Experience in Production of ^{68}Ga-DOTA-NOC

for Clinical Use Under an Expanded Access IND

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Abbreviated title: *Expanded Access IND [^{68}Ga]Ga-DOTA-NOC Production*

Abstract

[^{68}Ga]Ga-DOTA-NOC was produced under an Expanded Access IND for 174 clinical PET/CT studies to evaluate patients with neuroendocrine tumors. Production employed either the TiO_2-based Eckert & Ziegler (EZAG) ^{68}Ge/^{68}Ga-generator (with fractionated elution), or the SiO_2-based ITG ^{68}Ge/^{68}Ga-generator. In both cases, [^{68}Ga]Ga-DOTA-NOC was reliably produced, *without pre-synthesis purification of the ^{68}Ga generator eluate,* using readily-implemented manual synthesis procedures. [^{68}Ga]Ga-DOTA-NOC radiochemical purity averaged 99.2 ± 0.4%. Administered ^{68}Ga dose averaged 181 ± 22 MBq, and administered peptide mass averaged 43.2 ± 5.2 µg (*n* = 47) and 23.9 ± 5.7 µg (*n* = 127), respectively, using the EZAG and ITG generators. At dose expiration, ^{68}Ge breakthrough in the final product averaged 2.7 x 10^{-7}% and 5.4 x 10^{-5} % using the EZAG and ITG generators, respectively.

Introduction

Gallium-68-labeled somatostatin-receptor-targeted peptides, such as □[^{68}Ga]Ga-DOTA-NOC, [^{68}Ga]Ga-DOTA-TOC, and [^{68}Ga]Ga-DOTA-TATE, have found widespread clinical use in Europe for positron emission tomography (PET) detection of neuroendocrine tumors (Virgolini, et al., 2010; Pettinato, et al., 2008; Prasad and Baum, 2010; Prasad, et al., 2010; Ambrosini, 2010), but none are FDA-approved drug products in the USA. These three targeting peptides vary slightly in amino acid sequence, resulting in variations in their receptor affinities and receptor-sub-type selectivity (Antunes, et al., 2007), but all appear suitable for use in clinical imaging (Virgolini, et al., 2010).

The Expanded Access IND (Investigational New Drug exemption) can be a mechanism for providing patient access to a drug product that is not FDA-approved, but that is clinically needed in treatment of a serious disease (21CFR312.305, 2013). In response to a local clinical need to better define the location and extent of disease in neuroendocrine cancer patients who are candidates for multivisceral transplant (Mangus , el al., 2013), a manual synthesis method was developed for on-demand preparation of the [^{68}Ga]Ga-DOTA-NOC peptide-chelate conjugate in a formulation suitable for intravenous administration, and an Expanded Access IND submitted to the FDA documenting the production procedure and the intended clinical use. We selected [^{68}Ga]Ga-DOTA-NOC because our clinical focus was to define extent of disease, and this agent offers affinity for a broader range of receptor sub-types than [^{68}Ga]Ga-DOTA-TOC or [^{68}Ga]Ga-DOTA-TATE ([^{68}Ga]Ga-DOTA-NOC exhibits significant affinity for ssrt3, sstr4, sstr5, as well as the sstr2 receptor sub-type most commonly expressed by neuroendocrine tumors) (Atunes, et al., 2007).

We describe here our experience with manual radiochemical synthesis of [^{68}Ga]Ga-DOTA-NOC for clinical use under Expanded Access IND 117,255. The manual approach to synthesis was chosen because of the expected limited production volume, and the desire for a simple process that could be rapidly implemented and validated with minimal expense, since start-up and dose production costs needed to be recovered by charges to the patient.

MATERIALS and METHODS

As required for an Expanded Access IND by the U.S. Food and Drug Administration (FDA), our clinical use of [^{68}Ga]Ga-DOTA-NOC in clinical PET/CT imaging was reviewed and approved by an Indiana University Institutional Review Board (IRB). All patients provided written informed consent prior to administration of the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical. Clinical imaging was generally performed as an outpatient procedure using a Siemens mCT extended FOV time-of-flight PET/CT (128 slice) camera, with a few in-patient studies instead performed using a Siemens Biograph-64 PET/CT. Whole-body (head to mid-thigh) PET acquisitions were started at 60-minutes post-injection with data collection occurring over a period of ~24-minutes.

The DOTA-NOC peptide conjugate was purchased from ABX GmbH as commercial cGMP-grade product packaged at 60-µg per vial. Two TiO$_2$-based Eckert & Ziegler (EZAG) IGG100 ^{68}Ge/^{68}Ga generators (50-mCi; 1.85 GBq), and four SiO$_2$-based ITG Isotope Technologies Garching GmbH ^{68}Ge/^{68}Ga generators (30-mCi; 1.11 GBq), have been employed to supply ^{68}Ga for manual synthesis of [^{68}Ga]Ga-DOTA-NOC under Expanded Access IND #117,255. While not specified by the generator manufacturers, in both cases we filtered the aqueous HCl generator eluent through an HCl-stable 25-mm sterile 0.2-µm filter (Supor® polyethersulfone membrane in acrylic housing, part #H938210023, Baxa, Englewood, CO) attached to the generator inlet. To minimize introduction of trace metal impurites that would compete with ^{68}Ga^{3+} for binding the DOTA-NOC chelator, generator eluate was prepared by dilution of ultrapure concentrated HCl (HCl 30%, Suprapur®, EM Science, Gibbstown, NJ) with ultrapure water (NERL®, Thermo Scientific, Middletown, VA). Reaction mixture buffering employed

only ultrapure sodium acetate (99.999%; Atomergic Chemetals Corporation,

Farmingdale, NY) in a 0.25M solution prepared using ultrapure water.

Synthesis of the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical employed no-carrier-added

^{68}Ga^{3+} in either 1.5 mL 0.1M ultrapure HCl (fractionated elution of the EZAG generator),

or 4.0-mL 0.05M ultrapure HCl (ITG generator, without fractionation). The eluate was

buffered to pH ~4.8 by addition of ultrapure NaOAc and reacted with the DOTA-NOC

conjugate (60-μg for the EZAG eluate; 30-μg for the ITG eluate) with heating for 10-

minutes. For our initial manual synthesis method, the reaction mixture was heated in a

sterile 15-mL polypropylene centrifuge tube using an Eppendorf Thermomixer (Figure 1)

set at 80°C. Using the ITG generator we initially employed this same synthetic method,

but then adapted our process to employ ITG's manually controlled Fluidic Module (Vis,

et al., 2015; Tworowska et al., 2016; Roesch, 2012) for better radiation shielding during

solution transfers. Required solution transfers in our process using the EZAG generator

were simply made using syringes and needles (4-inch B Braun Medication Transfer

Filter Straws and 3.5-inch 18-gauge spinal needles), employing tungsten syringe shields

to minimize hand exposure. The ITG Fluidic Module (Vis, et al., 2015; Tworowska et al.,

2016; Roesch, 2012) employs a single-use assembly of a reaction vessel that is

plumbed with sterile medical tubing and Luer adapters, connectors, and valves; the

radiochemical synthesis can then proceed in a compact shielded bench-top unit using

external syringes for reagent additions and transfers, with the operator manually

controlling fluid pathways via external knobs for changing the positions of the enclosed

3-way and 2-way valves. Following ITG's recommended protocol, the thermostat for the

Fluidic Module heating element was set to 105°C, resulting in a reactor solution

temperature of 90-100°C.

The [^{68}Ga]Ga-DOTA-NOC product was always isolated by C18 solid-phase extraction (Waters C18 SepPak® Light), and then washed by passage of 5-10 mL of either sterile water or sodium chloride for injection. (Prior to use, the C18 solid phase extraction cartridge was conditioned by flushing with 5-10 mL absolute ethanol USP, followed by 10-mL sterile water for injection.) To reliably maintain trapping efficiency for the [^{68}Ga]Ga-DOTA-NOC product, loading to the C18 solid-phase extraction cartridge needed to occur very slowly (*i.e.,* with drop-wise flow at the outlet) if the reaction mixture was transferred without prior cooling.

The [^{68}Ga]Ga-DOTA-NOC was then recovered by elution of the C18 SepPak® with ethanol:saline (0.6-mL, 85:15; or 1.0-mL, 50:50), collecting the intermediate product in a sterile polypropylene centrifuge tube where it was diluted to ≤5% ethanol with either 12-mL or 10-mL sterile saline. The [^{68}Ga]Ga-DOTA-NOC intermediate product solution was then drawn into a shielded sterile syringe for terminal sterilizing filtration (13-mm 0.2-μm PVDF filter, Whatman^{TM} 6791-1302, GE Healthcare Life Sciences) within a laminar flow hood into a sterile evacuated vial (30-mL, vial #7521ZA, Jubilant HollisterStier, Spokane, WA; Figure 2). Since the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical was always being prepared for immediate use, the dose expiration time was set as 60-minutes after the sterilizing filtration to yield final product.

Pre-release product quality control procedures included: half-life measurement for confirmation of radionuclidic identity; pH measurement; ITLC assessment of radiochemical purity; endotoxin testing (Endosafe®-PTS, Charles River Laboratories); and a bubble point measurement to confirm the integrity of the single-use sterile 0.2-μm filter employed for terminal product sterilization. The half-life determination was made using a radionuclide dose calibrator (Capintec CRC-55tW) to make eight timed

measurements of ^{68}Ga radioactivity over a 7-minute period, calculating the corresponding half-life from the slope of the regression line in a spreadsheet plot of ln(radioactivity) *vs.* time (Apple iPad® running *Numbers®* application). The measured half-life was required to fall in the range of 64.6 - 71.4 minutes. The ITLC determination of radiochemical purity employed ITLC-SG strips developed with 0.1M HCl to quantify levels of ionic ^{68}Ga, and ITLC-SG strips developed with 1:1 MeOH:1M NH$_4$OAc to quantify colloidal ^{68}Ga-hydroxide plus ionic ^{68}Ga (Gallium Edotreotide Injection, 2010). In process validation, the ITLC strips were analyzed with a Bioscan AR-2000 radiochromatogram scanner fitted with high-resolution collimator (Figure 3). But, for speed and simplicity, our routine quality control instead employed a NaI(Tl) well scintillation counter to quantify radioactivity levels on the sectioned ITLC strip. For gamma counting, the ITLC-SG strip developed with 0.1M HCl was cut at the mid-point between the origin and solvent front, while the strip developed with 1:1 MeOH:1M NH$_4$OAc was cut for counting at one-third the distance from the origin to the solvent front.

Retrospective analysis of each production batch included sterility testing, and measurement of ^{68}Ge breakthrough. Breakthrough was measured by NaI(Tl) scintillation counting of [^{68}Ga]Ga-DOTA-NOC dose samples at both 15-20 hours, and 48-96 hours, after dose preparation, thereby quantifying original ^{68}Ga, and breakthrough ^{68}Ge/^{68}Ga, respectively. (Beckman Gamma 8000 automatic gamma counter with 3-inch large-bore NaI(Tl) crystal. Counting window centered at 511 keV. 60-minute counting periods were employed for the final assay, since at the lowest observed breakthrough levels the sample count rates were at, or near, the background count rate.)

A more detailed description of the production processes employed with the EZAG and ITG generators, including SOPs and Batch Record documentation, is provided in the on-line Supplementary Material.

RESULTS AND DISCUSSION

Our objective was to reliably produce the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical for clinical use in accordance with the EANNMI procedure guidelines (Virgolini, et al., 2010), while minimizing both start-up and recurring costs. While automated synthesis systems are commercially available for peptide labeling with ^{68}Ga, given the simplicity and scale of the required chemistry, our objectives were most effectively accomplished with the manual synthesis procedures described above.

The elution profile of the EZAG and ITG generators are similar, with nearly all the available ^{68}Ga delivered in ≤2 mL of the total 4-5 mL elution volume. We employed fractionated elution of the EZAG generator system to minimize introduction of trace metals into the [^{68}Ga]Ga-DOTA-NOC reaction mixture, allowing labeling with consistently high yields while avoiding pre-synthesis clean-up of the generator eluate (Di Pierro, et al., 2008; Schultz, et al., 2013; Eppard, et al., 2014)]. Specifically, after discarding the generator void volume, we collected the next ~1.8-mL of EZAG generator eluate for synthesis, transferring 1.5-mL of that volume to the reaction mixture, and using the remainder for the regulatory-mandated half-life measurement (performed during the synthesis heating period), plus a subsequent measure of the level of ^{68}Ge breakthrough that was present in the reaction mixture. The generator void volume always proved stable over the 12-month period of generator use; however, void volume did vary slightly from generator-to-generator, making it critical to establish elution profile as part of the initial generator set-up testing if one expects to employ fractionated elution.

Since it does not employ a metal oxide stationary phase, the ITG generator provides an eluate with very low contamination by trace metals (Vis, et al., 2015; Tworowska et al.,

2016; Roesch, 2012). After pilot syntheses, we did not fractionate the ITG generator eluate, because we were able to obtain reliable product synthesis using the full 4-mL elution volume even employing a lower mass of the DOTA-peptide conjugate than used with the fractionated EZAG generator eluate (30-µg *vs.* 60-µg DOTA-NOC). In the case of product prepared with the ITG generator, the required half-life measurement was made using the final patient dose while awaiting completion of the endotoxin test.

The ITG Fluidic Module is designed to minimize worker hand exposure, while enabling efficient manual performance of the steps required in radiopharmaceutical synthesis (Vis, et al., 2015; Tworowska et al., 2016; Roesch, 2012). ITG's detailed operating procedure concludes with delivery of the ^{68}Ga-DOTA-peptide into a final product vial *via* in-line sterilizing filtration. However, to minimize revisions to the IND production protocol we had already established using the EZAG generator, upon switching to the ITG generator we continued to process the ethanol:saline eluate from solid-phase-extraction (*i.e.,* the [^{68}Ga]Ga-DOTA-NOC intermediate product) without modification to our prior procedure. Thus, the ITG Fluidic Module was simply employed to remotely effect addition of reagents and generator eluate to the heated reaction vessel, and subsequent product loading to, and recovery from, the C18 SepPak® cartridge. Thus, as implemented, our protocol always applied the terminal sterilizing filtration (Figure 2) to the fully formulated [^{68}Ga]Ga-DOTA-NOC product in 5% ethanol:saline.

Table 1 summarizes our radiopharmaceutical production experience for the 174 patient doses of [^{68}Ga]Ga-DOTA-NOC prepared in the first 3-years of Physician-Sponsored Expanded Access IND #117,255. Two Eckert & Ziegler (EZAG) and four ITG ^{68}Ge/^{68}Ga generators were employed in this period. Generator elution yields were higher with the ITG generator than the EZAG generator; and in both cases the elution yields were

consistent with the manufacturer's specifications. The radiochemical purity of the [^{68}Ga]Ga-DOTA-NOC product was consistently high, averaging 99.2 ± 0.4% (Table 1), and never approached our 92% lower limit. All doses passed retrospective 14-day USP sterility testing, and had endotoxin levels at <5 EU/mL. The quantity of DOTA-NOC in the administered doses (Table 1) was always in keeping with the European Association of Nuclear Medicine Procedure Guidelines recommendation of ≤50 μg (Virgolini, et al., 2010).

^{68}Ge breakthrough in the [^{68}Ga]Ga-DOTA-NOC radiopharmaceutical (Table 1) was always far below the very conservative 0.001% upper limit (Virgolini, et al., 2010; Velikyan, et al., 2013), regardless of generator manufacturer. Consistent with the manufacturers' generator specifications, ^{68}Ge breakthrough was higher with the ITG generator (Table 1).

The C18 solid-phase extraction procedure used in [^{68}Ga]Ga-DOTA-NOC isolation provided a >100-fold reduction in the level of ^{68}Ge breakthrough carried through to the final product. For 44 doses produced using the EZAG generators we directly measured ^{68}Ge breakthrough in a residual sample of the fraction of generator eluate used in [^{68}Ga]Ga-DOTA-NOC synthesis, as well as in the final [^{68}Ga]Ga-DOTA-NOC product. ^{68}Ge breakthrough in the fractionated generator elute averaged $8.6 \times 10^{-5} \pm 1.3 \times 10^{-4}$% (median 4.2×10^{-5}%), but dropped to $3.0 \times 10^{-7} \pm 3.6 \times 10^{-7}$% (median 1.9×10^{-7}%) in the subsequent [^{68}Ga]Ga-DOTA-NOC final product. Note, all breakthrough values were calculated for the time of [^{68}Ga]Ga-DOTA-NOC dose expiration, not the time of generator elution, since the objective was to characterize product quality. Generator elution occurred, on average, 84-minutes and 86-minutes prior to the labeled dose expiration time using the EZAG and ITG generators, respectively (median values 83

minutes and 85 minutes).

Total synthesis time, from initiation of generator elution to post-QC release of final product, averaged 47 ± 5 minutes. Endotoxin testing was the rate-limiting QC test in progression to final dose release. The overall process required slightly more time when the ITG Fluidic Module was employed for solution transfers during tracer synthesis (Table 1), although the difference is judged to be inconsequential.

Clinical whole-body (head to mid-thigh) PET/CT imaging with [68Ga]Ga-DOTA-NOC has consistently delivered high quality PET images that are fully consistent with prior literature reports on [68Ga]Ga-DOTA-NOC in evaluation of patients with neuroendocrine cancer (Figures 4 and 5). The primary motivation for pursuing clinical [68Ga]Ga-DOTA-NOC imaging via an Expanded Access IND was a critical local need for the best available approach to defining the extent of disease in patients with advanced neuroendocrine cancer who were being considered for multi-visceral organ transplantation (Mangus, et al., 2013). PET/CT with [68Ga]Ga-DOTA-NOC has also be quite useful in clinical evaluation of patients with either suspected neuroendocrine cancer, or a suspected neuroendocrine cancer recurrence, with the PET procedure often locating disease in patients for whom conventional ^{111}In-Octreoscan imaging and conventional radiographs were negative, but inconsistent with clinical presentation (Figure 5).

CONCLUSIONS

The manual [68Ga]Ga-DOTA-NOC synthesis methods, whether implemented with the EZAG or ITG generators, have been convenient, reliable and robust in

radiopharmaceutical production for clinical use. With reasonable measures to minimize introduction of unnecessary trace metals (use of ultrapure reagents, an effort to minimize reagent volumes, and fractionated elution of the generator), we consistently obtained high purity [^{68}Ga]Ga-DOTA-NOC while reliably remaining below the 50-μg limit for acceptable peptide mass (Virgolini, et al., 2010), *even using the EZAG generator without pre-synthesis purification of the ^{68}Ga^{3+}.* The Expanded Access IND has provided a valuable regulatory pathway for supplying this investigational drug, allowing [^{68}Ga]Ga-DOTA-NOC PET/CT to fulfill a critical need in the clinical care of patients with neuroendocrine cancer.

Supplementary Material

Supplementary data to this article, including detailed synthesis protocols and associated batch record sheets, can be found online at:

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Figure 1. Eppendorf Thermomixer fitted with the heating element for a 15-mm centrifuge tube. In our initial manual synthesis method, a single-use sterile centrifuge tube containing the [^{68}Ga]Ga-DOTA-NOC reaction solution was simply heated in the 80°C thermomixer with swirling at ≥300 rpm for 10-minutes to complete the labeling reaction (with the apparatus shielded within >5-cm walls of lead bricks).

Figure 2. Disposable syringe and vial assembly used (with shielding, inside a laminar flow hood) for final [^{68}Ga]Ga-DOTA-NOC product sterilization, and dispensing of the patient dose. The 25-gauge needle (blue hub) with attached 0.2-µm filter is used to vent the headspace during dose withdrawal.
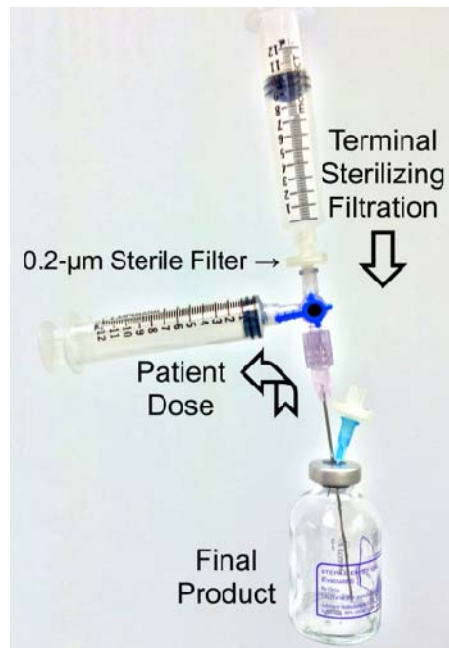
Figure 3. Thin layer chromatography results for the [68Ga]Ga-DOTA-NOC product on ITLC-SG strips developed with 0.1M HCl or 1:1 methanol:1M aqueous NH₄OAc, and corresponding behavior of the potential impurity of [68Ga]Ga-acetate (buffered reaction solution lacking DOTA-NOC). For each chromatogram, the dotted red line on the left side is the position of the origin, while the dotted line on the right is the position of the solvent front.
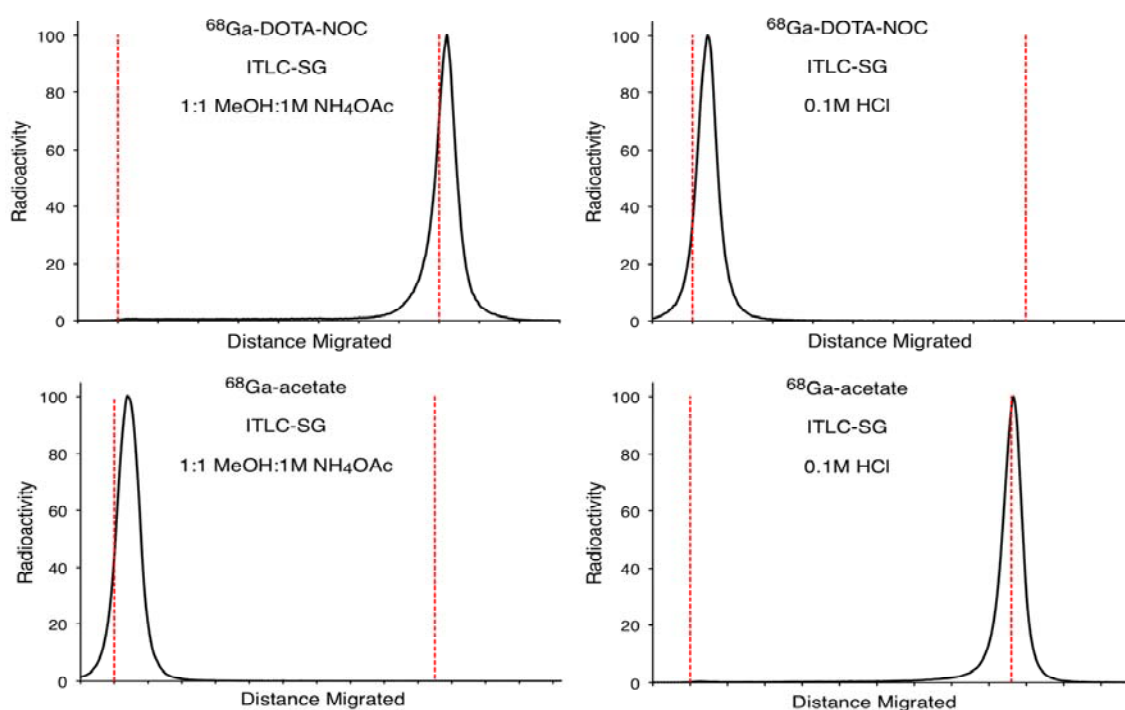
Figure 4. Sample whole-body [68Ga]Ga-DOTA-NOC PET images obtained for two patients at approximately☐60-minutes post-injection (Siemens mCT camera). In both cases the patient dose of 68Ga was 170 MBq (4.6 mCi) and the DOTA-NOC dose 46-μg. The images of the patient on the left show extensive [68Ga]Ga-DOTA-NOC uptake in previously unknown metastatic lesions throughout the body. Images from the patient on the right also show multiple sites of metastatic disease, but these are confined to the liver and abdominal cavity. Following evaluation with [68Ga]Ga-DOTA-NOC PET, only the patient on the right remained a candidate for treatment by multi-visceral transplant.
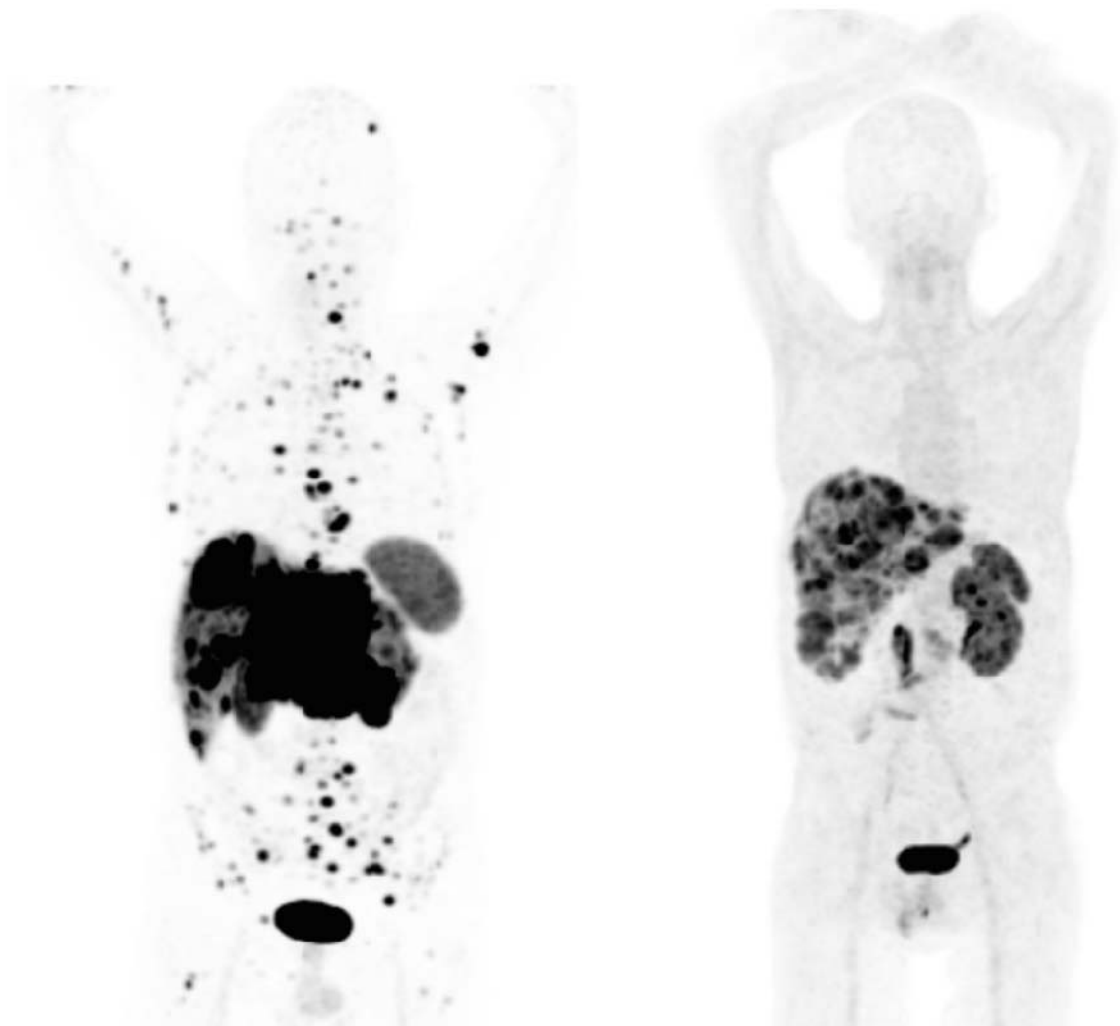
Figure 5. Images of a carcinoid tumor patient obtained with both [^{68}Ga]Ga-DOTA-NOC (196 MBq, 34-μg DOTA-NOC; imaged at 60-minutes post-injection) and ^{111}In-Octreoscan (231 MBq; imaged at 4-hours post-injection), the only FDA-approved agent for somatostatin-receptor-targeted neuroendocrine tumor imaging. In contrast to the ^{111}In image, which appears normal, the ^{68}Ga image reveals multiple metastatic lesions in the liver. (The pituitary also expresses somatostatin receptors and is visualized in the ^{68}Ga PET image, along with normal uptake in the spleen, kidneys, and bladder.) The ^{68}Ga PET scan was performed 2-weeks after the ^{111}In scan because the patient's symptoms were inconsistent with the ^{111}In-Octreoscan findings.
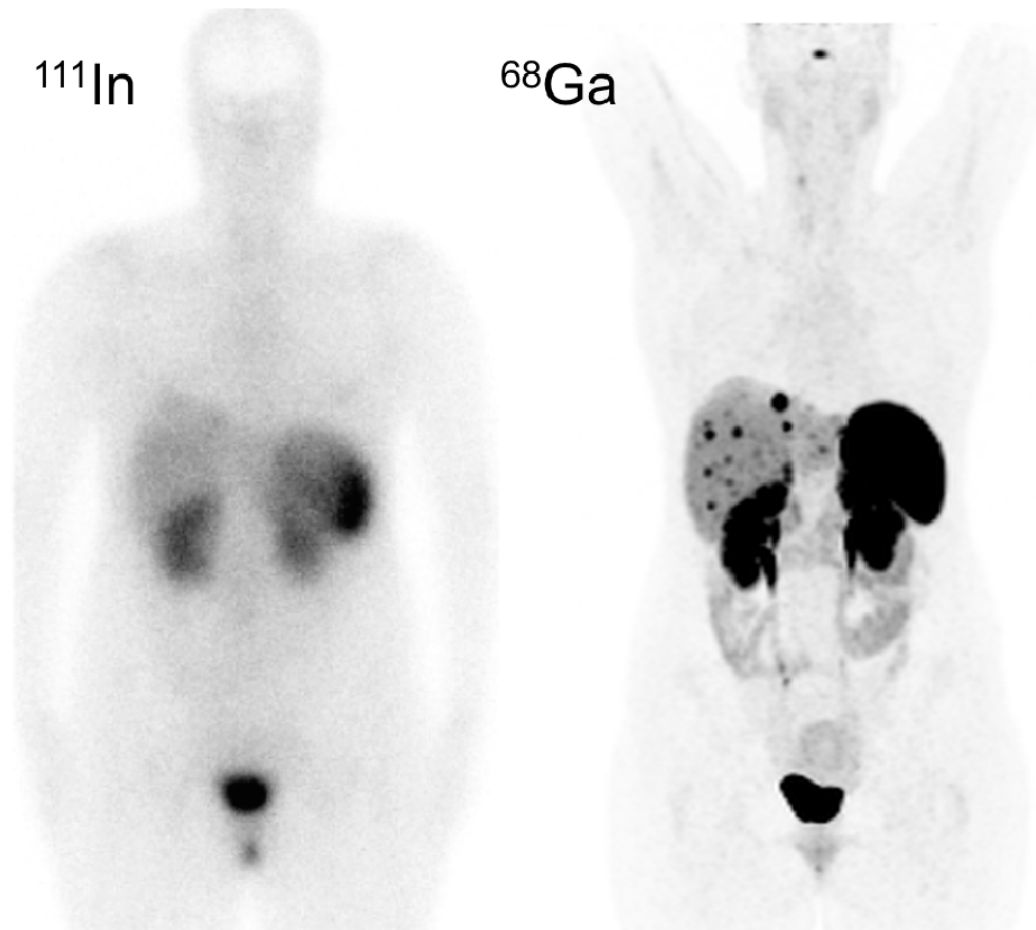
Table 1. [68Ga]Ga-DOTA-NOC Dose Characteristics

Parameter	EZAG Generator	ITG Generator	Aggregate Data
Number of Patients	47	127	174
Administered Dose (mCi)	4.5 ± 0.7 (median 4.6)	5.0 ± 0.5 (median 5.2)	4.9 ± 0.6 (median 5.1)
Administered DOTA-NOC Dose (μg)*	43.2 ± 5.2 (median 46)	23.9 ± 5.7 (median 23.5)	29.1 ± 10.2 (median 25.1)
Radiochemical Purity (%)	98.9 ± 0.4 (median 98.8)	99.4 ± 0.3 (median 99.5)	99.2 ± 0.4 (median 9.4)
^{68}Ge Breakthrough at Dose Expiration Time (%)	2.8×10^{-7} ± 3.5×10^{-7} (median 1.8×10^{-7})	5.4×10^{-5} ± 7.4×10^{-5} (median 1.9×10^{-5})	4.0×10^{-5} ± 6.8×10^{-5} (median 1.5×10^{-5})
Synthesis Time, Initiation of Elution to Post-QC Dose Release (minutes)	46 ± 5 (median 44)	47 ± 4 (median 46)	47 ± 5 (median 46)
Elapsed Time, Initiation of Elution to Dose Expiration (minutes)	84 ± 5 (median 83)	86 ± 6 (median 85)	85 ± 6 (median 85)

*Maximum possible value, assuming the total DOTA-NOC mass employed in the synthesis remains present in the final product solution (*i.e.,* assuming no mass loss in material transfers or in the purification of product by C18 solid-phase extraction).