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^{68}Ga-DOTATATE Prepared from Cyclotron Produced Gallium-68: An Integrated Solution from Cyclotron Vault to Safety Assessment and Diagnostic Efficacy in Neuroendocrine Cancer Patients

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ABSTRACT

Cyclotron production of gallium-68 (^{68}Ga) is a promising approach to supply ^{68}Ga radiopharmaceuticals. To validate this capability, an integrated solution for a robust synthesis of ^{68}Ga-DOTATATE prepared from cyclotron produced ^{68}Ga (further on referred to as cyclotron produced ^{68}Ga-DOTATATE) was achieved. A retrospective comparison analysis was performed in patients who underwent PET/CT imaging after injection of DOTATATE labeled with ^{68}Ga produced by cyclotron or eluted from a generator to demonstrate the clinical safety and diagnostic efficacy of the radiopharmaceutical for a routine standard-of-care diagnostic tool in clinic. **Methods:** An enriched zinc-68 pressed target was irradiated by cyclotron with a proton beam set at 12.7 MeV for 100 min. The fully automated process utilizes an in-vault dissolution system where a liquid distribution system transfers the dissolved target to a dedicated hotcell for the purification of $^{68}GaCl_3$ and radiolabeling of DOTATATE using a cassette-based automated module. Quality control tests were performed on the resulting tracer solution. The internal radiation dose for ^{68}Ga-DOTATATE was calculated based on extrapolation from rat biodistribution experiments. A retrospective comparison analysis was performed in patients who underwent PET/CT imaging after injection of DOTATATE labeled with ^{68}Ga produced by cyclotron or eluted from a generator. **Results:** The synthesis of ^{68}Ga-DOTATATE (20.7 ± 1.3 GBq) with high apparent molar activity (518 ± 32 GBq/µmole at end of synthesis (EOS)) was completed in 65 min and the radiopharmaceutical met the requirements specified in the European Pharmacopoeia monograph on Gallium (^{68}Ga) chloride (accelerator produced) solution for radiolabeling. ^{68}Ga-DOTATATE was stable for at least 5 h after formulation. The dosimetry calculated with OLINDA for ^{68}Ga-DOTATATE from cyclotron produced ^{68}Ga and generator eluted ^{68}Ga was roughly equivalent. The SUVmean or SUVmax of tumoral lesions with cyclotron produced ^{68}Ga-DOTATATE was equivalent to that with generator-eluted ^{68}Ga. Among physiological uptakes, a significant

difference was found in kidneys, spleen and stomach wall, with lower values in cyclotron produced ^{68}Ga-DOTATATE in all cases. **Conclusion:** Integrated cyclotron production achieves reliable high yields of clinical-grade ^{68}Ga-DOTATATE. The clinical safety, and imaging efficacy of cyclotron produced ^{68}Ga-DOTATATE in humans provide supporting evidence for its use in routine clinical practice.

Key words: Cyclotron Ga-68, In-vault dissolution system, ^{68}Ga-DOTATATE, PET imaging, Cancer patients

INTRODUCTION

The commercial production of the germanium-68 (^{68}Ge)/gallium-68 (^{68}Ga) generator increased accessibility and kick-started metal radiolabeling of peptides for medical diagnosis. The demand for ^{68}Ga now greatly exceeds the production capacity of generators (*1*) and the use of cyclotrons for production of ^{68}Ga by a ^{68}Zn(p,n)^{68}Ga reaction at energies of 12-14 MeV on a larger scale is becoming a necessity.

The use of cyclotrons for the production of ^{68}Ga first expanded with liquid targets for a yield increase of 10 times generator production, with the convenience of enriched zinc-68 (^{68}Zn) recycling and compatibility with existing distribution systems for the liquid targets (*2–4*). However, problems of target density, high pressure and metal contamination by the targets limit the maximum quantity production and labeling efficiency (*2–4*). The use of solid targets allows much higher yields from 50 to 100 times generator capacity. However, the complexity of target production, the recovery of the solid target while avoiding a high dose for handling and the complex expensive systems required for cyclotron vault to units of synthesis transfers limit its spread on different sites (*5–11*).

The aim of this study was to give a complete high yield integrated solution, from simple target preparation, irradiation and dissolution to a production of good manufacturing practice (GMP) compliant ^{68}Ga-DOTATATE. To take advantage of the higher production capacity of cyclotrons with solid targets, we first investigated the quality of ^{68}Ga produced at 12.7 MeV to demonstrate the robustness in the production of multiple doses of ^{68}Ga-DOTATATE. The chemical and radiochemical purity as well as dosimetry of this radiopharmaceutical were examined for its human use. A phase 3 study aiming to evaluate the innocuity/safety profile of ^{68}Ga-DOTATATE prepared from ^{68}Ga produced by cyclotron was initiated to establish the procedure as a routine standard-of-care diagnostic tool for all neuroendocrine cancer patients. This is a single-center study, but with recruitment across all Canada. The trial is prospective, non-randomized, open-label and with no

control group (ClinicalTrials.gov identifier: NCT04847505; approved by Health Canada). From this study, a retrospective comparison analysis was performed in patients who underwent PET/CT imaging after injection of DOTATATE labeled with ^{68}Ga produced by cyclotron or eluted from a generator (ClinicalTrials.gov identifier: NCT02810600; completed Phase 2 study with 2120 participants).

MATERIALS AND METHODS

^{68}Zn metal powder (≥98.1% enriched) was purchased from ISOFLEX USA (San Francisco, USA) and Neonest AB (Solna, Sweden). Nitric acid 70% (≥99.999% trace metals basis), hydrochloric acid 37% (≥99.999% trace metals basis), ammonium formate (≥99.995% trace metals basis), sodium phosphate dibasic (≥99.99% trace metals basis) and potassium phosphate monobasic (99.99% trace metals basis), acetonitrile, hydroxylamine hydrochloride 99% (ReagentPlus), 2,3,5,6-tertrafluorophenol, sodium hydroxide 98% (ACS grade) were purchased from Aldrich Chemical (St-Louis, MO, USA). Ascorbic acid (≥ 99.99998% trace select) was obtained from Honeywell (Charlotte, North Carolina, US). All solutions and dilutions were prepared with Optima UPLC/HPLC water. Methanol HPLC grade and sodium chloride (NaCl) were purchased from Fisher Scientific (Ottawa, ON, CA). The reverse phase cartridge and AccellPlus CM cationic exchange resin were purchased from Waters (Milford, Massachusetts, USA). Empty cartridges were purchased from UCT (Bristol, PA, USA) and EDAC-HCl from Matrix Innovation (Quebec, Qc, CA). DOTATATE was obtained from AUSPEP (Tullamarine, Australia). The radio TLC were performed using iTLC-SG paper from Agilent (Santa Clara, CA, USA) and a radio-TLC scanner (Bioscan AR-2000, Washington, DC, USA). Gamma-ray spectrometry was conducted on a high-purity germanium detector (GMX HPGe, Ortec, IL, USA) calibrated with NIST traceable Gamma set (Ba-133, Cd-109, Co-57, Co-60, Cs-137, Mn-54, Na-22) from Eckert & Ziegler Isotope Products (Valencia, CA, USA). The pH strips (range 2-10)

were purchased from Millipore-Sigma (Oakville, On, Ca), Quantofix® (Macherey-Nagel, Düren, Germany) iron and zinc test strips from Aldrich. Hydroxamate resin was prepared from the modified AccellPlus CM (Waters, Millford,USA) cationic exchange resin following the procedure developed by Verel *et al.* (*12*) and was packed in a 1 mL cartridge (United Chemical Technologies, Bristol, PA, USA). Benzene sulfonic resin (CUBCX123 and CUBCX111) was bought from UCT, (Bristol, PA, USA). IGGl00 ^{68}Ge/^{68}Ga Generator was obtained from Eckert and Ziegler EUROTOPE (Berlin, Germany).

Target Preparation

The target preparation was already described by Alnawhi *et al.* (*6*), briefly isotopically enriched zinc-68 powder was pressed in dye of 8 mm (155 mg) by a hydraulic press (Module number: 3912, Carver, Wabash, IN, US) and deposed in the appropriate cavity diameter of the magnetic target carrier (*6*).

Irradiation Procedure

Targets were irradiated facing a perpendicular proton beam in a solid target holder TA-1186D ACSI (Richmond, BC, Canada) mounted to a target selector installed directly on a TR-19 or a TR-24 cyclotron (Advanced Cyclotron Systems, Richmond, BC, Canada) in conjunction with our customized magnetic target carrier (*6*). Beam degradation was achieved by the combined density of a tantalum foil (125-150 µm, Goodfellow Cambridge, Huntington, England) and the target carrier. The resulting energy was determined using the SRIM 2013 simulator (*13*). For irradiation, the incident energy (E_{in}) beam was set to 18.2 MeV and degraded to 12.7 MeV with the aluminum degrader of 0.4 mm to minimize the formation of ^{67}Ga by the nuclear reaction ^{68}Zn(p,2n)^{67}Ga (*14*) with a target current of 20 µA applied during ~100-min irradiations on both cyclotrons.

In-Vault Dissolution System

After the irradiation in the cyclotron target holder the target carrier was released down a tube line into a dissolution system (Figure 1). This custom-built system is located in the

cyclotron vault and remotely automated by an industrial programmable logic controller. The top portion of the system funnels the target carrier into an air activated vacuum clamp that opens and closes the magnetic target carrier to release the ^{68}Zn target payload into the polyvinylidene fluoride (PVDF) dissolution chamber. The middle section gates the passage of the target to the dissolution chamber with an air activated union ball valve (19 mm opening) that seals off the chamber during the target dissolution process. The final portion of the system is the dissolution chamber where an air/vent port (Figure 1A) and an air activated distribution valve (VICI, Houston, Texas, USA) governs the incoming injections of 1.5 mL of nitric acid 7 M, 3 mL of water and 2.75 mL of 2.5 M ammonium formate buffering solution through the liquid port (Figure 1A) during the dissolution sequence and selects the destination line of the dissolved target to the proper synthesis unit. Inside the chamber a magnetic stirring bar is activated for 2 min for a complete dissolution (*6*), after which water and ammonium formate were added. The dissolved target solution arrives ~7 min after the cyclotron irradiation in the destination hot cell. With the process completed the vacuum clamp and air actuated release pin (Figure 1B) allow the magnetic target carrier to exit the system via the ejection slide (Figure 1C), at this point all valves are reset, and the system is ready for another synthesis, dissolution process combined to target water flushing, the overall step is accomplished in 20 min after end of bombardment.

« Figure 1 »

Peptide Radiolabeling

The $^{68}GaCl_3$ purification (*6*) and peptide radiolabeling steps were both performed on an AllInOne automated module (TRASIS, Ans, Belgium), Figure 2. The $^{68}GaCl_3$ purification was performed following the optimized procedure described by Alnawhi *et al.* (*6*). After the transfer of $^{68}GaCl_3$, the line was rinsed with HCl 0.01M (0.5 mL) for a maximum recovery. The pH was adjusted to 3.5 with 1.2 mL of a 0.2 M ammonium formate metal trace buffer

solution. The buffered solution was transferred to the reactor prefilled with a 1 mL solution of 60 µg of DOTATATE and 25 mg of ascorbic acid trace select grade. After mixing with nitrogen, the pH was 3.4-3.8 and the reaction mixture was raised to 100 °C during 13 min. The radiolabeling yield was greater than 98%. After the labeling step, the reactor was cooled to 50 °C, then the solution was drawn into a syringe prefilled with 5 mL of water at room temperature. The peptide solution was passed through 500 mg C18 reversed phase resin and the reactor was rinsed with an extra 4 mL of water. The column was then washed twice with 10 mL of water. The recovery of ^{68}Ga-DOTATATE was achieved with 3.5 mL of 55% (V/V) ethanol/water solution through the C18 column to the product vial for final formulation. The formulation is achieved by adding 17.5 mL solution containing 0.14 g Na_2HPO_4, 0.024 g KH_2PO_4, 0.1 g NaCl and 100 mg ascorbic acid to the product vial for a total volume of 21 mL and 9.4% ethanol. This solution was filtered through a sterile 0.22 µm PVDF membrane filter (Millipore, USA) and fractionized with the Eckert & Ziegler module in the clean room.

« Figure 2 »

Quality Control Tests

Quality control tests were performed on formulated ^{68}Ga-DOTATATE. The pH was measured with pH strips. The radiochemical identity and purity were determined by ultra-high-performance liquid chromatography (Waters Acquity UPLC system, Waters, USA) with an evaporative light scattering detector and flow-count radio-detector (Bioscan, USA) and iTLC. Samples (1 µL) were injected and analyzed on an Acquity UPLC BEH C18 column (1.7 µm, 2.1 x 50 mm) and compared with home-made non-radioactive Ga-DOTATATE standard. The iTLC-SG paper was eluted with a solution of 77 g/L ammonium acetate: MeOH (1:1). The radionuclidic purity was verified by γ-ray spectrometry on a calibrated high purity germanium (HPGe) detector with a zoom energy window of 1-2000

keV. Samples were counted for 2 min after end of synthesis. In addition, the tests were repeated after 16-24 h EOS to quantify radionuclidic impurities ^{67}Ga ($t_{1/2}$ = 3.26 d) and ^{66}Ga ($t_{1/2}$ = 9.49 h). Chemical purity was evaluated using commercially available indicator strips to measure iron and zinc in the formulated ^{68}Ga-DOTATATE. The endotoxin levels were assayed by the Limulus amebocyte lysate method with an Endosafe-PTS test system (Charles River Laboratories International, SC, USA). Sterility tests were performed by a licensed laboratory (Nucro-Technics, ON, Canada).

Animals

All animal studies were conducted in compliance with the Canadian Council on Animal Care guidelines and with the approval of the Animal Care Committee of the Université de Sherbrooke.

Biodistribution Studies

Biodistribution studies were conducted on 12 weeks Fisher female rats (150-175 g) (Charles River, Kingston, NY) to determine the uptake of ^{68}Ga-DOTATATE in various organs. A dose between 7-14 MBq of ^{68}Ga-DOTATATE produced by cyclotron or eluted from a generator was injected into a tail vein of the isoflurane anesthetized rats. After 15, 30, 45, 60 or 120 min post-injection while maintaining anesthesia, blood was taken by cutting the femoral artery. The animals were then sacrificed by CO_2 inhalation and the organs of interest were removed, rinsed and blotted dry before counting the radioactivity in a Hidex γ-counter (Turku, Finland). The results were expressed as percentage of injected dose per gram of tissue (% ID/g).

Clinical PET Imaging

A retrospective comparison analysis was performed in patients who underwent PET/CT imaging after injection of DOTATATE labeled with ^{68}Ga produced by cyclotron or

eluted from a generator. The institutional ethic board approved this study, and all subjects signed a written informed consent.

Patients with progressive disease between the two exams (defined by at least a new lesion) or exams performed with different cameras were excluded.

PET/CT imaging was performed from head to mid-thigh, on a Philips Gemini TF or Gemini GXL PET/CT (Philips Medical Systems, Cleveland, OH, USA). An unenhanced CT scan was obtained using the following parameters: slice thickness, 3 mm; increment, 3 mm; 120 kVp and 55 to 83 mAs depending on patient's weight. Immediately after CT scanning, whole-body PET was performed in 3-dimensional mode (matrix, 144 x 144). For each bed position (15 cm; over- lapping scale, 5 cm), a 2-min acquisition time with a 57.6 cm field of view was used.

The emission data were corrected for decay, and random and scatter events. Reconstruction was conducted with the 3D Row Action Maximum Likelihood Algorithm (RAMLA-3D) with 2 iterations, relaxation parameter of 0.5 and a 2 mm radius spherically-symmetric basis functions (blobs). Attenuation correction was performed using the low-dose unenhanced CT data. Image analysis was performed using OASIS software (Segami, Columbia, Maryland, USA).

To compare both cyclotron and generator produced ^{68}Ga-DOTATATE, regions of interest were drawn in transaxial slices, around areas of focal uptake in pituitary gland, lacrimal, parotid, submandibular, and sublingual glands, nasal mucosa, thyroid gland, mediastinal blood pool (aortic arch), adrenals, liver, spleen, stomach wall, bowel, kidneys cortex, uncinate process and gluteal musculature (as background). Isocontour volumes at 70% of the maximum pixel value were drawn automatically, and the mean and maximum standardized uptake values (SUVmean and SUVmax, respectively) were measured in all these volumes. SUVmean and SUVmax of neuroendocrine lesions were also recorded, up to ten lesions per patient if there were more.

Comparisons between cyclotron and generator produced ^{68}Ga-DOTATATE values were performed using Wilcoxon matched-pairs rank tests in each patient. A *p*-value of less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Target Preparation and Irradiation

As previously described by Alnawhi *et al.* (*6*), the preparation and assembly of ^{68}Zn-pressed target was easy, time effective for serial production and inexpensive. The ^{68}Zn-pressed target irradiation challenge was to manage the low melting point of the zinc (419.5 °C) and the focused beam on the solid target. To avoid target overheating at low current, a 125 µm tantalum foil was efficiently used to diffuse the beam and reduce the proton energy to 12.7 MeV on target.

^{68}Ga-DOTATATE Preparation

A fully automated dissolution system was developed to facilitate the radiosynthesis of ^{68}Ga for large-scale and routine production using a ^{68}Zn pressed target. The activity of the transferred $^{68}GaCl_3$ solution from the vault to the hot cell was 46.2 ± 2.2 GBq (56.6 GBq at end of bombardment) with a saturated yield of 4.4 ± 0.1 GBq/µA when using the 8 mm diameter ^{68}Zn target irradiated at 12.7 MeV for 100.3 ± 2.4 min at 20 ±0.4 µA. The $^{68}GaCl_3$ purification was performed following the optimized procedure described by Alnawhi *et al.* (*6*).

DOTATATE aliquots (60 µg) formulated in water (300 µL) were stable for up to 30 days when the solution was kept frozen at -20 °C. To avoid radiolysis at high activity levels, the peptide precursor was loaded in the reaction vessel in presence of ascorbic acid and the pH was adjusted before the transfer of the purified $^{68}GaCl_3$ solution. A mean of 20.7 ± 1.3 GBq (n=14) at EOS of ^{68}Ga-DOTATATE was produced in less than 35 min for a global

decay corrected yield of 66 ± 5% (n=14). The final formulation, filtration and distribution process was performed within 10 to 15 min.

The estimated apparent molar activity (AMA) at EOS was 518 ± 32 GBq/µmole (n=14), which is 20-fold higher compared to the value of 25 GBq/µmole reported by Thisgaard *et al.* (*11*) for cyclotron produced ^{68}Ga-DOTATATE. From our previous studies, new generators produce 0.665 ± 0.043 GBq (n=10) of ^{68}Ga-DOTATATE with an AMA of 63 ± 13 GBq/µmole with a performance that decays over time.

Quality Control Results

Samples of all productions (n=14, Table 1) were found to comply with all specifications. Gallium-67 and gallium-66 contents were respectively 0.052 ± 0.004% and 0.017± 0.006% at EOS (n=14). ^{68}Ga-DOTATATE can safely be used up to 5 h after EOS, when the combined value for gallium-66 and gallium-67 content reaches 1.25% of the activity of gallium-68 as compared to the 2% limit prescribed in the European Pharmacopoeia monograph (*15*).

« Table 1 »

Assessment of Internal Radiation Dose

In order to estimate the dosimetry of the ^{68}Ga-DOTATATE, biodistibution experiments were conducted in female Fischer rats at different time points post-injection (Figure 3). Cyclotron produced ^{68}Ga-DOTATATE showed significantly higher uptake in adrenals and pancreas, organs of interest rich in somatostatin receptors (SSTR), at early time points (15 and 30 min, $p < 0.005$) post-injection. A potential explanation is that the cyclotron produced ^{68}Ga-DOTATATE has the larger AMA value. Cyclotron- and generator produced ^{68}Ga-DOTATATE were shown to be biologically equivalent at late time points, giving identical kinetic and biodistribution patterns in animals.

« Figure 3 »

Dosimetry extrapolated to humans was computed using OLINDA/EXM (Vanderbilt University, 2003) from the residence times scaled to humans. Since female rats were used for the biodistribution experiments, the adult female model provided by the software was applied for computations. Extrapolated dosimetry is detailed in Table 2 as absorbed dose.

Estimated ^{68}Ga-DOTATATE dosimetry is acceptable when compared with other PET tracers in use in humans and shows that dosimetry for ^{68}Ga-DOTATATE synthesized from cyclotron produced ^{68}Ga and generator-produced ^{68}Ga is roughly equivalent. The main difference in calculated dosimetry between the two tracers is in pancreas, kidneys, and adrenals.

« Table 2 »

Clinical Studies

Comparison analysis was performed in 12 patients (14 lesions) between PET/CT exams performed after injection of ^{68}Ga-DOTATATE produced by cyclotron or eluted from generator, four using the Gemini GXL and eight the Gemini TF PET/CT scanner (Philips). The mean interval between the exams was 373.5 $\pm$ 315.8 days.

Cyclotron production allowed injection of higher radiotracer activity than for generator-eluted ^{68}Ga-DOTATATE: 3.9 $\pm$ 1.0 MBq/kg versus 1.9 $\pm$ 0.6 MBq/kg respectively, p=0.01. There was no difference between the injection-acquisition intervals between the exams (69.5 $\pm$ 11.9 and 65.4 $\pm$ 11.6 min respectively, p=0.34).

Results of SUVmax and SUVmean comparisons are summarized in Table 3 and Table 4 respectively. There was no difference between the SUVmean or SUVmax of tumoral lesions. Among physiological uptakes, a significant difference was found in kidneys, spleen and stomach wall, with lower values in cyclotron produced ^{68}Ga-DOTATATE in all cases, Figure 4. All these organs correspond to large, highly SSTR-expressing organs (*16*) but to our knowledge the effect of injected activity or apparent

molar activity on physiologic uptake of SSTR PET imaging has not been described. Nonetheless, the lower physiological uptakes and similar tumor uptake could only result in better tumor / background ratio in these areas. For the last eighteen months, a weekly production of ^{68}Ga-DOTATATE was successfully performed and more than 1067 clinical scans where done. One should note that 10 patients were scheduled from a single production of ^{68}Ga-DOTATATE produced by cyclotron for two simultaneously running PET-scanners, compared to 2 patients with ^{68}Ga-DOTATATE eluted from generator.

« Tables 3 and 4 »

In recent years, several groups including ours have developed new liquid and solid targets and robust separation procedures to manufacture high-purity ^{68}Ga with cyclotrons (*2–11*). There is clear and convincing evidence that the quality of cyclotron produced ^{68}Ga is comparable to that of generator ^{68}Ga (*2–11*) and that large quantities can be prepared (*5,6,10,11*), which enable transportation of ^{68}Ga tracer. The present clinical trial confirmed that ^{68}Ga-DOTATATE prepared from cyclotron produced ^{68}Ga is safe and provides diagnostic efficacy equivalent to that of the radiopharmaceutical prepared from generator produced ^{68}Ga.

CONCLUSION

We proposed a complete high yield integrated solution for cyclotron produced and GMP compliant ^{68}Ga-DOTATATE. The use of the in-vault dissolution system combines the high-yield production of the solid target with the versatility of the liquid target distribution to multiple synthesis units. The results of the present study provide further supporting evidence for the adoption of cyclotron produced ^{68}Ga-DOTATATE in clinical practice.

DISCLOSURE

This research was made possible thanks to the financial support of the Oncopole, which receives funding from Merck Canada and from Fonds de recherche du Québec – Santé, as well as from the Cancer Research Society. One PCT patent was filed for some of the material presented in this article. No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

Question: How does the development of cyclotron produced ^{68}Ga-DOTATATE facilitate PET imaging of neuroendocrine cancer patients?

Pertinent Findings: A robust and GMP compliant synthesis of ^{68}Ga-DOTATATE from cyclotron produced ^{68}Ga was achieved expanding the imaging time window and the number of patients per production compared to generator-based ^{68}Ga-DOTATATE. We also showed that cyclotron produced ^{68}Ga-DOTATATE is safe for clinical use.

Implication for Patient Care: Cyclotron produced ^{68}Ga-DOTATATE can provide high-contrast detection of neuroendocrine tumors with reduced physiological uptakes in highly SSTR-expressing organs.

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FIGURES

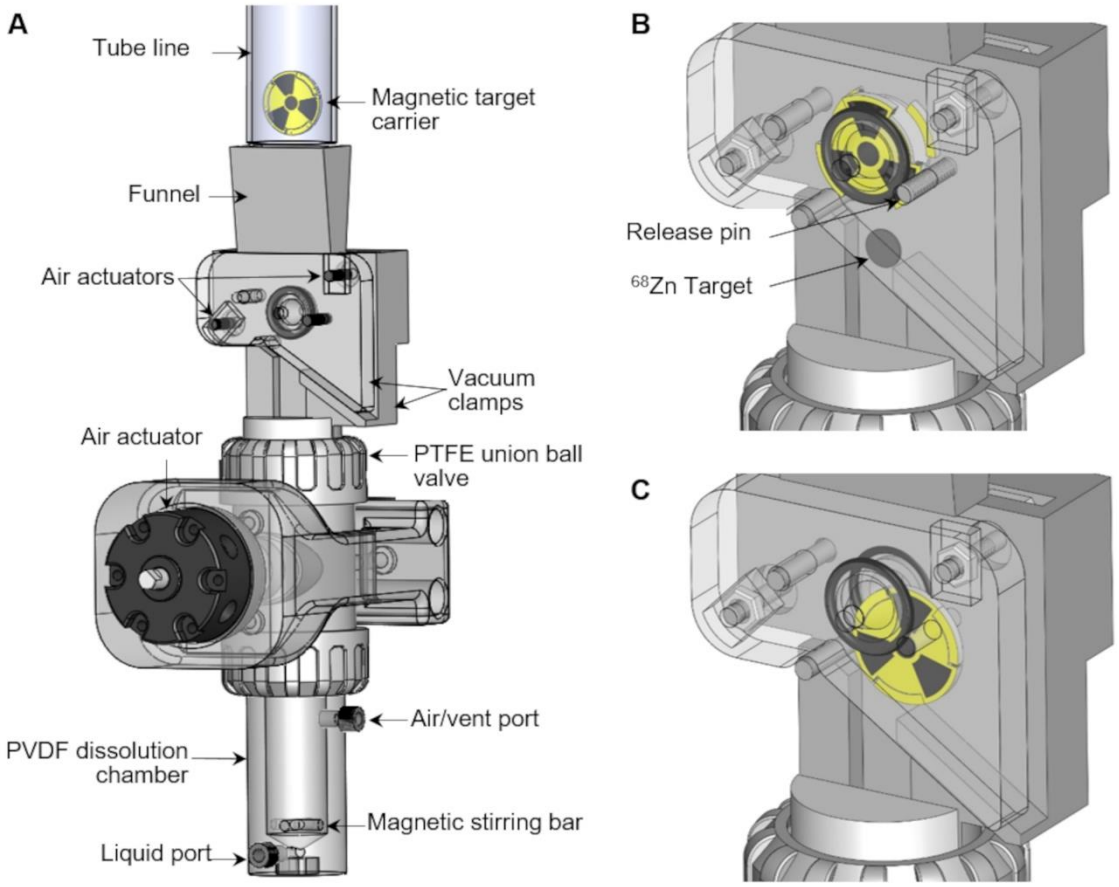

Figure 1. In-vault dissolution system , 1A component assembly, 1B Zinc-68 enriched target release and 1C magnetic target carrier release

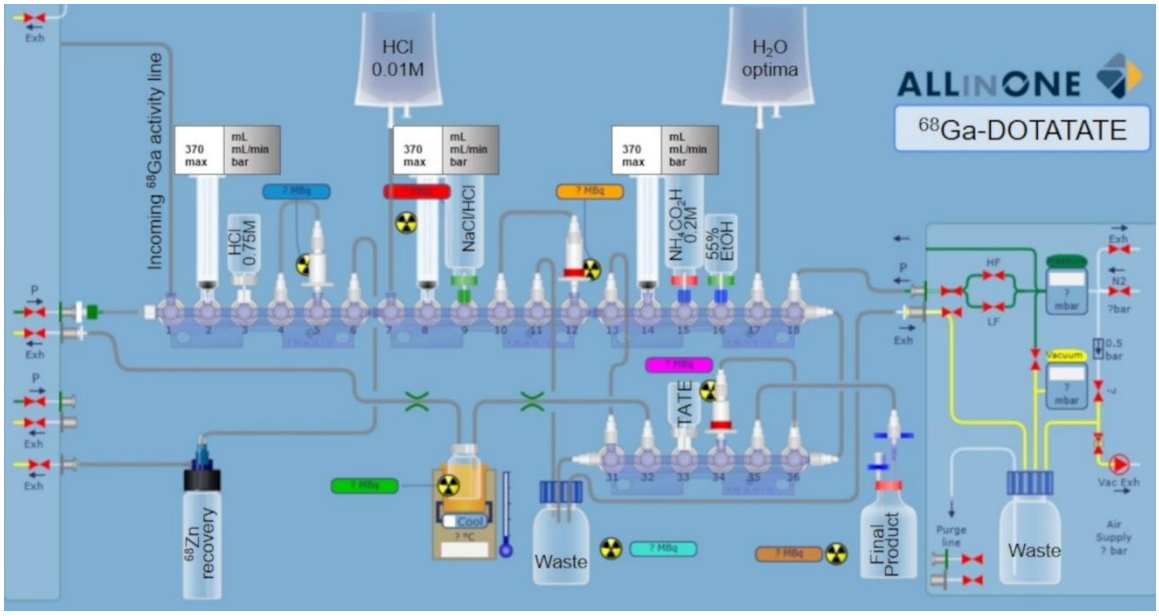

Figure 2. AllinOne schematic of ^{68}Ga-DOTATATE synthesis including $^{68}GaCl_3$ purification

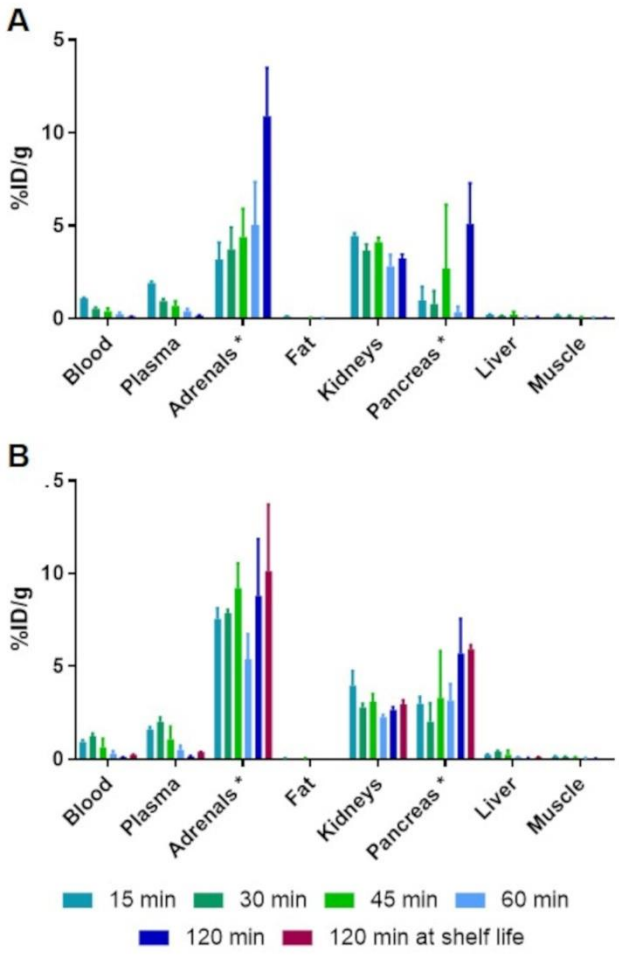

Figure 3. Biodistribution in rats of DOTATATE labeled with A) Generator and B) Cyclotron produced ^{68}Ga at various time points

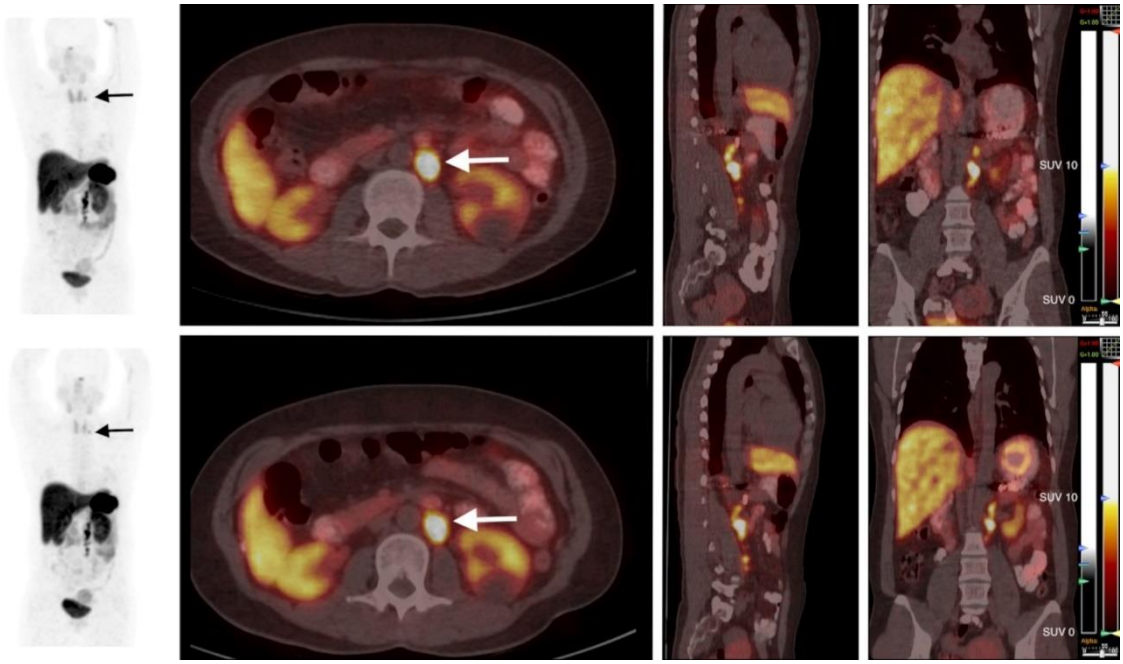

Figure 4. Example of two exams, with cyclotron- (top row) and generator-produced (bottom row) ^{68}Ga-DOTATATE, 16 months apart for the same patient followed for a left pheochromocytoma, removed but with secondary supraclavicular (black arrows) and retroperitoneal (white arrows) node metastasis

TABLES

Table 1. Quality control results for ^{68}Ga-DOTATATE

Analysis	Method	Specifications EOS	Results (n=14)
Appearance	Visual	Clear, no color	Pass
pH	pH strip	4.0-8.0[a]	5.4 ± 0.2
Peptide DOTATATE	Calculation	≤ 60 µg[a]	57.3 ± 0.5 µg
Radiochemical identity	UPLC retention time	± 10%	0.90 ± 0.05%
Radiochemical purity	(100-A) x T=%	≥ 91%[a]	98.4 ± 0.9%
Radionuclidic purity	Gamma 511 and 1077 KeV	≥ 98%	99.7 ± 0.3%
Radionuclide identification	Half-live	62-74 min[a]	67.5 ± 0.5 min
Pyrogenicity	Inoculation	≤ 8.3 IU/mL[a]	Pass
Filter integrity	Bubble point	≥ 345 kPa (50 psi)	Pass
Zinc/Iron	Strips	≤ 10 µg/GBq	< 1 µg/GBq
^{67}Ga and ^{66}Ga contents	γ-ray analysis	≤ 2%	^{67}Ga ≤ 0.052 ± 0.004%[b] ^{66}Ga ≤ 0.017 ± 0.006%[b]

[a]Our release criteria; [b]Values recalculated to the moment of EOS from the results obtained 16-24 h after EOS

Table 2. Dosimetry extrapolated to humans for ^{68}Ga-DOTATATE

Tissue	Absorbed dose (mGy/MBq)	
	Generator ^{68}Ga	**Cyclotron ^{68}Ga**
Adrenals	1.33e-01	1.52e-01
Brain	5.45e-04	7.41e-04
Breasts	8.99e-04	9.52e-04
Gallbladder Wall	1.66e-03	1.85e-03
LLI Wall	9.41e-04	9.78e-04
Small Intestine	1.21e-03	1.20e-03
Stomach Wall	1.42e-03	1.79e-03
ULI Wall	1.14e-03	1.14e-03
Heart Wall	2.52e-02	2.69e-02
Kidneys	9.01e-02	6.29e-02
Liver	4.42e-03	5.30e-03
Lungs	1.12e-02	1.17e-02
Muscle	3.23e-03	3.41e-03
Ovaries	7.95e-03	4.94e-03
Pancreas	1.36e-02	7.28e-02
Red Marrow	6.46e-03	6.68e-03
Osteogenic Cells	7.25e-03	8.96e-03
Skin	6.10e-04	6.35e-04
Spleen	5.42e-03	5.79e-03
Thymus	1.61e-03	1.70e-03
Thyroid	7.12e-04	7.60e-04
Bladder Wall	7.51e-04	7.83e-04
Uterus	5.28e-03	6.67e-03
Total Body	2.83e-03	3.00e-03

Table 3. Comparison of SUVmax of physiologic and tumoral uptakes between cyclotron produced and generator eluted ^{68}Ga-DOTATATE

Tissue	**SUVmax**		
	Cyclotron ^{68}Ga	**Generator ^{68}Ga**	
	Mean ± SD	Mean ± SD	*p*
Pituitary	4.56 ± 1.57	5.13 ± 1.54	0.3291
Liver	8.33 ± 2.19	8.95 ± 2.47	0.3804
Thyroid	4.25 ± 2.03	4.25 ± 2.11	>0.9999
Parotid	2.37 ± 1.01	2.41 ± 1.04	0.8657
Sub-mandibular	2.77 ± 1.21	2.87 ± 1.17	0.6079
Nasal mucosa	2.16 ± 0.54	2.34 ±0.45	0.9463
Aortic arch	0.95 ± 0.36	0.97 ± 0.20	0.6221
Kidneys	14.30 ± 5.23	16.76 ± 4.12	0.0024*
Spleen	22.79 ± 5.29	26.44 ± 5.33	0.0015*
Uncinate process	5.31 ± 2.45	5.96 ± 2.88	0.1475
Stomach wall	6.30 ± 3.36	8.69 ± 2.37	0.0093*
Bowel	6.91 ± 1.94	7.96 ± 1.92	0.1294
Adrenal	11.09 ± 4.41	12.44 ± 4.39	0.0923
Gluteal musculature	1.19 ± 0.49	1.31 ± 0.33	0.292
Tumors	9.13 ± 6.18	7.94 ± 5.61	0.346

Table 4. Comparison of SUVmean of physiologic and tumoral uptakes between cyclotron and generator produced ^{68}Ga-DOTATATE

Tissue	**SUVmean**		
	Cyclotron ^{68}Ga	**Generator ^{68}Ga**	
	Mean ± SD	Mean ± SD	p
Pituitary	3.82 ± 1.34	4.32 ± 1.31	0.457
Liver	6.56 ± 1.67	6.95 ± 1.81	0.4131
Thyroid	3.43 ± 1.65	3.42 ± 1.72	>0.9999
Parotid	1.89 ± 0.83	1.91 ± 0.82	0.8657
Sub-mandibular	2.22 ± 0.96	2.31 ± 0.95	0.6377
Nasal mucosa	1.75 ± 0.45	1.85 ± 0.33	0.8945
Aortic arch	0.76 ± 0.29	0.79 ± 0.19	0.5879
Kidneys	11.09 ± 4.07	13.00 ± 3.36	0.0049*
Spleen	18.72 ± 4.24	21.41 ± 4.14	0.002*
Uncinate process	4.25 ± 1.56	4.80 ± 2.29	0.083
Stomach wall	5.04 ± 2.74	6.96 ± 1.87	0.0093*
Bowel	5.49 ± 1.56	6.33 ± 1.48	0.1099
Adrenal	9.01 ± 3.59	10.05 ± 3.55	0.1133
Gluteal musculature	0.97 ± 0.39	1.09 ± 0.28	0.207
Tumors	5.14 ± 5.42	6.52 ± 4.59	0.583

GRAPHICAL ABSTRACT