

[¹¹¹In-DTPA]octreotide Tumor Uptake in GEPNET Liver Metastases After Intra-Arterial Administration: An Overview of Preclinical and Clinical Observations and Implications for Tumor Radiation Dose After Peptide Radionuclide Therapy

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Abstract

Aims: With the aim to improve peptide receptor radionuclide therapy effects in patients with gastroenteropancreatic neuroendocrine tumor (GEPNET) liver metastases we explored the effect of intra-arterial (IA) administration of [¹¹¹In-DTPA]octreotide (¹¹¹In-DTPAOC) on tumor uptake in an animal model and in a patient study.

Methods: Preclinical study: After administering ¹¹¹In-DTPAOC intra-venously (IV) or IA, biodistribution studies were performed in rats with a hepatic somatostatin receptor subtype 2 (sst₂)-positive tumor. Clinical study: 3 patients with neuroendocrine liver metastases were injected twice with ¹¹¹In-DTPAOC. The first injection was given IV, and 2 weeks later, the second was injected IA (hepatic artery). Planar images of the abdomen were made up to 72 hours after injection. Blood samples were taken and urine was collected. Pharmacokinetic modeling was performed on the IV and IA data of the same patient. Based on this model, additional ¹⁷⁷Lu dosimetry calculations for IV and IA administrations were performed.

Results: The preclinical study showed a two-fold higher ¹¹¹In-DTPAOC tumor uptake after IA administration than after IV injection. Patient data showed a large variability in radioactivity increment in liver metastases after IA administration compared with IV administration. Renal radioactivity was not significantly lower after IA administration; ¹⁷⁷Lu dosimetry simulations in 1 patient using a maximum kidney radiation dose of 23 Gy showed IA administration resulted in a mean increase in tumor radiation dose of 2.9-fold.

Conclusion: Preclinical and clinical data both indicate that IA administration of radiolabeled somatostatin analogs via the hepatic artery can significantly increase radionuclide uptake in GEPNET, sst₂-positive, liver metastases up to 72 hours postinjection, although the effect of IA administration can differ between patients.

Key words: intra-arterial injection, liver metastases, neuroendocrine tumor, radionuclide therapy, somatostatin

Introduction

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) are usually slow growing tumors that are often metastasized at time of diagnosis. In these cases curative treatment by surgery is most often not an option anymore. Various chemotherapeutic agents like streptozotocin, doxo-

rubicin, 5-fluorouracil, chlorozotocin, etoposide, and cisplatin have been and are still being used alone or in combination for treatment of GEPNETs. Variable objective response rates and considerable toxicity were encountered though.¹ Recent studies show encouraging results in terms of tumor growth control by inhibition of growth factor receptors like vascular endothelial growth factor receptor, platelet-

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derived growth factor receptor, and C-kit by sunitinib maleate.² In addition, inhibition of the mammalian target of rapamycin signal transduction pathway in GEPNETs by Everolimus (RAD001) most recently demonstrated a significantly improved progression-free survival of 11 months compared with 4.6 months observed in the placebo-treated patients.³ Unfortunately, the affect on overall survival has not been shown yet. Despite these promising developments the standard biotherapy treatment at present is by somatostatin analogs like octreotide (short acting or long acting release). Octreotide treatment mainly aims at prevention of carcinoid syndrome and has been described to inhibit tumor growth to some extent.⁴ Overexpression of the somatostatin 2 receptor (sst₂) on GEPNETs resulted in the 1980s in the development of radiolabeled somatostatin analogs like [¹¹¹In-DTPA]octreotide (¹¹¹In-DTPAOC) for visualization of sst₂-expressing NETs. In the past decade, several radiolabeled somatostatin analogs have not only been applied for visualization of NETs but also for peptide receptor radionuclide therapy (PRRT).

Initial PRRT studies were performed with high doses of the Auger electrons and γ -emitting ¹¹¹In-DTPAOC⁵ and later with the β - and γ -emitting radiopeptide [¹⁷⁷Lu-DOTA, Tyr³]octreotate (¹⁷⁷Lu-DOTATATE) and the β -emitting [⁹⁰Y-DOTA, Tyr³]octreotide (⁹⁰Y-DOTATOC), both being applied now for treatment of GEPNETs. ¹⁷⁷Lu-DOTATATE and ⁹⁰Y-DOTATOC studies have shown very convincing results with regard to tumor response, overall survival, and quality of life.^{6,7} Few side effects have been reported. Dose limiting organs due to radiotoxic effects are bone marrow⁸ and the kidneys, the organs of excretion in PRRT. Co-infusion of amino acids reduces kidney uptake and the renal radiation dose.^{9,10} The maximum administered activity is usually 29.6 GBq for ¹⁷⁷Lu-DOTATATE and 22.2 GBq/m² for ⁹⁰Y-DOTATOC. Complete responses are still rare though. We hypothesized that a higher tumor uptake of the radiopharmaceutical would improve the currently suboptimal tumor response.

Up to 75% of GEPNET patients have liver metastasis at time of diagnosis.¹¹ The aim of this study was to use intra-arterial (IA) administration of the radioligand via the common hepatic artery to increase tumor uptake of ¹¹¹In-DTPAOC. McStay et al. demonstrated IA PRRT with ⁹⁰Y-lanreotide to be safe and at least as effective as intravenous (IV) administration.¹² Limouris et al. also showed encouraging results with IA PRRT with ¹¹¹In-DTPAOC, ⁹⁰Y-DOTATOC, and/or ¹⁷⁷Lu-DOTATATE.^{13,14} There was little proof of increased radiolabeled somatostatin analogue tumor uptake, until a 2009 study by Beauregard et al. reported that 3 patients had a 72% increased tumor to kidney ratio after IA ¹⁷⁷Lu-DOTATATE, in comparison with IV ¹⁷⁷Lu-DOTATATE PRRT. Intra-individually in 1 patient IV and IA administered ⁶⁸Ga-DOTATATE was quantified by PET imaging at 30 minutes postinjection (pi), showing a five-fold increase in tumor uptake after IA administration.¹⁵ Kratochwil et al. showed IA administration resulted in a 1.4–7.8-fold (mean 3.75) higher tumor uptake of ⁶⁸Ga-DOTATOC as quantified by PET imaging at 40 minutes pi.¹⁶ The same group also reported on the pharmacokinetics after IA and IV 20 minutes infusion of ¹¹¹In-DOTATOC intra-individual in patients with GEPNETs. At the end of IA infusion tumor uptake was 3.5-fold higher compared with IV. This tumor uptake showed a decrease to a 2-fold ratio at 4 hours pi and a 1.3-fold ratio at

72 hours pi. Additionally, impressive objective responses were reported after IA administration of ⁹⁰Y- and/or ¹⁷⁷Lu-DOTATOC in 15 patients with GEPNET liver metastasis.¹⁶ In our study, we explored the effect of IV versus IA administration of ¹¹¹In-DTPAOC on tumor uptake in an sst₂-expressing liver metastasis model in the rat and intra-individually in 3 GEPNET patients with liver metastasis up to 72 hours pi. Based on the longitudinal measurements with ¹¹¹In-DTPAOC we performed pharmacokinetic modeling and simulated ¹⁷⁷Lu dosimetry on tumor tissue and healthy organs. Here, we describe major differences between 3 patients with regard to the ratio of tumor radioactivity up to 72 hours pi after IV versus IA injection in the same patient.

Materials and Methods

Radionuclides, peptide, chemicals

For the animal experiments ¹¹¹InCl₃ was purchased from Covidien (Petten, The Netherlands). DTPAOC (Octreoscan[®]) was obtained from Tyco Health Care (Petten, The Netherlands). Radiolabeling was performed according to previously published procedures.¹⁷ The labeling efficiency exceeded 99%, as confirmed by thin-layer chromatography. The specific activity of ¹¹¹In-DTPAOC was 3 MBq/0.5 μ g peptide.

For the human study the commercially available Octreoscan kit (¹¹¹In-DTPAOC) was used in a specific activity of 220 MBq/10 μ g peptide.

Liver metastasis model in the rat

The animal studies were in accordance with the Animal Welfare Committee requirements of our institution and were

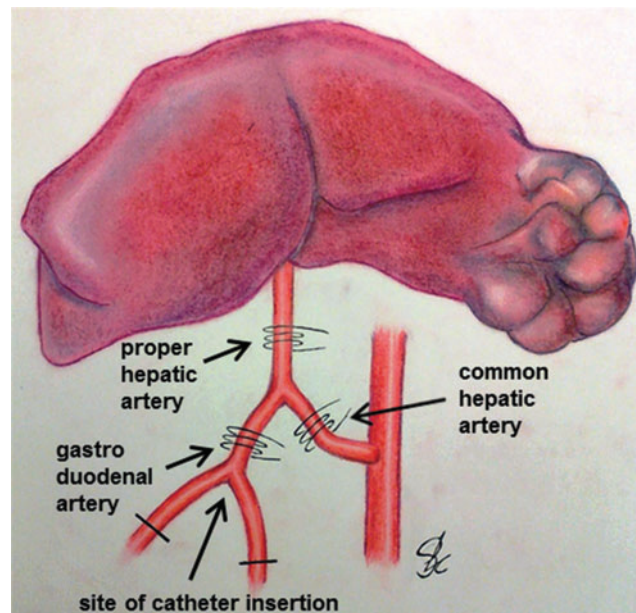


FIG. 1. Schematic representation of the surgical technique used in rats to provide an intra-arterial (IA) route of administration to the liver. Before injection of [¹¹¹In-DTPA]octreotide (¹¹¹In-DTPAOC) the ligatures around the common and proper hepatic artery were removed to restore normal blood flow towards the liver. Color image available online at www.liebertpub.com/cbr

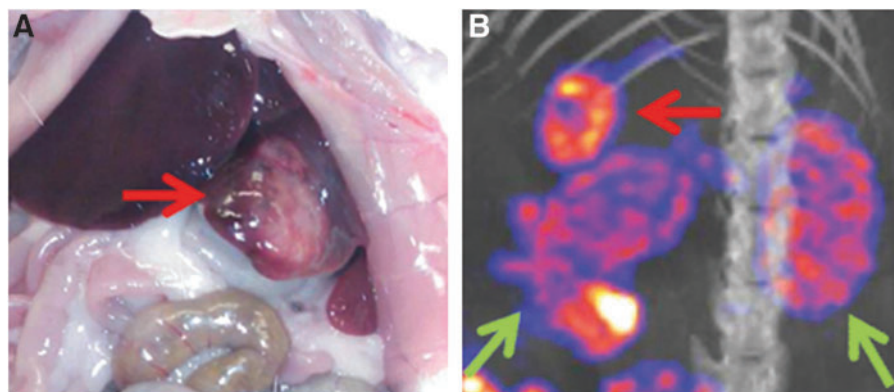


FIG. 2. (A) Intrahepatic CA20948 tumor 10 days after inoculation. (B) ¹¹¹In-DTPAOC uptake in an intrahepatic CA20948 tumor visualized by micro-SPECT/CT. Red arrow, intrahepatic CA 20948 tumor; green arrows, kidneys. Color images available online at www.liebertpub.com/cbr

conducted following generally accepted guidelines. For the experiments, male Lewis rats (Harlan, Horst, The Netherlands) bearing an intra-hepatic CA20948 tumor¹⁸ were used ($n=6$ per group, 2 groups). Mean bodyweight at the time of tumor inoculation was 300 g. All surgical and injection procedures were performed under isoflurane/O₂ anesthesia and using a microsurgery microscope. During surgery, animals were kept warm with a heating pad.

After laparotomy of the rat's upper abdomen, the main liver lobe was fixated between two swabs and 1.5×10^6 CA20948 tumor cells suspended in 100 μ L matrigel basement membrane matrix (BD Biosciences, San Jose, CA) were injected subcapsularly via a 27-gauge needle. The abdomen was closed by absorbable sutures.

On day 14 after inoculation, laparotomy of the abdomen was performed again by a 3.5 cm incision along the linea alba. Silicon tubing (inner diameter 0.012 inch and outer diameter 0.025 inch) was placed in the gastroduodenal artery with the tip just in front of the bifurcation of the common and proper hepatic arteries. A sham laparotomy was performed on all animals that received IV ¹¹¹In-DTPAOC administration. A schematic representation of the surgical technique used to provide an IA route of administration to the liver is shown in Figure 1.

Before injection, the blood supply to the liver was restored by removing the ligatures around the proper and common hepatic arteries, necessary for placement of the silicon tubing without major blood loss. One hundred fifty microliters of 3 MBq/0.5 μ g ¹¹¹In-DTPAOC was injected in about 3 seconds. After injection the catheter was flushed with saline and removed.

After euthanasia at 24 hours pi normal organs and tumors were dissected and blood samples were taken. Organs and tumors were weighed and radioactivity was measured with a gamma counter (Wallac, 1480 Wizard 3"; PerkinElmer, Turku, Finland). The uptake of radioactivity was expressed as the percentage of injected activity per gram tissue (%IA/g).

MicroSPECT/CT imaging

One additional rat with a subcapsular CA20948 tumor in the liver was imaged by microSPECT/CT imaging. Twenty-four hours before scanning, the rat was injected IV with 30 MBq/0.5 μ g ¹¹¹In-DTPAOC. Scanning was performed with a four-headed multi-pinhole NanoSPECT/CT camera (Bioscan, Inc., Washington, DC). Nine pinhole-apertures with a diameter of 2.5 mm were used with 24 projections (1 minute per projection). The ¹¹¹In energy peaks were set at 171 and 245 keV. Guided by the CT topogram, the upper abdomen was scanned for 60 seconds per projection. The whole procedure was performed under Isoflurane/O₂ anesthesia. SPECT scans were reconstructed iteratively using InVivoScope software version 1.32 (Bioscan, Inc.) with medium noise reduction, a voxel size of 0.3 mm³, and standard reconstruction settings.

Patient study

Three patients (age 32, 54, and 64 years) with metastatic nonresectable pancreatic NETs were enrolled to receive two injections of ¹¹¹In-DTPAOC; one IV injection and one IA injection with a 2 week-interval. From previous imaging it was known that these patients had hepatic metastasis enabling

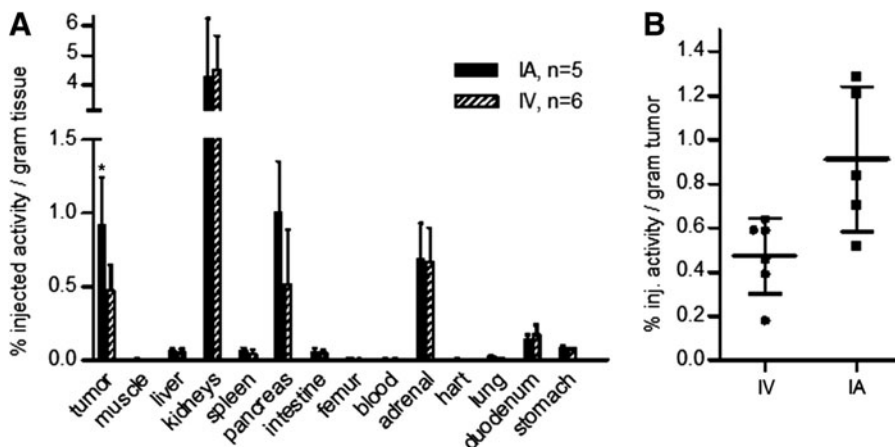


FIG. 3. (A) Percentage injected ¹¹¹In-DTPAOC activity per gram tissue in tumor and several organs after intravenous (IV) and IA administration in CA20948 intrahepatic tumor bearing rats (mean \pm standard deviation [SD]) * $p < 0.05$. (B) Dotplot of ¹¹¹In-DTPAOC uptake in the intrahepatic tumor after IV and IA administration (mean, \pm SD), $p < 0.05$.

dosimetry measurements. All patients were on short acting octreotide treatment (Sandostatin; Novartis, Basel, Switzerland), which was discontinued 24 hours prior to both injections. This 24 hours discontinuation was chosen because before standard ^{177}Lu -DOTATATE treatment the same period of short acting octreotide treatment discontinuation is used. The study was performed after written informed consent from the patient to participate in this study, which was approved by the Erasmus MC Medical Ethical Committee.

IA administration. IA administration was performed via a catheter placed angiographically through Seldinger's technique via the femoral artery with the tip into the common hepatic artery. Immediately after this procedure the patient was placed on the gamma camera bed in a supine position. The ^{111}In -DTPAOC was injected in about 10 seconds. The catheter was flushed with 10 mL of 0.9% saline. The same injection protocol was used for IV injected ^{111}In -DTPAOC.

Imaging. All images were acquired with a dual-head gamma camera Picker Prism 2000 XP (Philips, Eindhoven, The Netherlands). The windows were centered over both ^{111}In photon peaks (245 and 171 keV) with a width of 20%. Parallel-hole, medium-energy general-purpose collimators were used. After each injection method, the same scan protocol was followed: dynamic imaging up to 30 minutes pi with a field of view over the kidneys and liver for the anterior and posterior projections (120 images, 15 seconds

per image). Upper abdomen anterior and posterior scans were obtained at 1, 4, 24, 48, and 72 hours after injection. The acquisition time for all scans was 20 minutes. The accumulated radioactivity in tumor and organs was quantified by drawing regions of interest (ROIs) in Phillips odyssey LX software.

Measurement of radioactivity in blood and urine. Blood samples were drawn at 1 minute before and 2, 5, 10, 15, 20, 30 minutes and 1, 4, 24, 48, and 72 hours pi. Urine was collected in four intervals: 0–1, 1–4, 4–24, and 24–48 hours after pi. Radioactivity in blood samples was quantified using a gamma counter (Cobra II Autogamma, Packard, a Canberra Company). Radioactivity in urine samples was quantified using a dose calibrator (VCD-404; Veenstra Instruments, Joure, The Netherlands).

Pharmacokinetics and dosimetry. ROIs were drawn manually on the anterior and posterior spot views of the upper abdomen around tumor lesions, liver, spleen, and kidneys. The background region was placed close to the ROIs for background correction. The geometric mean value, derived from the anterior and posterior scans, was taken and corrected for attenuation and physical decay. The activity in the syringe before injection minus the remaining activity in the syringe after injection was defined as 100% of the injected activity. A compartmental pharmacokinetic model was used to fit double-exponential curves through the uptake data. ^{177}Lu dosimetry calculations were performed on tumor

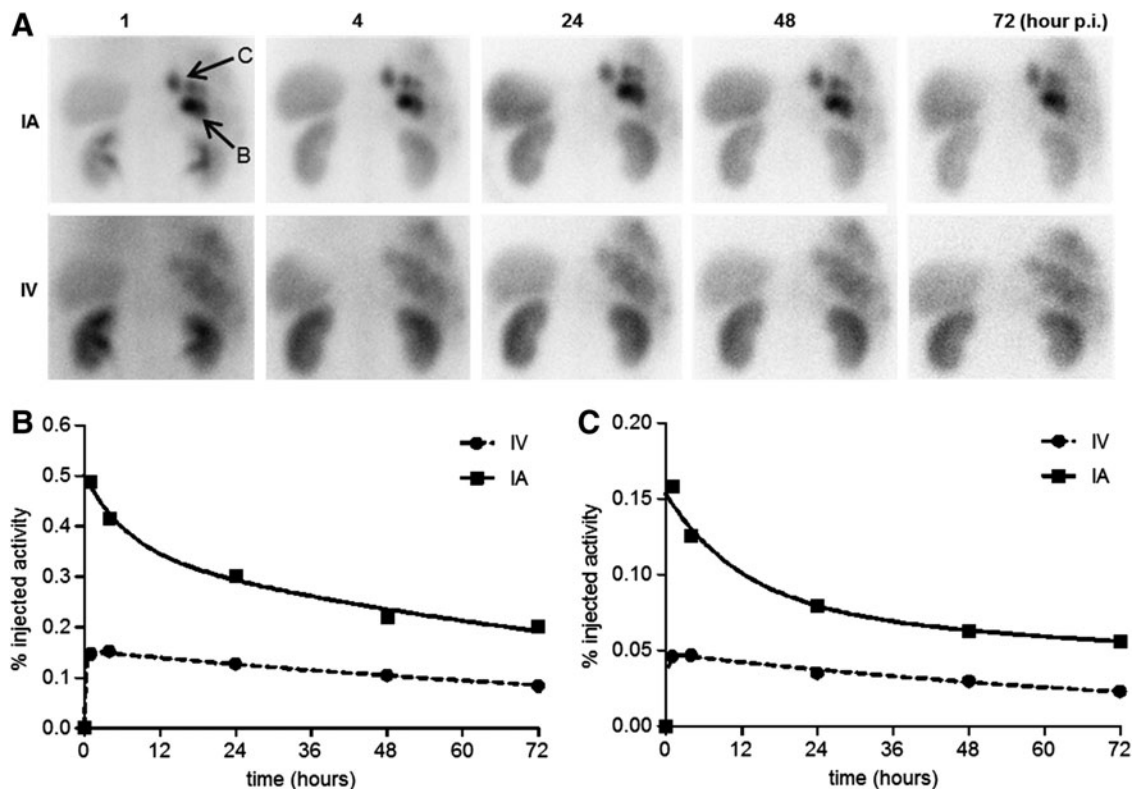


FIG. 4. Patient 1; (A) planar posterior upper abdomen images showing higher ^{111}In -DTPAOC uptake in neuroendocrine liver metastasis at 1, 4, 24, 48, and 72 hours after IA and IV administration of ^{111}In -DTPAOC. (B, C) Quantification of ^{111}In uptake in liver metastasis B and C (see first picture A) after IA and IV administration. IA administration resulted in both liver metastases in a 2.4-fold increase of the area under the curve (AUC) compared with IV administration.

and organs based on a supposed 23 Gy radiation dose to the kidneys after IV administration. Tumors were modeled as spheres. Actual tumor diameters were measured by CT and MRI. The organ and tumor residence times were used as input into the Olinda/EXM radiation dosimetry code.¹⁹ The bone marrow residence time was calculated from the plasma activity concentration curve.⁸ The dosimetry output was not corrected for the actual volumes of the organs. The dose to the tumors was calculated by the spherical node option within the Olinda/EXM code.

Statistics

Data were expressed as mean ± standard deviation. Statistical analysis was performed using the unpaired Student's *t*-test.

Results

Liver metastasis model in the rat

Inoculation of CA20948 tumor cells from *in vitro* cultures, mixed with matrigel, resulted in a palpable solid tumor (Fig. 2A) 10 days later. The tumor could clearly be visualized by micro-SPECT scanning 24 hours pi of ¹¹¹In-DTPAOC (Fig. 2B). *Ex vivo* biodistribution at 24 hours after injection revealed the tumor uptake of ¹¹¹In-DTPAOC administered via the common hepatic artery to be twofold higher (*p*<0.05) than the uptake after systemic (IV) administration (Fig. 3A, B). Uptake in kidney, liver, stomach, duodenum, adrenals, blood, and muscle did not significantly differ after both injection methods. Surprisingly, after IA administration the radioactivity in the pancreas was higher than after IV administration.

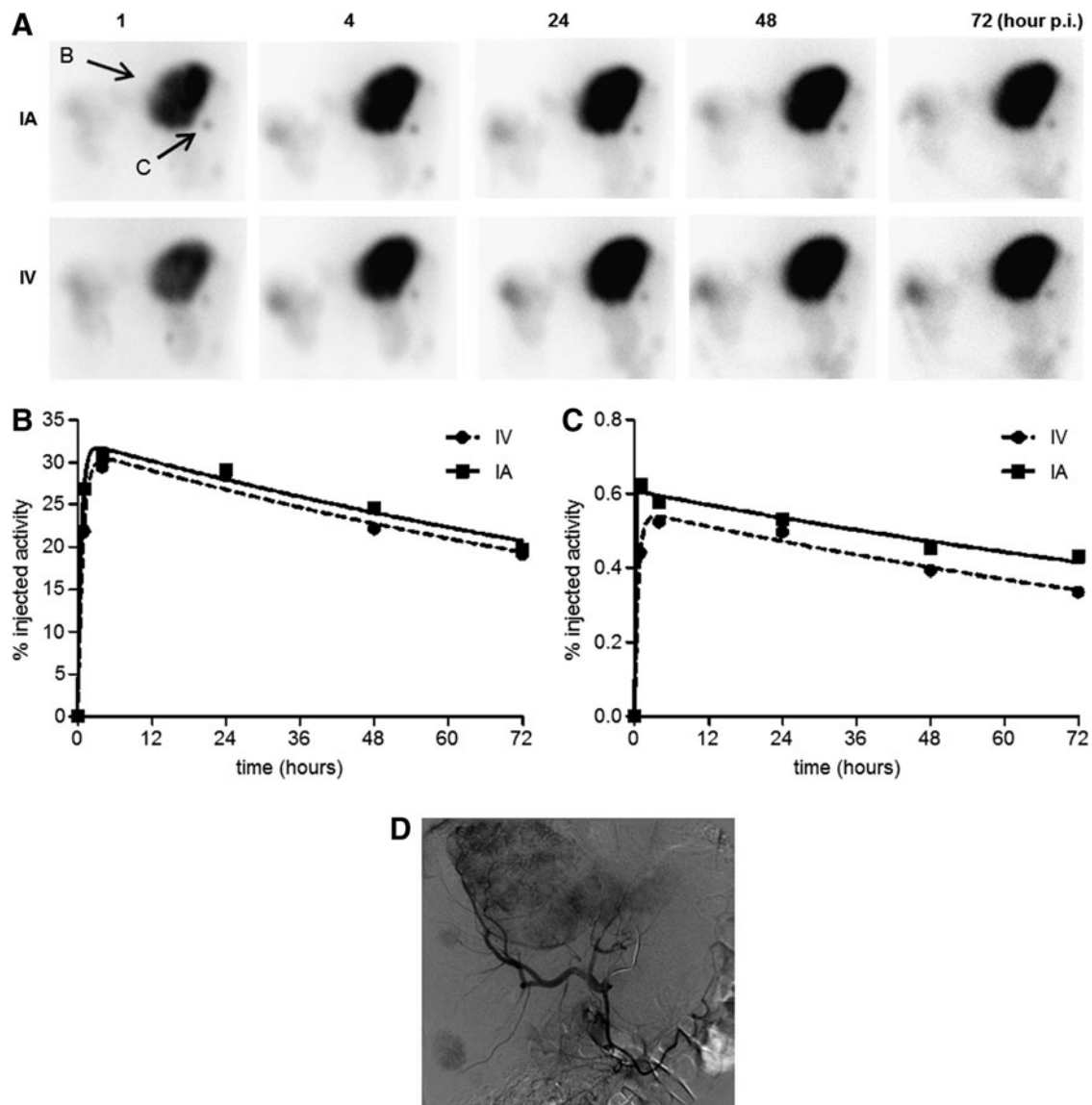


FIG. 5. Patient 2; (A) planar posterior upper abdomen images showing almost comparable ¹¹¹In-DTPAOC uptake in neuroendocrine liver metastasis at 1, 4, 24, 48, and 72 hours after IA and IV administration of ¹¹¹In-DTPAOC. (B, C) Quantification of ¹¹¹In uptake in liver metastasis B and C (see first picture A) after IA and IV administration. IA administration resulted in liver metastasis B in a 1.06-fold increase of the AUC and in liver metastasis C in a 1.14-fold increase of the AUC compared with IV administration. (D) Digital subtraction angiography illustrating the arterial blood supply and positioning of the catheters tip during IA administration.

Patient study

Low ^{111}In -DTPAOC uptake (iso-intense compared to the liver) was seen in the liver metastases of the first patient after IV administration on all images made at 1, 4, 24, 48, and 72 hours pi. After IA administration in this patient clear visualization of the liver metastases was obtained (Fig. 4A). Quantification data of tumor uptake after IA administration

showed a 2.4-fold higher ^{111}In -DTPAOC uptake (Fig. 4B, C) in these liver metastases in comparison with that after IV administration. Kidney uptake and urine radioactivity was not significantly different after either route of administration.

Strikingly, in the second patient IA administration did not result in significantly higher ^{111}In -DTPAOC uptake in the liver metastases. Quantification showed a 1.06- and 1.14-fold increase of ^{111}In -DTPAOC uptake after IA versus IV

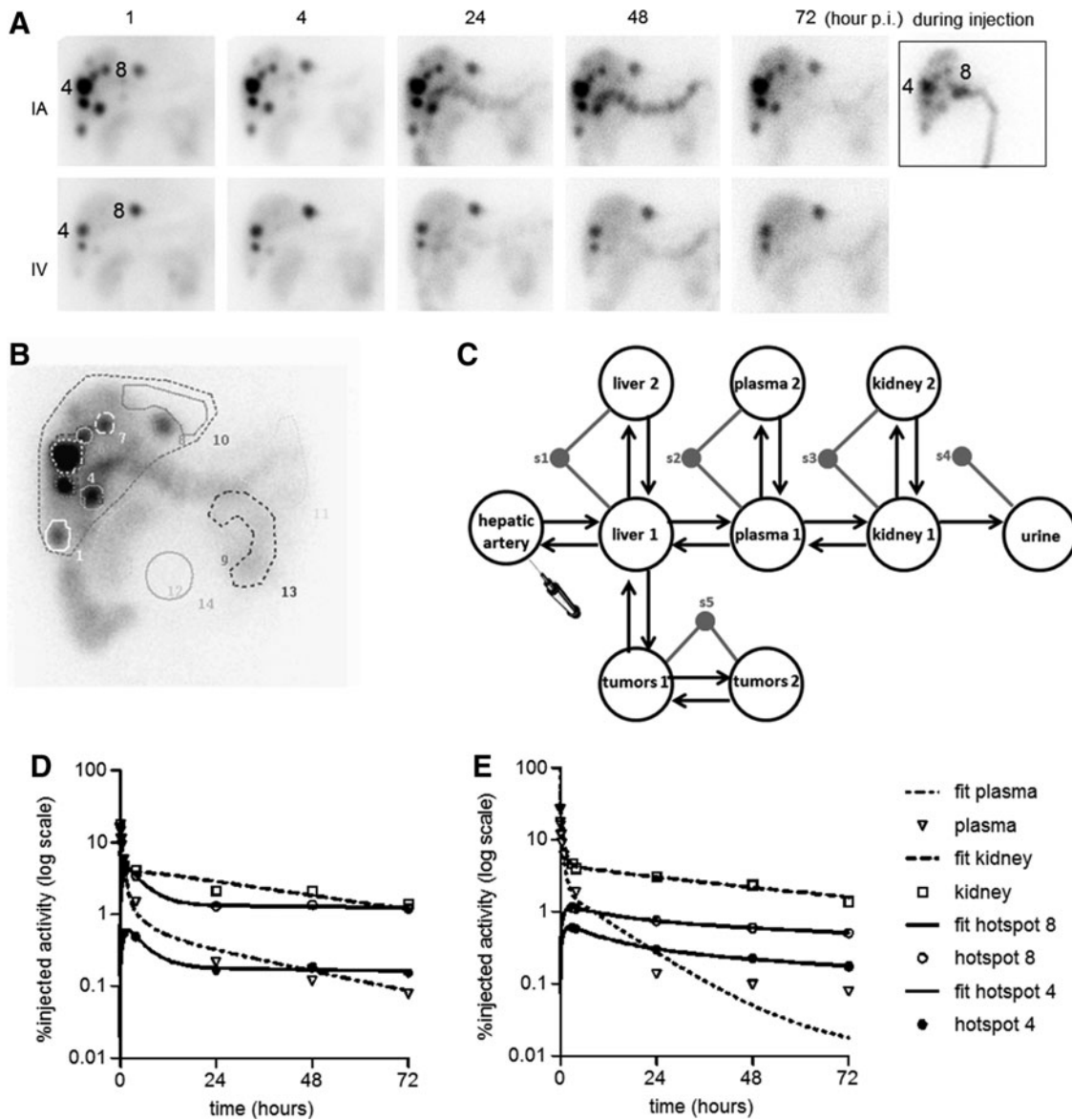


FIG. 6. Patient 3; (A) planar anterior upper abdomen images showing ^{111}In localization, 1, 4, 24, 48, and 72 hours after IA and IV administration of ^{111}In -DTPAOC. Notice the higher uptake after IA administration in comparison with IV administration in hotspot 4 (2.3-fold increase of the AUC), which is not seen for hotspot 8. An additional image taken during IA injection is shown. Notice only half the liver is receiving IA administration resulting in ^{111}In -DTPAOC uptake comparable to systemic administration in the metastasis located in segment 5 of the liver (hotspot 8). (B) Regions of interest (ROI) as used for calculating accumulated activity in tumors and organs. (C) Simplified compartmental model as used in the SAAM II software. Organs and tumors were modeled as two compartmental. (D, E) Post IA (D) and IV (E) administration data of patient 3 fitted in a pharmacokinetic model. (F) Plasma values and fits after IA and IV administration. Notice the only difference in plasma values between IA and IV administration is only in the early time point (2 minutes postinjection). (G) ^{177}Lu tumor dosimetry after IV and IA administration. Radiation dose on all liver metastasis in the right part of the liver (ROI 1–7) would be significantly increased by IA administration while the dose on the liver metastasis in the left part of the liver (ROI 8) would not be significantly higher or lower compared with IV administration. (H) ^{177}Lu organ dosimetry after IV and IA administration.

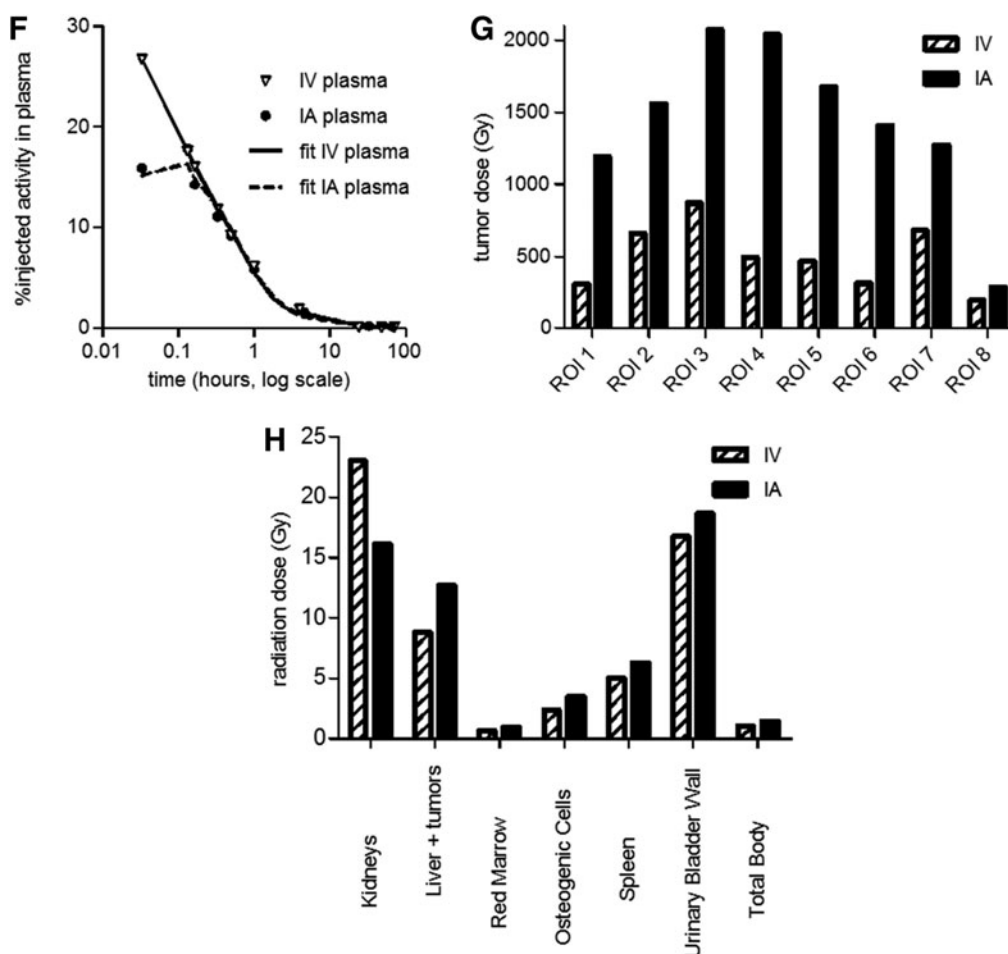


FIG. 6. (Continued)

administration for metastasis B and C (Fig. 5A), respectively. When compared with the first patient, the tumor uptake was exceptionally high in patient 2. At 4 hours pi after IV and IA administration around 30% of the injected activity was located in the very large liver metastasis B (Fig. 5A), whereas for the first patient the maximum uptake was only 0.5% of the injected activity in liver metastasis (Fig. 4A, metastasis B). So, tumor uptake in the second patient was already exceptionally high after IV administration.

In a third patient three liver metastases were clearly visualized at 1, 4, 24, 48, and 72 hours post IV administration. The equivalent scans after IA administration revealed several additional liver metastatic lesions (Fig. 6A), whereas the lesions that were visible on the IV scan showed higher uptake after IA injection. Surprisingly, one metastatic nodule (hotspot 8, Fig. 6A) also shown on the scan after IV injection and located in liver segment 5 did not show an increased ¹¹¹In-DTPAOC uptake after IA administration. Analysis of the dynamic scans made during the injection phase, showed that the tip of the catheter in this patient was not situated in the common hepatic artery, but in the right hepatic artery (Fig. 6A, picture in the right upper corner). As a result, ¹¹¹In-DTPAOC was administered IA to the right part of the liver, whereas the left part received the ¹¹¹In-DTPAOC after first pass through the body via systemic administration.

Urine sample data, blood sample data, and region of interest (tumors and kidneys, Fig. 6B) quantification data of this patient were fitted in a compartmental pharmacokinetic model (Fig. 6C) for IA and IV administration in Figure 6D and E, respectively. Quantification of ¹¹¹In-DTPAOC uptake in liver metastasis 4 (in the right part of the liver) over 72 hours showed a mean 2.3-fold increase after IA versus IV administration (Fig. 6D, E). ¹¹¹In-DTPAOC uptake in the metastasis (hotspot 8) located in the left part of the liver showed to be comparable after IA and IV administration. ¹¹¹In-DTPAOC kidney uptake was 13% lower after IA administration compared with IV administration. The percentage injected activity in plasma only differed significantly between IA and IV administration at 2 minutes pi. Five minutes pi, IA and IV plasma values were almost comparable (Fig. 6F).

Based on the compartmental pharmacokinetic model ¹⁷⁷Lu dosimetry calculations were performed (Fig. 6G) for all liver metastasis after IA and IV administration assuming similar pharmacokinetics for ¹¹¹In-DTPAOC and ¹⁷⁷Lu-DOTA-TATE. Radiation dose with ¹⁷⁷Lu-DOTA-TATE PRRT was calculated for all metastases based on a radiation dose to the kidneys of 23 Gy after IA and IV administration. These calculations showed for all metastases located in the right part of the liver an increase of the radiation dose by a factor 1.9–4.5 after IA administration. The calculated radiation dose for hotspot 8 in Figure 6A was not significantly different after IA

or IV administration. The estimated radiation dose to several organs is shown in Figure 6H after an injected activity leading to a renal radiation dose of 23 Gy. Please note the relative large (30%) renal radiation dose reduction after IA administration. These calculations are performed on the data collected from only 1 patient and definitely have no statistical significance in predicting the results of IA administration in a group of GEPNET patients.

As biodistribution study in rats showed increase of ^{111}In -DTPAOC in the pancreas after IA administration we looked for pancreas uptake on the patient scans. But none of the scans showed ^{111}In -DTPAOC uptake in the pancreas. Therefore, a possible increase of uptake in the pancreas after IA administration via the hepatic artery could not be shown.

Discussion

Both the preclinical and clinical studies indicated that IA hepatic administration of ^{111}In -DTPAOC can result in a significantly increased ^{111}In -DTPAOC tumor uptake compared with that after IV administration. This increased uptake in the hepatic NET metastases will, when applying a therapeutic radiolabeled analogue such as ^{177}Lu -DOTATATE or ^{90}Y -DOTATOC, result in a higher tumor absorbed radiation dose.

In the animal study IA administration resulted in a doubling of the ^{111}In -DTPAOC uptake in both tumor and pancreas. This unexpected increase in pancreas (a sst_2 -positive organ in the rat) uptake is most likely explained by backflow of ^{111}In -DTPAOC via the common hepatic artery and coeliac trunk into the aorta during injection.

In patient 2, IA administration did not result in significantly higher tumor uptake. The large tumor volume in combination with the high tumor sst_2 expression (grade 4) and the limited amount of peptide, only $10\ \mu\text{g}$ DTPAOC was used, could have played a role here. Interesting is the fact that in patient 2 within the time frame of 1–4 hours pi after IA administration the uptake in the liver metastases was still increasing while in both other patients the slope of the curve was already declining at 1 hours pi. We cannot fully explain this phenomenon right now, but we assume all receptors in the liver metastases in patient 1 and 3 to be saturated after IA administration, whereas in patient 2 binding of ^{111}In -DTPAOC was still possible at relatively low ^{111}In -DTPAOC plasma concentrations at later time points.

In patient 3, IA administration resulted in a 2.3-fold increase in ^{111}In -DTPAOC uptake in the metastasis located in the right part of the liver. The fact that the one metastasis located in the left part of the liver showed to have equal uptake as measured after systemic administration suggests that ^{111}In -DTPAOC uptake in tumor lesions outside the liver compartment, which was supplied by the IA-route, was apparently not affected by the IA administration route. The ^{111}In -DTPAOC plasma values showed significant difference between IA and IV administration at 2 minutes pi (Fig. 6F) and were almost equal at 5 minutes pi. Apparently, there was sufficient radiopharmaceutical left to enter the systemic circulation and reach other tumors. Therefore, an unsuspected metastasis outside the liver (if this patient had one) would probably also have taken up the same amount of ^{111}In -DTPAOC after IA administration as after IV administration. Certainly, this assumption can only be made in this

patient. Probably a higher hepatic tumor mass and/or sst_2 density could even result in a lower uptake in extra hepatic tumor lesions after IA administration compared with IV administration. Despite kidney uptake and excretion was minimally decreased by IA administration, ^{177}Lu dosimetry calculations in patient 3 showed a 30% dose reduction to the kidneys by IA administration. This reduced kidney and higher intrahepatic tumor radiation dose resulted in a significant increase of the therapeutic index. IA ^{177}Lu -DOTATATE PRRT would administer a 1.9–4.5 times higher estimated tumor radiation dose when the kidney radiation dose would be 23 Gy. The radiation dose to the bone marrow did not show a significant increase after IA administration. For these calculations we assumed the pharmacokinetics for ^{111}In -DTPAOC and ^{177}Lu -DOTATATE to be equal, but the fact that ^{177}Lu -DOTATATE has a four-fold higher affinity for the sst_2 and also shows some affinity for the sst_5 indicates that our dosimetry calculations are a rough estimation.

In the studies described here, the procedure differed from the routine PRRT treatment with ^{177}Lu -DOTATATE in our institution. PRRT with ^{177}Lu -DOTATATE is administered in a 30 minutes infusion whereas in the current study ^{111}In -DTPAOC was injected as a bolus in 10 seconds. Second, the amount of peptide used in a PRRT setting is 20 times the amount of peptide we used in this study ($200\ \mu\text{g}$ DOTATATE versus $10\ \mu\text{g}$ DTPAOC). In addition, DTPAOC has a four-fold lower affinity for the sst_2 compared DOTATATE. In our study, DTPAOC and not DOTATATE was used because the scans were included in the standard clinical workup for PRRT and not for research purposes only. Future experiments with DOTATATE as ligand using a therapeutic peptide dose and injection protocol will be performed to show the additional effect of locoregional administration in a therapeutic setting. In 2008 Limouris et al. showed a relatively high tumor response rate after IA PRRT with ^{111}In -DTPAOC in patients with GEPNET liver metastasis.¹³ This relatively high tumor response could be (partially) caused by an increased ^{111}In uptake after the IA administration. Recently, Kratochwil et al. showed a mean 3.75-fold increase of ^{68}Ga -DOTATOC uptake at 40 minutes pi after selective IA administration in GEPNETs.¹⁶ Considering our observations at later time points obtained with ^{111}In -DTPAOC we feel this mean increase of 3.75-fold cannot be translated to the tumor radiation dose. At 1 hours pi IA administration the slope in the curve showing the % injected activity present in the liver metastasis is still quite steep (Fig. 4B, C). Probably a measurement at 24 hours pi, after the curve has a more stable slope, would be more predictive in estimating the increase in tumor uptake after IA administration. In this study, we demonstrated that IA administration resulted in the same (1 patient) or an increased ^{111}In -DTPAOC uptake in NET liver metastasis up to 2.4-fold compared with IV administration over a period of 72 hours. The increase in uptake after IA administration is probably depending on sst_2 density, tumor load, and tumor perfusion. We therefore conclude that locoregional IA administration should be considered as the optimal route of administration in patients in which the GEPNET tumor load is mainly localized in the liver. Though, an increase in radionuclide tumor uptake after IA administration in comparison to IV administration is not guaranteed, as in one of our patients tumor uptake was high, but similar after IV and IA administration. If IA PRRT will

be applied, the positioning of the catheter should be well planned using contrast enhanced CT for imaging of possible hepatic arterial vasculature abnormalities.

Disclosure Statement

No competing financial interests exist.

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