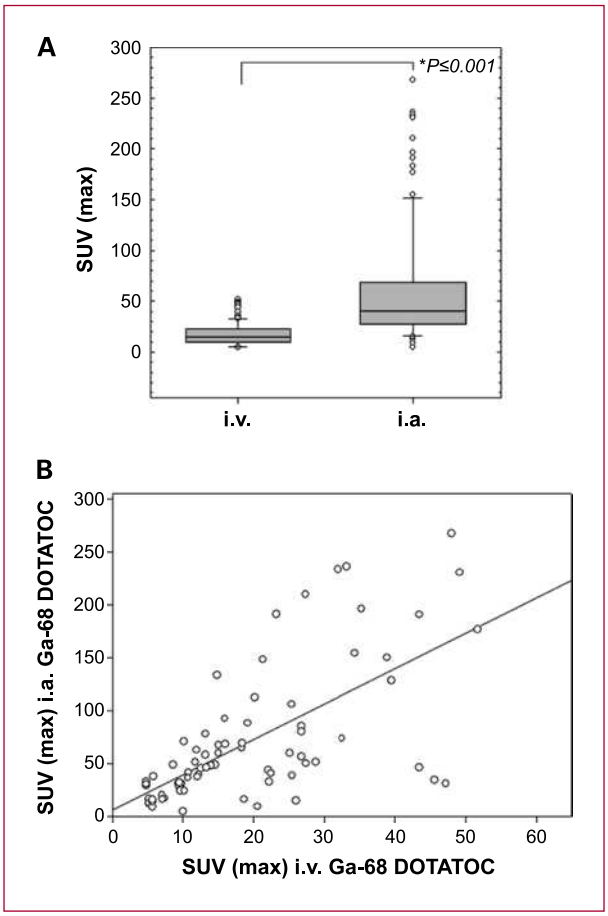

Fig. 1. A-B, comparison of maximal SUVs after i.v. and i.a. application, respectively, of ^{68}Ga-DOTATOC in 122 liver metastases of 11 patients suffering from metastasized gastroenteropancreatic cancer (paired *t* test, $P < 0.001$). The main statistic is summarized as a box plot (A). The individual lesions are also presented in a scatter plot (B; note the different scales in *X*- and *Y*-axes). However, it was previously shown that vascular fraction and receptor binding are independent factors determining the SUV in DOTATOC-PET and therefore the linear regression analysis (line) might be insufficient to predict the benefit of a particular lesion.

approach. Figure 2 presents a typical patient with isolated liver metastases after resection of the primary tumor.

Primary tumor. Uptake in inoperable primary tumors was predominantly dependent on the ability to selectively catheterize the feeding arteries. In three patients with tumor in the pancreatic head, ^{68}Ga-DOTATOC could be injected highly selectively in the gastroduodenal artery and the enhancement of SUV(max) was 5.3-fold (119.9 i.a. versus 22.5 i.v.), 6.1-fold (436.4 i.a. versus 72.1 i.v.), and 7.8-fold (279.4 i.a. versus 35.7 i.v.; see Fig. 3), respectively. In one patient with neuroendocrine cancer in the pancreatic tail, the feeding artery could not be accessed directly and therefore ^{68}Ga-DOTATOC was injected unselectively into the splenic artery, resulting in only a 3.2-fold enhancement of the SUV(max) (92.6 i.a. versus 28.8 i.v.). In two patients, the unresectable gastric or pancreatic tumor was small in comparison with the liver metastases. In these cases, a nonselective catheterization of the celiac artery was chosen. Even with this approach, the SUV (max) of the primary tumor was increased by 2.6-fold (58.4 versus 22.4; P-NET) and 1.44-fold (36.3 versus 25.2; G-NET).

Nontumor tissue (pituitary gland, kidney, and liver background). After i.v. injection of ^{68}Ga-DOTATOC, the average SUV(max) in the pituitary gland was 4.9 (median, 4.9; SD, 1.5; range, 2.1-6.9), whereas after i.a. injection, the value decreased to 3.7 (median, 3.5; SD, 2.3; range, 1.2-8.4). This reduction was significant (paired *t* test, $P < 0.05$).

From an average SUV(max) of 7.4 (median, 6.3; SD, 2.8; range, 4.3-13.5) after i.v. injection in comparison with the average SUV(max) of 5.6 (median, 4.7; SD, 2.5; range, 2.8-10.4) after i.a. administration, the reduction of kidney uptake trended toward lower values with the i.a. route ($P = 0.08$ in paired *t* test). On visual inspection (Fig. 4), the changes in whole-body distribution of DOTATOC seemed more pronounced in patients with higher tumor burden but subgroup analysis was not meaningful due to the limited number of cases. The chart of our statistic is represented in Fig. 5.

There was neither a relevant change of DOTATOC uptake in the normal liver comparing i.v. injection (average SUV, 4.7; SD, 1.5; range, 1.9-7.2) with i.a. injection (average SUV, 6.2; SD, 2.1; range, 3.0-8.9) nor comparing the i.a. administration directed toward the primary tumor with DOTATOC reaching the liver by the portal vein (average SUV, 6.8; SD, 2.0; range, 4.3-7.7) and the i.a. administration with DOTATOC reaching the liver by the hepatic artery (average SUV, 5.9; SD, 2.2; range, 3.0-8.9); in each case $P > 0.05$ using paired *t* test (difference not significant). The nonimpact of the injection site for the unspecific uptake within the liver is illustrated in Fig. 2 i.v. infusion (*a*) versus injection into the hepatic artery (*b*) and Fig. 3 i.v. infusion (*b*) versus injection into the gastroduodenal artery which is draining into the portal vein (*c*).

Discussion

Peptide-receptor radiation therapy is an accepted option for the palliation of metastasized GEP-NET. A correlation between higher tumor dose and improved therapy response has been reported (13). An arterial infusion would increase tumor uptake while reducing nontarget exposures (14). The concept of escalating dose by arterial infusion of radioactive drugs has only recently been considered. Brogsitter et al. (15) used an intraarterial infusion of I-131 MIBG to treat GEP-NET. The tumor uptake in 17 patients was 1.7-fold (mean) increased for arterial injection compared with a venous infusion. However, cellular uptake of MIBG depends on membrane transporters and the first-pass effect might be less pronounced than with receptor-targeted molecules. A first attempt for receptor-targeted intraarterial therapy was carried out by McStay et al. with ^{90}Y-DOTA-lanreotide and showed a promising

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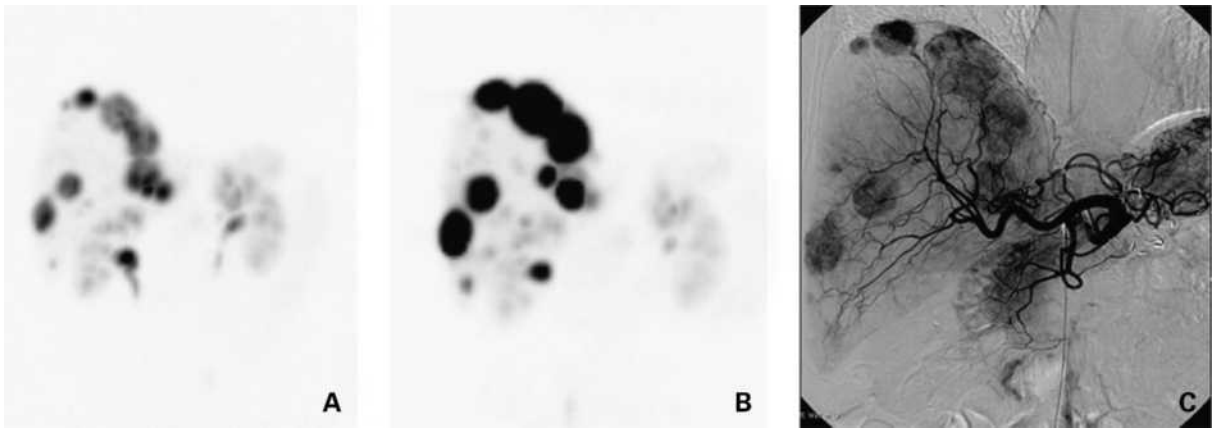

Fig. 2. Comparison of intraindividual ^{68}Ga-DOTATOC PET/CT in a patient with multiple liver metastases, presented as a maximum intensity projection after i.v. (A) versus i.a. (B) application. Average SUV(max) presents a 3.2-fold higher value (122.9 versus 38.5) after i.a. ^{68}Ga-DOTATOC infusion. C, digital subtraction angiography illustrates the nearly exclusive arterial perfusion of neuroendocrine liver metastases.

therapy response. However, a direct comparison with venous administration was lacking (16). Arterial infusion of ^{111}In-DPTA-octreotide in patients with GEP-NET resulted in an increased tumor-to-kidney dose ratio, which was 1.57 times higher after transhepatic than after venous infusion (17, 18). DOTA-lanreotide and DTPA-octreotide are both characterized by a lower receptor affinity in comparison with the more recent DOTA-D-Phe-Tyr-octreotide(DOTATOC). This may have resulted in a lower first-pass extraction of the previously introduced somatostatin analogues.

In our investigation, ^{68}Ga-DOTATOC was used as a surrogate marker to provide dosimetric biodistribution *in vivo* for the somatostatin analogues ^{90}Y- and ^{177}Lu-DOTATOC, which are currently used for therapy. By using a PET-labeled surrogate, it was possible to quantify tumor uptake after i.v. and. i.a. administration in the same individual without interference from other therapies. The coordination geometry of the radiometal complex remote from the pharmacophoric amino acids has some small effect on somatostatin receptor binding and affinity to SSR-2 is slightly higher for ^{68}Ga- than for ^{90}Y- or ^{177}Lu-DOTATOC (19). However, these small differences between the diagnostic and the therapeutic derivates should not affect the uptake ratios. Furthermore, an intraindividual comparison was done to avoid a systematic error caused by differences in affinity.

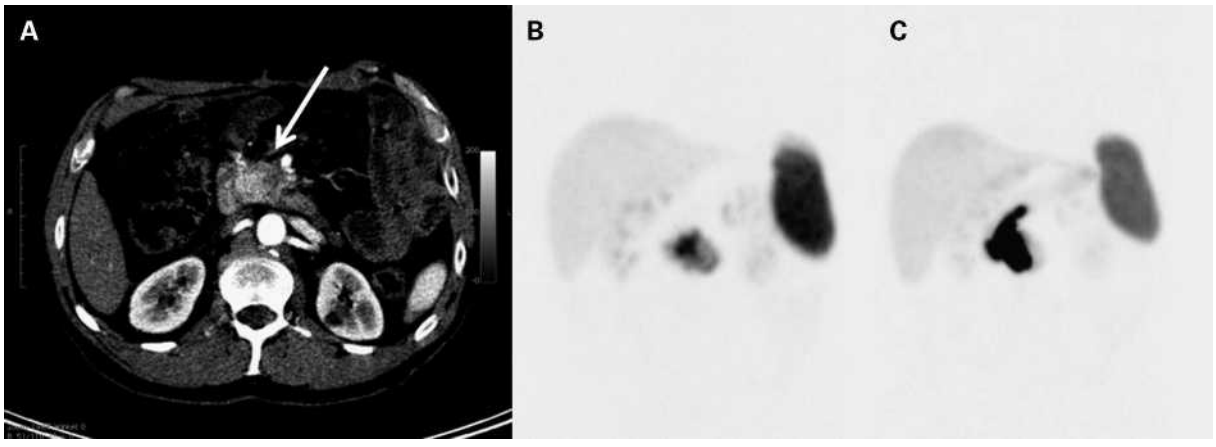

Fig. 3. Patient with neuroendocrine cancer in the mesenteric root (P-NET) shown by contrast-enhanced CT (arrow, tumor lesion). After selective exploration of the gastroduodenal artery, tumor uptake was enhanced 7.8-fold (SUV 279.4 versus 35.7) after i.a. (C) in comparison with i.v. (B) injection of ^{68}Ga-DOTATOC.

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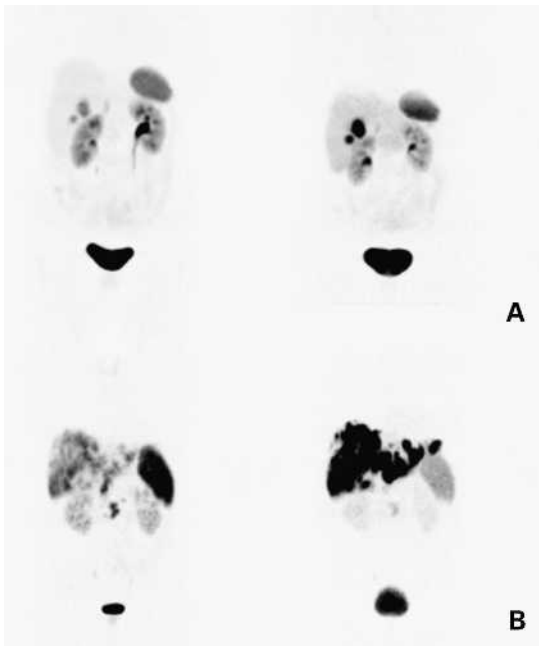

Fig. 4. DOTATOC biodistribution presented as maximum intensity projections. A, ^{68}Ga-DOTATOC PET/CT in a patient with low tumor burden. The two solitary liver metastases (arrows) show enhanced uptake after arterial injection (right), whereas whole-body distribution (kidneys, spleen) did not differ significantly. B, ^{68}Ga-DOTATOC PET/CT in a patient with high tumor burden of the liver. After i.v. application (left), the most intense uptake was seen inside the spleen and there is circumscribable uptake in the kidneys. After i.a. application, the main volume of DOTATOC was trapped in the liver metastases during the first-pass effect, whereas the uptake from the kidneys and spleen was decreased remarkably.

Radiofrequency ablation, transarterial chemoembolization, and selective internal radiation therapy are established regional treatments for liver metastases (20, 21). Transarterial chemoembolization and selective internal radiation therapy are based on arterial embolization and are considered to be contraindicated in cases of complete portal vein occlusion. Radiofrequency ablation is commonly applied when the number of metastases is limited (22). Regional DOTATOC therapy could be an additional option for patients with portal vain thrombosis and disseminated liver involvement when an occlusive treatment is contraindicated. After i.a. application in the hepatic artery, we regularly observed an increased uptake in liver metastases which was 3.75-fold higher compared with i.v. injection; however, uptake decreased in 5 of 122 metastases evaluated. Even retrospectively, we could not identify the particular cause for this observation. It is possible that collateral vessels of the common hepatic artery, i.e., branches of the mesenteric or right gastric artery, diverted the agent from the target. Additionally, deviation, kinking, or even compression of single vessels might occur, dependent on patient positioning. Another possibility could be an incomplete amalgamation of DOTATOC within the bloodstream of the hepatic artery and laminar flow might prefer some metastases with concentrated cords of the radiopeptide. It is known that not all metastases express SSR sufficiently, resulting in no change in uptake after arterial infusion.

There are few options in unresectable primary GEP-NET. Embolization of vessels might lead to gastric ulceration or necrotic pancreatitis (23–25). We observed an up to 7.8-fold higher primary tumor uptake of DOTATOC with highly selective arterial infusion therapy. Presumably, this increase in local concentration will improve tumor response.

Conventional DOTATOC radiopeptide therapy is limited by the kidney dose (26). Renal radiation burden is difficult to assess because there is no specific receptor-mediated uptake of DOTATOC to the kidneys, but the excretion of the radiopeptide to the urine is a dynamic process and kidney uptake depends on the time after injection. We observed a wide variability of kidney uptake,

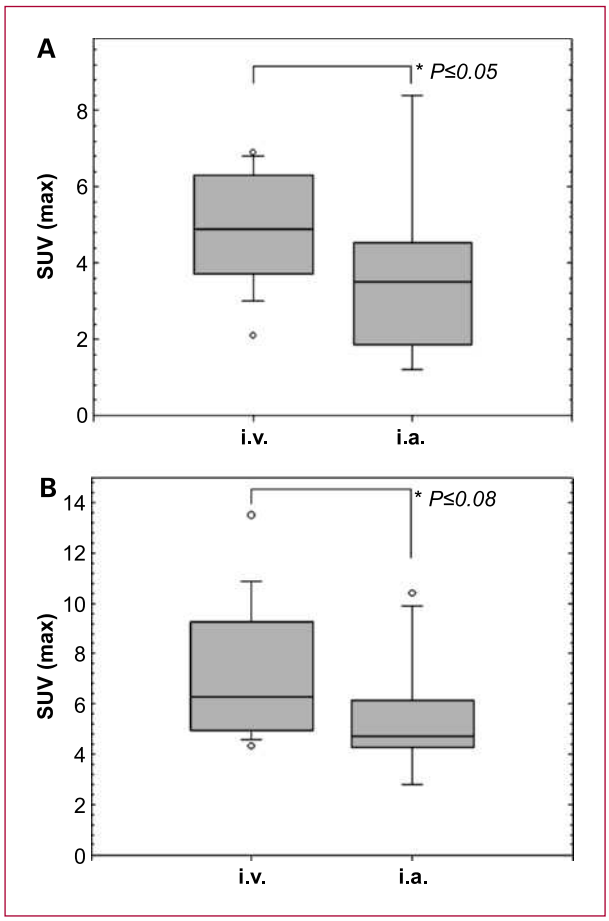

Fig. 5. NOA-B, comparison of maximal SUVs after i.v. and tumor-targeted i.a. application of ^{68}Ga-DOTATOC in the pituitary gland (A) and kidney (B) of 15 patients suffering from gastroenteropancreatic neuroendocrine cancer. A significant decrease was shown for the pituitary gland ($P < 0.05$, paired t test), the reduction of kidney uptake only tends to be significant ($P = 0.08$, paired t test).

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perhaps due to different tumor burdens. This effect is illustrated in Fig. 4. Due to this wide variety of individual tumor burdens and the still limited number of patients (kidney, $n = 15$), the intraindividual comparison of the kidney SUV failed to reach statistical significance. However, we also evaluated DOTATOC uptake in the pituitary gland, which is specifically receptor-mediated and where time-activity curves show a plateau phase (27). Therefore, we considered pituitary uptake as a suitable proxy for systematic exposure to DOTATOC. Although we again observed a wide interindividual variability of DOTATOC uptake in the pituitary gland, we showed a significant reduction of DOTATOC uptake after i.a. injection of the agent. The reduction of exposure outside of tumor sites could be explained by a relevant elimination of the radiopeptide from systemic circulation during the first pass of the tumor. Tracer uptake by the normal liver tissue was not significantly increased after i.a. injection. This might be a statistical limitation caused by the small number of patients. However, in our study, the range of liver SUV after i.a. and i.v. administration were widely overlapping and because the liver is relatively radioresistant, we would not expect that this organ could become a dose-limiting factor for radiopeptide therapy.

A shortcoming of this study is that it only evaluated biodistribution. Therefore, the improvements in local concentration might not translate to improved therapy response. However, initial results from our first patients treated with i.a. application of ^{90}Y- and ^{177}Lu-DOTATOC indicated a promising benefit using this new approach. Further research will be necessary to optimize treatment protocols for intraarterial radiopeptide therapy, e.g., how much peptide can be given per hour without introducing receptor saturation. Additionally, the dosimetry for i.a. versus i.v. administration of the longer-living therapeutic compounds with Y-90 or Lu-177 should be compared in some suitable individuals. If there is a late redistribution of DOTATOC, possibly due to the therapeutic effects of the β-emitter, the initial uptake measured with the short-living Ga-68 might overestimate the ultimate difference in tumor dose. Finally, it has yet to be determined whether our approach improves the clinical outcome of patients with GEP-NET.

In conclusion, uptake of DOTATOC might be several fold higher after i.a. administration in comparison with i.v. injection both in the primary lesion and in the metastases of neuroendocrine cancer. Therefore, DOTATOC may be a promising carrier molecule for regionally intensified radiopeptide therapy in patients with regionally limited tumor spread.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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