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Intra-arterial Peptide Receptor Radionuclide Therapy using ^{90}Y DOTATOC for Hepatic Metastases of Neuroendocrine Tumors

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ABSTRACT

Background: Given the high frequency of liver metastases in neuroendocrine tumor (NET) patients, we aimed to determine whether hepatic intra-arterial (IA) administration of ^{90}Y-DOTATOC peptide receptor radionuclide therapy (PRRT) would increase treatment efficacy while reducing systemic toxicity compared to previously reported systemic toxicity from IV administration in the literature.

Methods: PRRT-naïve adult NET patients with liver-dominant metastases enrolled in a prospective pilot, single-center, open-label study. Patients underwent baseline PET/CT using IV ^{68}Ga-DOTATOC. Then 94.7±5.4 mCi ^{90}Y-DOTATOC were administered into the proper hepatic artery over 30 minutes. The first five patients also received IA ^{68}Ga-DOTATOC and underwent a PET/CT. All patients were followed for response (RECIST 1.1) (primary aim 2: safety) and toxicity (CTCAE v4.0) (primary aim 1: efficacy) for at least 6 months, with optional follow-up up to 1 year. In the subset of 5 patients who received both IV and IA ^{68}Ga-DOTATOC PET/CTs, tumor SUVmax was compared between IV and IA administration for hepatic tumors, intrahepatic tumors, and uninvolved background organs (secondary aim: IV versus IA uptake).

Results: The study was terminated after a planned analysis of the first 10 patients due to lack of efficacy. Best response was stable disease (SD) in 90% (n=9/10) and progressive disease (PD) in 10% (n=1/10) at 3 months, SD in 8/10 and PD in 2/10 at 6 months. One additional patient developed PD after the 6-month followup period but within the optional 1-year follow-up period. No partial response (PR) or complete response (CR) was observed. The two patients with the highest liver tumor burden died within 6 months of treatment, with treatment considered a possible contributor. Patients

who received IA ^{68}Ga-DOTATOC failed to demonstrate increased uptake by hepatic metastases compared to IV, with median IA:IV SUVmax ratio of 0.81 (range 0.36-2.09) on a lesion level.

Conclusion: Our study found that administration of PRRT via the proper hepatic artery did not reproduce the increase in hepatic tumor radiotracer uptake that was previously reported. In addition, the single treatment using ^{90}Y-DOTATOC did not induce tumor shrinkage, indicating that more treatment cycles may be required. Possible safety concerns in patients with high liver tumor burden should inform patient selection for future studies.

BACKGROUND

Peptides targeting the somatostatin receptor (SSTR), which is commonly overexpressed in gastroenteropancreatic neuroendocrine tumors (GEP-NETs) but not in normal tissues, can be radiolabeled to deliver targeted radiation therapy.[1] Peptide receptor radionuclide therapy (PRRT) carries radioactivity inside tumor cells by triggering internalization of the SSTR-radiolabeled analog complex. In patients with metastatic midgut G1 or G2 NETs, PRRT prolongs radiographic progression-free survival and improves quality of life compared to high dose octreotide alone;[2] [3,4] a trend toward improved overall survival was also noted.[5-8]

Toxicity from intravenous (IV) PRRT is due to off target exposure, primarily to bone marrow and kidneys,[2] as demonstrated on dosimetry studies.[9] Radiation dose in PRRT is due to beta particles emitted by the radionuclide, typically either ^{177}Lu or ^{90}Y. ^{90}Y has a higher energy beta particle than ^{177}Lu and thus may be more effective for treating bulky tumors, but IV administration of ^{90}Y-based PRRT has been associated with higher rates of marrow toxicity compared to ^{177}Lu-based PRRT.[10]

Liver is the most common site of GEP-NET metasases, affecting up to 75% of patients at diagnosis.[11] Directly targeting the liver with intra-arterial (IA) ^{90}Y-based PRRT is appealing as it has potential to increase dose to hepatic metastases while decreasing systemic toxicity. Preliminary work with ^{68}Ga-DOTATOC in Heidelberg demonstrated increased hepatic tumor uptake when administered IA compared with IV, hypothesized to be due to increased first pass extraction.[12] A study using small doses (<172 MBq/4.6 mCi) of SSTR analog ^{111}In-DTPAOC also demonstrated increased (though variable) hepatic tumor uptake with IA administration compared to IV.[13]

Given these promising findings, the current study was undertaken to determine whether one IA administration of ^{90}Y-DOTATOC into the proper hepatic artery would achieve higher hepatic intratumoral concentrations of radionuclide (measured by SUVmax) and provide more effective treatment of hepatic metastases while possibly reducing marrow and renal toxicity.

METHODS

Patient selection

This was a prospective pilot, single-center, open-label study (NCT03197012) approved by the local Institutional Review Board for patients with biopsy-proven well-differentiated NET liver metastases from any site of origin, and of any World Health Organizaiton grade, any Ki67, and either functional or nonfunctional. Presence of tumoral SSTR positivity was required as demonstrated on prior SSTR-PET, with 10%-70% of liver parenchyma replaced by tumor. Patients were required to have liver-dominant disease, which was defined as a qualitatively greater volume of receptor-positive tumor in the liver than outside the liver as determined by a nuclear radiologist. Disease progression within the past twelve months defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 was also required.[14] The presence of low-volume extrahepatic disease was not considered a disqualifier. Other inclusion criteria were: unresectable liver metastases, ECOG performance status 0-2, and age > 18.

Exclusion criteria were: serious intercurrent illness, impaired renal function (glomerular filtration rate <60 mL/min), impaired liver function (including total bilirubin >1.8 mg/dL, serum albumin <3.0 g/dL), impaired bone marrow reserve (hemoglobin

concentration <6.0 g/dL, white blood cell count <3.0 x 10^9/L, or platelets <100,000/uL), portal vein thrombosis, prior PRRT, a contraindication to hepatic arteriography, prior external beam radiation treatment to the liver or more than 25% of bone marrow, intracranial metastases, systemic therapies other than somatostatin receptor agonists (SSAs) (e.g. mTOR inhibitors, sunitinib) within 4 weeks prior to enrollment, liver-directed therapy within 12 weeks prior, and inability to hold short acting SSAs for 48 hours prior or long acting SSAs for 4 weeks prior. All patients provided written informed consent prior to participation.

IV ^{68}Ga-DOTATOC imaging

^{68}Ga-DOTATOC was produced as previously described using 25 μg of precursor.[15] Patients underwent ^{68}Ga-DOTATOC PET/CT up to four weeks before treatment. 5.6±0.9 mCi [207±33 MBq] of ^{68}Ga-DOTATOC was injected IV. PET/CT was acquired 63±7 minutes after injection on either a Biograph 16 (Siemens Healthcare Sector, Erlangen, Germany) or a Discovery VCT (GE Healthcare, Waukesha, WI). PET was then performed with ten 3-minute bed positions, extending from the vertex to the mid-thighs with arms overhead. PET data was reconstructed using iterative reconstruction with four iterations and 14 subsets, and a matrix size of 168 × 168. The PET transaxial field of view was 620 mm, and axial slice thickness was 5.0 mm.

^{90}Y-DOTATOC administration

Long-acting octreotide was held 4 weeks prior to treatment, and short-acting octreotide was held 24 hours prior. Two liters of Aminosyn II 8.5% (amino acid solution,

920 mOsmol/L) were infused intravenously over a minimum of four hours, beginning 30 minutes prior to administration of the ^{90}Y-DOTATOC dose for renal protection.[2] Compounded solutions containing only positively-charged amino acids were not yet available for use at the time of this study.

^{90}Y-DOTATOC was produced in-house under good manufacturing practices (GMP). A maximum of 115 µgrams of precursor was used per synthesis using the Eckert & Ziegler ModularLab PharmTracer (Berlin, Germany). The precursor was obtained from ABX Advanced Biochemical Compounds (Radeberg, Germany), and Yttrium-90 chloride solution was purchased from PerkinElmer (Waltham, MA). Under fluoroscopic guidance, 94.7±7.5 mCi (3.5±0.3 GBq) ^{90}Y-DOTATOC was administered through a proper hepatic artery catheter over 30 minutes. One patient with variant hepatic artery anatomy (replaced left hepatic artery) received ^{90}Y-DOTATOC to the predominantly involved right liver lobe via the right hepatic artery. The first five patients also received IA ^{68}Ga-DOTATOC via the hepatic artery catheter over 30 minutes concurrent with the therapeutic dose. Those five patients underwent subsequent post-treatment PET/CT (same imaging protocol as above) approximately 90±20 minutes from the midpoint of the IA infusion.

Analysis Plan

The study had two primary endpoints. The first was response rate (RR) for treated liver lesions at three and six months, based on change in lesion size meeting threshold for complete response (CR) or partial response (PR) by RECIST 1.1.[14] Baseline and follow-up liver MRIs were evaluated by a fellowship-trained abdominal

radiologist for changes in size of hepatic metastases using RECIST 1.1.[14] The second primary endpoint was safety based on laboratory values and clinical evaluation, the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.[16]

The secondary endpoint, only evaluable in the subset of patients who received posttreatment ^{68}Ga-DOTATOC PET/CT, was change in SUVmax of target liver lesions, extrahepatic lesions, and uninvolved organ (spleen, or left kidney if spleen not present) between IV and IA administrations. From pre- and post-treatment ^{68}Ga-DOTATOC PET/CTs, changes in SUVmax were determined for up to 5 hepatic metastases and up to 5 extrahepatic metastases (if present). For uninvolved organ measurements, a volume of interest at least 20 mm in diameter was used. Comparisons between IA and IV SUVmax for hepatic tumors, intrahepatic tumors, and uninvolved organ were performed using a Wilcoxon signed rank test.

All patients received follow-up labs, symptom inventories, and liver protocol MRIs every 12 weeks for minimum 24 weeks or until disease progression.

For the primary endpoint, the study was powered to compare an expected objective response rate of 19% to a comparator objective response rate of 4% (based on everolimus and sunitinib estimates). The NETTER-1 trial[2] was selected as a comparator given that it was the only randomized data for PRRT to date. Assuming a type 1 error of 0.05 and power of 80%, it was determined that a total of 32 patients needed to be treated. An interim safety and efficacy analysis was planned after the first ten patients.

Statistical analysis was performed using R and Microsoft Excel 2016 for Mac.

RESULTS

Safety

Ten patients were enrolled in the study, with demographics and NET history as summarized in **Table 1**. The study was terminated after a planned interim analysis prior to the accrual of additional patients due to evidence of minimal treatment efficacy. During the study period, 5/10 patients experienced no adverse effects or mild (CTCAE grade 1) adverse effects, 4/10 developed moderate (CTCAE grade 2) adverse effects (anorexia, n=2; elevated alkaline phosphatase, n=1; elevated total bilirubin and anemia, n=1; upper respiratory infection deemed to be unrelated to treatment, n=1), and 3/10 developed severe non-life-threatening (CTCAE grade 3) adverse effects which were deemed unrelated to treatment (cholangitis in a patient who previously had bouts of cholangitis, urinary tract infection, and hyponatremia and pulmonary embolism in a patient with a prior history of both) (**Table 2**). Most Grade 1 adverse events were considered due to the Aminosyn administration rather than the treatment drug. There were no adverse effects on renal function. No patient developed CTCAE grade 4 (severe and life-threatening) adverse effects. 2/10 patients died (CTCAE grade 5) during the study period. Though it was not clear that the deaths were related to treatment, it was considered possible and attributed as such.

Both patients who died during the study period had extensive hepatic metastatic disease. The first patient was diagnosed with a G2 gastric neuroendocrine tumor (Ki67 5-15%) that progressed on SSAs, with 65-70% of liver replaced by metastases. Within a week of treatment, the patient developed abdominal pain, loss of appetite, and transient

hyperbilirubinemia (peak total bilirubin 1.7 mg/dL six days after treatment that resolved to 0.6 mg/dL two weeks later). This was considered treatment-related and possibly due to transient biliary obstruction caused by tumor swelling. The patient did not experience other signs of liver failure such as ascites or subsequent elevations in liver function tests. One month after treatment, the patient became dehydrated and developed a deep venous thrombosis, pulmonary embolism, hyponatremia, and herpes zoster. Symptoms improved with supportive care, although the patient continued to have nausea and weight loss (also present at baseline prior to treatment). Five months after treatment, the patient deteriorated further, was placed on hospice, and passed away. Upon review, it remained unclear whether the patient passed away due to IA PRRT, progressive disease, or other causes.

The second patient had a NET of unknown primary with Ki-67 <1%. Approximately 65% of his liver was replaced by tumor. He had previously been treated with sandostatin, everolimus, sunitinib, capecitabine/temozolamide, and ^{90}Y radioembolization to both lobes of the liver. Immediately after treatment he developed a urinary tract infection, and he developed a recurrence of lower extremity edema, which had been intermittently present previously and which was treated with furosemide. After treatment, the patient's alkaline phosphatase increased from 176 IU/L to a peak of 354 IU/L, with peak total bilirubin of 1.2 IU/L. Six weeks after treatment, the patient was hospitalized with pneumonia and supraventricular tachycardia. Ten weeks after treatment, the patient was admitted to hospice, and he passed away two weeks later (three months after treatment). As with the previous patient, it was unclear whether the patient passed away due to IA treatment, progressive disease, or other causes.

However because a high dose of radiation to the liver could not be entirely excluded as a cause of the patients' deaths, both were deemed possibly related to treatment. The other 8 patients remained alive at a minimum of 2 years post treatment.

Efficacy

During the follow-up period (24 weeks), the best response was stable disease (SD) in 70% of subjects (7/10) and progressive disease (PD) in 20% (n=2/10) (**Figure 1**). 1/10 developed PD at 12 weeks, while the second patient developed PD at 24 weeks No patients met the criteria for partial response (PR) or complete response (CR) during the follow-up period. Although 5 patients experienced a slight decline in tumor size from baseline at 12 weeks after treatment, the decrease in summed longest dimension (LD) (less than 10% in all cases) was not large enough to meet the criteria for PR.

Over the optional longer follow-up period of 1 year, all remaining experienced an increase in tumor size from baseline, with 1 additional patient meeting criteria for PD **(Figure 1).**

Change in radiotracer uptake with IA vs. IV administration

The 5 patients who received IA ^{68}Ga-DOTATOC with ^{90}Y-DOTATOC generally failed to demonstrate increased uptake by hepatic metastases compared to IV administration, with with median IA:IV SUVmax ratio of 0.81 (range 0.36-2.09) on a per-lesion basis and ratio 0.90 (range 0.54-0.97) on a per-patient basis. (**Figure 2)**. However, extrahepatic metastases and uninvolved organs demonstrated expected

decreased median uptake between IA and IV in all patients (ratio 0.73, range 0.42-0.87 for extrahepatic metastases and 0.53, range 0.41-0.76 for uninvolved organs). Radiotracer uptake in hepatic lesions, extrahepatic lesions, and uninvolved organs as represented by spleen (left kidney in one asplenic patient) generally decreased with IA administration compared to IV **(Figure 3A)**, with a trend toward statistical significance in the difference between IV and IA SUVmax in liver tumors ($p = 0.063$) and uninvolved organs ($p = 0.063$). There was no significant difference between IV and IA SUVmax for extrahepatic tumors ($p=0.125$).

At the individual patient level (**Figure 3B**), liver uptake patterns were not uniform. The patients with the highest burden of hepatic metastatic disease (50 – 70% of liver parenchyma involved, patients 3 and 4) experienced stable to slightly increased uptake in liver lesions with IA administration (patient 3, median IV SUVmax 22.0, median IA SUVmax 22.2; patient 4, median IV SUVmax 28.2, IA average SUVmax 31.5). The remaining patients demonstrated stable to decreased uptake in liver lesions upon IA administration (**Figure 4**). However, for individual patients, the ratio of radiotracer uptake in hepatic metastases compared to extrahepatic metastases slightly increased with IA administration (**Figure 3C**).

DISCUSSION

Our study demonstrated that a single treatment using ^{90}Y-DOTATOC resulted in minimal radiographic disease response. Additionally, administration of PRRT via the hepatic artery does not clearly recapitulate the increased hepatic uptake seen in previous studies.[12,13] Also, although some patients tolerated the therapy well, others experienced severe adverse events, which were possibly attributable to ^{90}Y-DOTATOC.

Previous studies have shown therapeutic efficacy with multiple IA administrations of PRRT: Kratochwil et al in 2011[17] demonstrated CR in 7% of patients and PR in 53% of patients treated with up to five IA administrations of ^{90}Y- or ^{177}Lu-PRRT, and Limouris et al in 2012 demonstrated PR in 66.7% of patients treated with up to six IA administrations of ^{177}Lu-PRRT. However, the efficacy of a single treatment remains to be determined, as does the minimum number of doses of IA PRRT required for effective treatment. Because Kratochwil and colleagues demonstrated a mean 3.75-fold increase in hepatic tumor uptake with IA compared to IV[12], and IV ^{90}Y-based PRRT is typically delivered over 2-3 cycles, we hypothesized that the efficacy of multiple IV cycles could be achieved in a single IA cycle. Another reason for opting for a single treatment was that NET patients have long life spans, and it is important to limit cumulative radiation dose, especially if efficacy of a single treatment is noninferior to that of multiple treatments. However, the lack of efficacy we observed with a single IA treatment suggests that multiple treatments are necessary to achieve a therapeutic effect, though exactly how many remains to be determined.

The major adverse effects associated with IV PRRT are bone marrow toxicity and renal toxicity. The largest study regarding toxicity from Bodei et al in 2015[18] involved 807 patients treated with either ^{90}Y or ^{177}Lu based IV PRRT. In that study, 14% of patients developed CTCAE grade 3 (severe) or 4 (life threatening) bone marrow toxicity. In addition, 2.8% of patients developed grade 3 or 4 renal toxicity, primarily in patients receiving ^{90}Y. In the NETTER-1 trial, at least 9% of patients developed acute bone marrow toxicity.[2] In our study using a single dose of IA PRRT, no patient

developed grade 3 or 4 bone marrow or renal toxicity. It remains unclear if systemic toxicity can be decreased with IA administration compared to IV.

In terms of hepatic toxicity, neither the NETTER-1 nor the study by Bodei et al. reported grade 3 or 4 hepatic toxicity with IV therapy,[2,18] as well as prior studies of IA PRRT. However although our study did not clearly demonstrate hepatotoxicity (e.g. through sustained laboratory evidence of liver failure), the death of two of the patients with high liver burden were concerning. It is possible that patients with higher liver disease burden and more advanced disease were more likely to have a poor outcome independent of IA PRRT-related toxicity.[17,19] The question about hepatotoxicity remains unanswered, and may be related to the use of higher-energy ^{90}Y rather than ^{177}Lu.

The two patients who died had markedly different treatment histories (1: SSA only; 2: multiple prior liver-directed therapies, chemotherapy, and targeted therapy). However, they shared one characteristic: the largest hepatic tumor burden of all study patients (65-70% of liver involved). Radiation induced liver toxicity (RILT) has been described as a clinical syndrome which includes weight gain, increased abdominal girth, ascites, and alkaline phosphatase elevation out of proportion to other liver enzymes.[20] One of the two patients did demonstrate elevated alkaline phosphatase following therapy, but neither patient displayed other significant signs of this clinical entity. In addition, they did not meet the criteria for “non-classic” RILT including jaundice or markedly elevated transaminases.[20] Although a number of factors unrelated to IA PRRT may have contributed to the patients’ deaths and there was no definitive evidence of RILT, there was concern that the high dose of radiation to the liver could have played some role. The potential treatment related toxicity suggests that future studies using IA

^{90}Y-DOTATOC should set a lower limit for liver involvement than the 70% threshold used in our study.

Most surprisingly, and in contrast to previous reports, we did not reproduce a significant increase in uptake of ^{90}Y-DOTATOC in hepatic metastases when delivered IA compared to IV.[12,13] Kratochwil et al in 2010[12] demonstrated a leveling off of the time-activity curve with the IA administration of 250 MBq (6.8 mCi) ^{111}In-DOTATOC within 10 minutes of a 20-minute administration period. By contrast, the IV time-activity curve demonstrated a nearly linear slope, and radiotracer uptake continued to increase after administration was concluded. This observation was attributed to receptor saturation. In our study, the imaged ^{68}Ga-DOTATOC was administered alongside a larger mass dose of ^{90}Y-DOTATOC (25 vs 115 μg), which may have resulted in rapid SSTR saturation. Future studies should be undertaken with an aim to overcome receptor saturation, with possible approaches including decreasing mass dose/increasing specific activity, prolonging administration time, and dose fractionation. Additionally, work is needed to determine the minimum number of IA treatments needed.

Limitations

One limitation of our study was the small number of patients, as the study was stopped after accrual of ten patients due to lack of efficacy. Combined with heterogeneous prior treatment histories, this small sample size limited the reliability of statistical conclusions and the generalizability of the findings. Unlike prior studies, patients received one treatment session of IA-PRRT, which limited

our ability to compare our findings with prior work. Another possible limitation was the inclusion of patients with a prior history of liver-directed therapy. These patients may have altered tumor vascularity and altered liver perfusion, which may in turn have altered distribution of IA-PRRT. Lastly, IV and IA SUVmax measurements may be less comparable due to differences in median uptake times, with IA PET acquisition occurring after a longer median delay than IV PET due to logistical factors related to the therapeutic interventional procedure.

CONCLUSION

Our study found that administration of PRRT via the proper hepatic artery did not reproduce the increase in hepatic tumor radiotracer uptake that was previously reported. One possible reason for the decreased uptake with IA versus IV administration is receptor saturation, as the imaged ^{68}Ga-DOTATOC was co-administered with a larger mass dose of ^{90}Y-DOTATOC. In addition, the single treatment using ^{90}Y-DOTATOC did not induce tumor shrinkage, indicating that more treatment cycles may be required. Possible safety concerns in patients with high liver tumor burden should inform patient selection for future studies.

KEY POINTS

QUESTION: Does direct administration of PRRT to the proper hepatic artery result in increased uptake in hepatic neuroendocrine tumor metastases compared to traditional intravenous administration, and is it safe and efficacious?

PERTINENT FINDINGS: In a prospective pilot study, patients underwent baseline PET/CT using IV 68Ga-DOTATOC, followed by 94.7±5.4 mCi 90Y-DOTATOC into the proper hepatic artery at a second visit. Uptake in hepatic metastases was not significantly increased with arterial administration compared to intravenous, and the study was stopped early due to evidence of lack of efficacy of a single treatment as well as possible safety concerns.

IMPLICATIONS FOR PATIENT CARE: More than a single intra-arterial PRRT treatment is likely required to show treatment efficacy, and possible safety concerns in patients with high liver tumor burden should inform patient selection for future studies.

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Age at baseline scan (years)	Median (range)	69.8 (46-76)
Gender	Female Male	2 (20%) 8 (80%)
Primary location	Small bowel Pancreas Large bowel Bronchial Gastric	4 (40%) 3 (30%) 1 (10%) 1 (10%) 1 (10%)
Percent of liver involvement with metastatic disease	<25% 25-50% 51-70%	3 (30%) 4 (40%) 3 (30%)
Extrahepatic disease (number of patients)	Yes No	7 (70%) 3 (30%)
Metastatic locations (number of patients)	Liver Lung Bone Other	10 (100%) 1 (10%) 3 (30%) 7 (70%)
Previous treatments (number of patients)	Surgery SSA Chemotherapy Targeted agents Liver-directed: TAE/TACE Y90 SIRT	6 (90%) 10 (100%) 4 (40%) 2 (20%) 3 (30%) 2 (20%)
Number of lines of prior therapy per patient	Median (range)	4 (1-6)
Tumor grade (number of patients)	1 (Ki-67 <3%) 2 (Ki-67 3-20%) 3 (Ki-67 >20%)	4 (40%) 5 (50%) 1 (10%)
Administered dose of ^{90}Y-DOTATOC (mCi)	Median (range)	95.95 (83.1-102.1)

Table 1. Patient characteristics. SSA: somatostatin analogues. TAE: trans-arterial embolization. TACE: trans-arterial chemoembolization. SIRT: selective internal radiation therapy.

Adverse event	Grade 1-2, N (%)	Possible/ Probable/ Definite Attribution	Grade 3, N (%)	Possible/ Probable/ Definite Attribution
Highest toxicity grade*	6 (60%)	6/6 (100%)	3 (30%)	0/3 (0%)
Fatigue	8 (80%)	8/8 (100%)	0 (0%)	n/a
Anorexia	2 (20%)	2/2 (100%)	0 (0%)	n/a
Vomiting	2 (20%)	2/2 (100%)	0 (0%)	n/a
Alk phos increased	2 (20%)	2/2 (100%)	0 (0%)	n/a
Hypoalbuminemia	2 (20%)	2/2 (100%)	0 (0%)	n/a
Upper respiratory tract infection	2 (20%)	0/2 (0%)	0 (0%)	n/a
Cholangitis	0 (0%)	n/a	1 (10%)	0/1 (0%)
Hyponatremia	0 (0%)	n/a	1 (10%)	0/1 (0%)
Pulmonary embolism	0 (0%)	n/a	1 (10%)	0/1 (0%)
Urinary tract infection	0 (0%)	n/a	1 (10%)	0/1 (0%)
Abdominal pain	1 (10%)	1/1 (100%)	0 (0%)	n/a
Anemia (Hgb)	1 (10%)	1/1 (10%)	0 (0%)	n/a
Blood bilirubin increased (Tbili)	1 (10%)	1/1 (10%)	0 (0%)	n/a
Diarrhea	1 (10%)	0/1 (0%)	0 (0%)	n/a
Dysuria	1 (10%)	0/1 (0%)	0 (0%)	n/a
Nausea	1 (10%)	1/1 (100%)	0 (0%)	n/a
PLT count decreased	1 (10%)	1/1 (100%)	0 (0%)	n/a
Supraventricular tachycardia	1 (10%)	0/1 (0%)	0 (0%)	n/a

Table 2. All adverse events during the study period using Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, with attributions. Highest toxicity grade is the highest toxicity grade each patient experienced during the study period. 1 patient did not experience any significant toxicity. Alk Phos: alkaline phosphatase. Hgb: hemoglobin. Tbili: total bilirubin. PLT: platelet count. There were no grade 4 adverse events. *Note: 2/10 patients died during the study period. Both deaths were deemed possibly attributable to treatment.

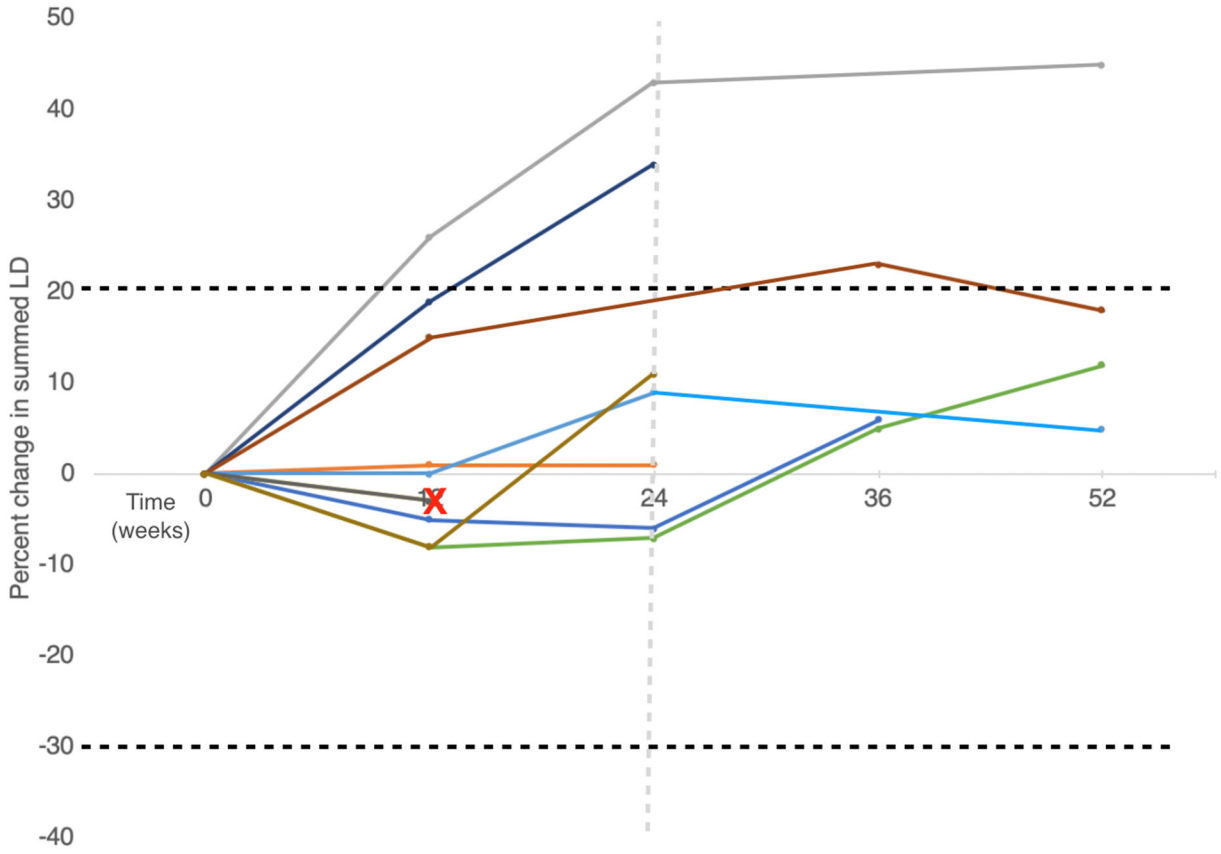

Figure 1. Percent change in summed longest diameter (LD) of target lesions per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. Over the course of the planned follow-up period (24 weeks), 2 patients met the criteria for PD. Over a longer optional 1-year follow-up period, 1 additional patient met the criteria for PD. No patients met the criteria for PR during the follow-up period. Two patients who ultimately expired had identical changes in summed longest diameter of their target lesions at 12 weeks, after which both were lost to imaging follow-up (black line with red X). PD = progressive disease. PR = partial response. Black dotted lines: thresholds for PD and PR per RECIST 1.1 criteria. Gray dotted line: planned follow-up period in study protocol.

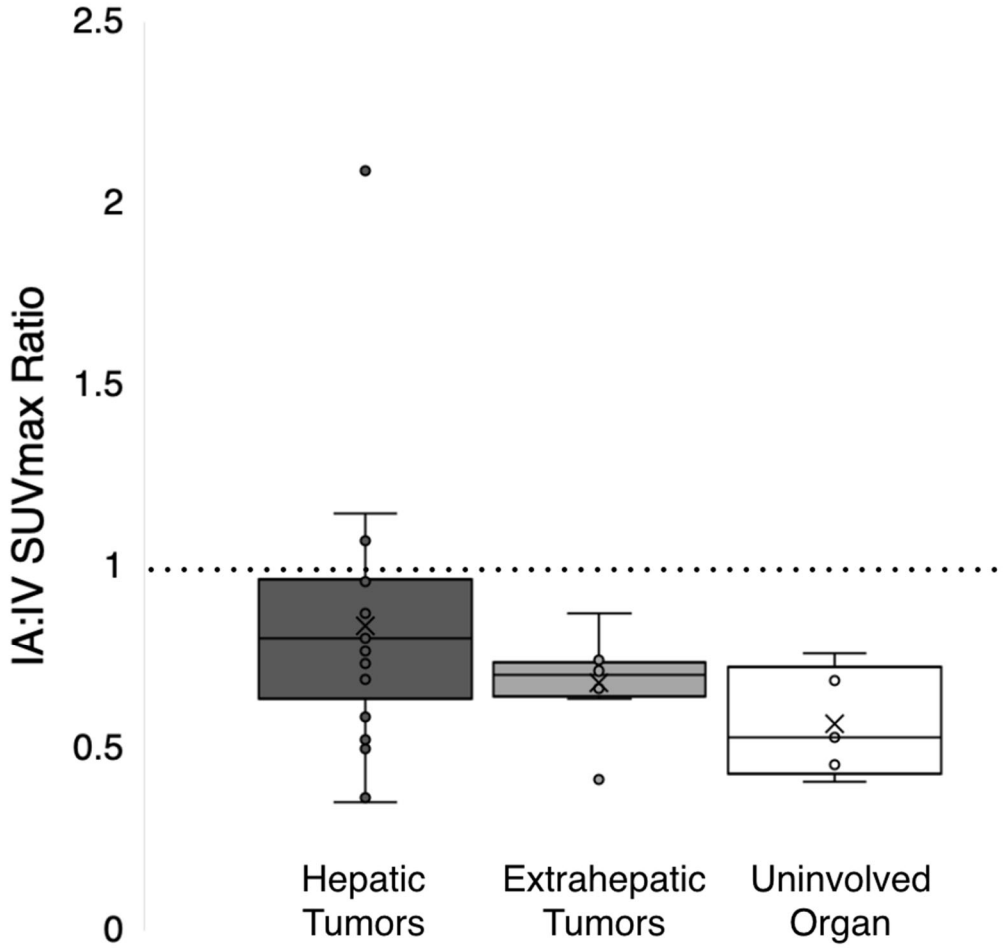

Figure 2. Ratio of median IA ^{68}Ga-DOTA-TOC SUVmax to median IV ^{68}Ga-DOTA-TOC SUVmax of hepatic tumors, extrahepatic tumors, and uninvolved organs. There was a trend toward statistical significance in the difference between IA:IV ratios of liver lesions and uninvolved organs (p=0.063).

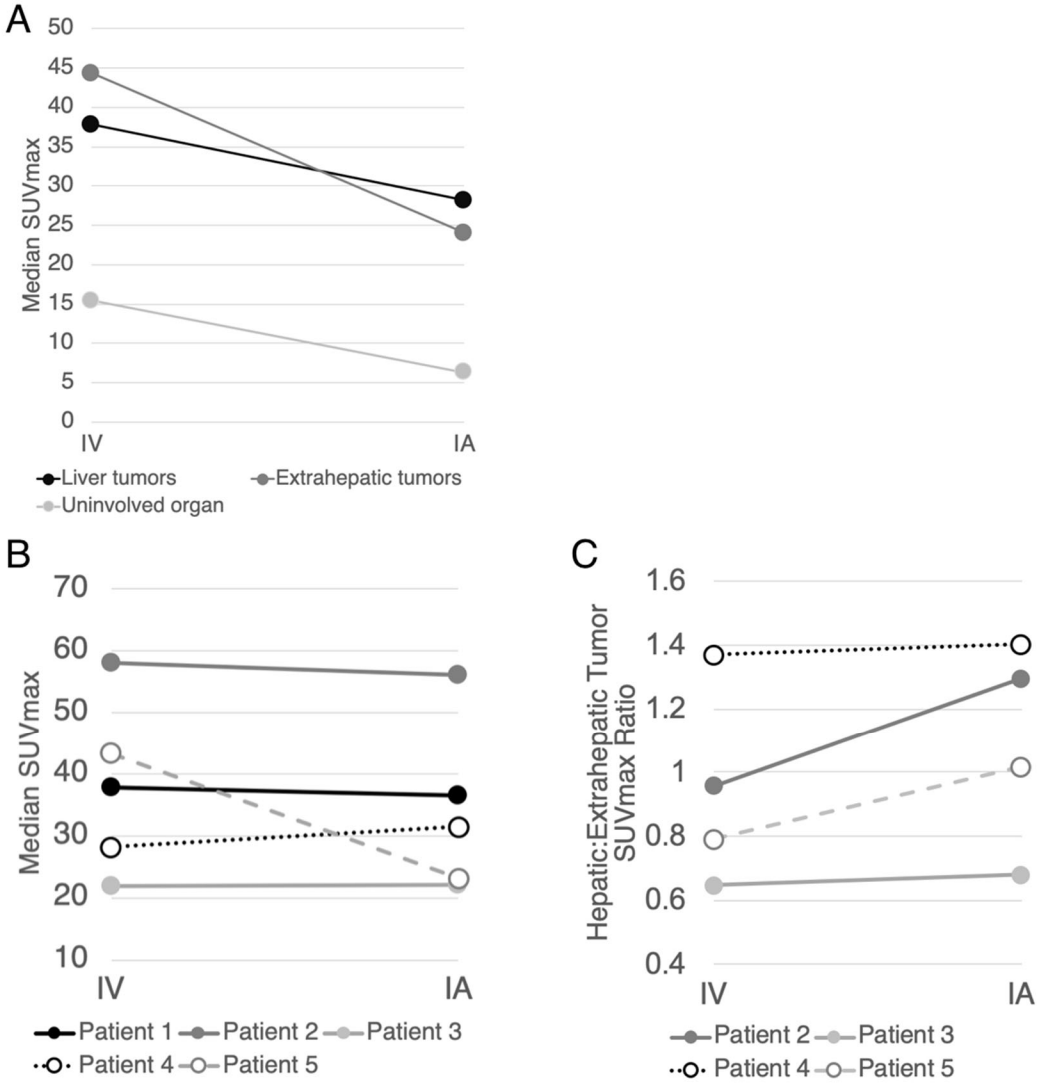

Figure 3. (A) Change in median SUVmax of hepatic tumors, extrahepatic tumors, and uninvolved organs (spleen in 4 patients, left kidney in one asplenic patient) from intravenous (IV) administration of ^{68}Ga-DOTATOC to intra-arterial (IA) administration. There was a trend toward statistical significance in the difference between IV and IA SUVmax in liver tumors ($p = 0.063$) and uninvolved organs ($p = 0.063$). **(B)** Change in median hepatic tumor SUVmax from IV administration of ^{68}Ga-DOTATOC to IA administration for each patient. Patients 1 and 5 had a low hepatic tumor burden (<25% of liver parenchyma), Patient 2 had a moderate hepatic tumor burden (25-50%), and Patients 3 and 4 had a high hepatic tumor burden (>50-75%). **(C)** Change in the median ratio of SUVmax of hepatic tumors compared to extrahepatic tumors from IV administration of ^{68}Ga-DOTATOC to IA administration for each patient. All extra-hepatic tumors had decreased uptake with IA compared to IV. Note: Patient 1 did not have extrahepatic metastatic disease.

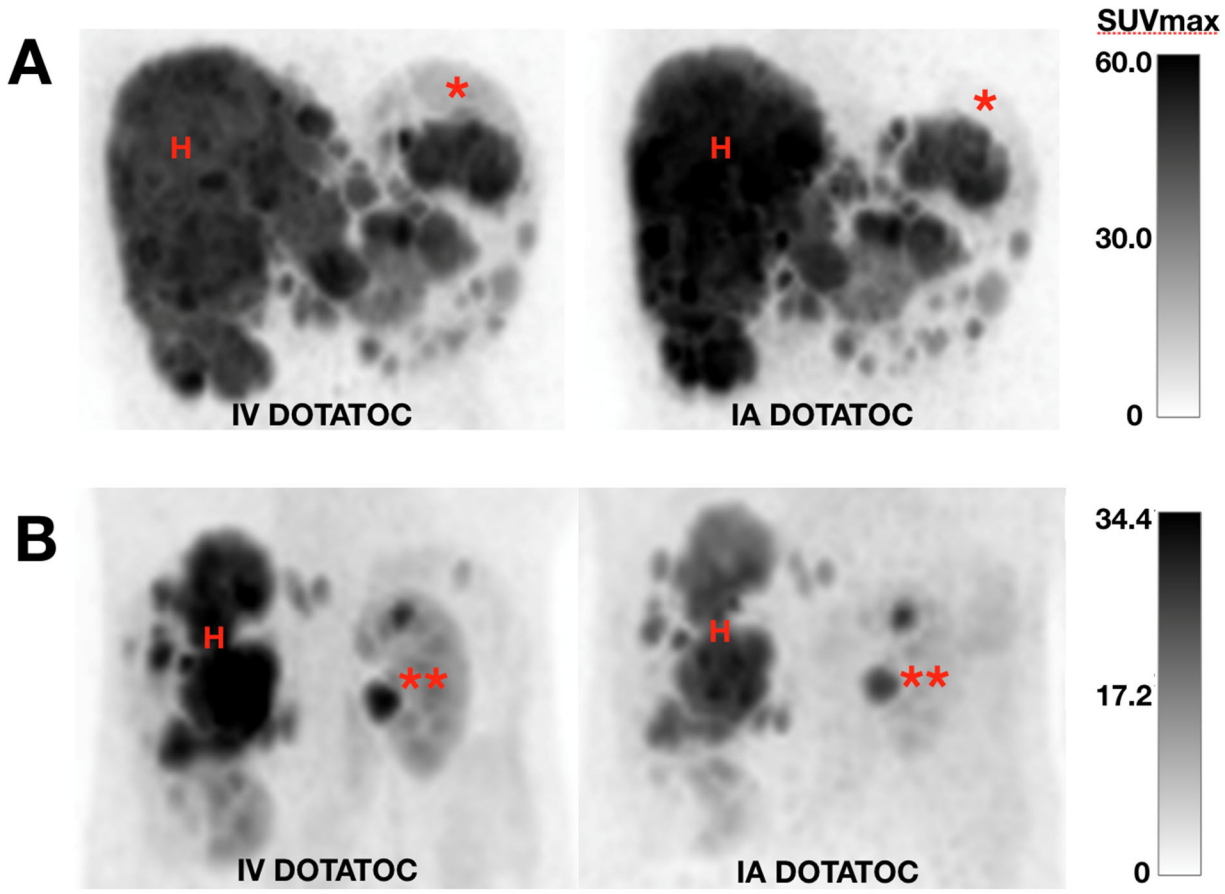

Figure 4. Changes in radiotracer uptake with IV versus IA administration of ^{68}Ga-DOTATOC: examples. **(A)** Maximum intensity projection (MIP) images through the abdomen in a patient with a high (50-70%) degree of liver involvement demonstrating slightly increased radiotracer uptake by hepatic metastases (H) with IA administration compared to IV. **(B)** Maximum intensity projection (MIP) images through the abdomen in a patient with a low (<25%) degree of liver involvement demonstrating slightly decreased radiotracer uptake by hepatic metastases (H) with IA administration compared to IV. For all patients, uninvolved organ radiotracer uptake decreased as expected upon IA administration; for example, note the spleen (*) in **(A)** and the left kidney (**) in **(B).**