Evaluation of the Efficacy and Safety of the ITM $^{68}Ge/^{68}Ga$ Generator After its Recommended Shelf-life

Tossaporn Sriprapa, M.Sc.*, Thanete Doungta, M.Sc., Nopparath Sakulsamart, B.Sc.***, Nilmanee Taweewatthanasopon, B.Sc.*, Lanyawat Madputeh, B.Sc.*, Pitima Ragchana, M.Sc.*, Napamon Sritongkul, M.Sc.*, Malulee Tantawiroon, M.Sc.*, Somlak Kongmuang, Ph.D.****, Benjapa Khiewvan, M.D.*, Shuichi Shiratori, Ph.D.***

**Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, **Thailand Institute of Nuclear Technology, Bangkok, Thailand, ***Bachelor of Pharmacy, Department of Pharmacy, Mahidol University, ****Department of Pharmaceutical Technology, Faculty of Pharmacy, Silpakorn University, Thailand.*

ABSTRACT

Objective: ^{68}Ga can be routinely produced by a $^{68}Ge/^{68}Ga$ generator without the need for a cyclotron. It is recommended to replace the $^{68}Ge/^{68}Ga$ generator after 250 elutions or 12 months of shelf-life whichever endpoint is reached first. However, a $^{68}Ge/^{68}Ga$ generator that has gone past its recommended lifespan can still be further used as a ^{68}Ga source for ^{68}Ga-labeled radiopharmaceuticals for use in animal experiments. To ensure the quality of ^{68}Ga eluates, we aimed to evaluate the efficacy and safety of the ITM (Isotope Technologies München) $^{68}Ge/^{68}Ga$ generator in our institute after its recommended shelf-life.

Materials and Methods: A 21-month-old ITM $^{68}Ge/^{68}Ga$ generator was eluted using 4.0 ml of 0.05 M HCl. The ^{68}Ga elution yields were calculated, and ^{68}Ge breakthrough was measured at least 48 h after elution in an aliquot amount using a multichannel analyzer (MCA) with a high-purity germanium probe. Metal impurities in the ^{68}Ga eluates were analyzed by ICP-MS.

Results: The elution yield of ^{68}Ga was 35.2 ± 8.1%; n = 5 (decay corrected). ^{68}Ge breakthrough from the ITM $^{68}Ge/^{68}Ga$ generator was below the detectable level. The average amounts of the metallic ions ^{57}Fe, ^{66}Zn, ^{203}Pb, ^{60}Ni, and ^{63}Cu were 18.60, 9.86, 2.42, 0.52, and 0.47 µg/GBq, respectively.

Conclusion: The ITM $^{68}Ge/^{68}Ga$ generator demonstrated consistent and reliable ^{68}Ga elution profiles with an absence of either ^{68}Ge breakthrough or other metal contaminants in the eluent samples as verified by the manufacturer. The use of the ITM $^{68}Ge/^{68}Ga$ generator could be extended past its recommended shelf-life to prepare ^{68}Ga radiopharmaceuticals that are considered safe and suitable for use in animal experimentation and other applications.

Keywords: $^{68}Ge/^{68}Ga$ Generator; ^{68}Ge Breakthrough; $^{68}Ge/^{68}Ga$ Generator impurities; Gallium-68, $^{68}Ge/^{68}Ga$ Generator shelf-life. (Siriraj Med J 2023; 75: 752-758)

INTRODUCTION

^{68}Ga is a positron-emitting isotope of gallium with a half-life of 68 min. Over the past two decades, ^{68}Ga-labeled tracers have increasingly attracted more attention in diagnostic molecular imaging and clinical research. Due to the nearly ideal nuclear properties of radiometals for positron emission tomography (PET) and chelation chemistry using a bifunctional chelating approach (BFCA)[1], various classes of ^{68}Ga-labeled tracers have been developed, including ^{68}Ga-DOTA-Bombesin[2],

Corresponding Author: Shuichi Shiratori
E-mail: Shuichi.shi@mahidol.ac.th
Received 21 July 2023 Revised 25 August 2023 Accepted 9 September 2023
ORCID ID:http://orcid.org/0000-0003-4560-0803
https://doi.org/10.33192/smj.v75i10.264289

^{68}Ga-NOTA-RGD[3], ^{68}Ga-albumin[4,5], and ^{68}Ga-DOTA-hEGF (human epidermal growth factor).[6] Moreover, ^{68}Ga was integrated with ^{177}Lu as a twin radiometal for use in a novel theranostic concept.[7] As part of precision medicine, tailor-made ^{68}Ga-based radiopharmaceuticals have been robustly employed in diagnostic prostate cancer imaging, including ^{68}Ga-PSMA-HBED-CC (^{68}Ga-PSMA-11®)[8,9] and ^{68}Ga-PSMA I&T[10,11], and in diagnosing neuroendocrine tumor imaging, including ^{68}Ga-DOTATATE[12,13], ^{68}Ga-DOTATOC[14,15], and ^{68}Ga-DOTANOC.[16,17] Recently, both ^{68}Ga-PSMA-HBED-CC and ^{68}Ga-DOTATATE were approved by the US FDA for the clinical imaging of prostate cancer and a rare neuroendocrine tumors, respectively. Moreover, a new class of radiotracers based on fibroblast-activation-protein inhibitors (FAPIs) labeled with ^{68}Ga, such as ^{68}Ga-FAPI-04[18] and ^{68}Ga-FAPI-46[19], have demonstrated high tumor-to-background ratios for PET imaging of a wide array of cancers.

^{68}Ga can be produced in an ionic form of the chemically active $^{68}GaCl_3$ by two methods: via a medium-energy cyclotron and a ^{68}Ge/^{68}Ga generator. Cyclotron-produced ^{68}Ga is obtained via ^{68}Zn(p,n)^{68}Ga activation using either a target foil or plate in a solid target[20] or solution in a liquid target.[21] ^{68}Ga production utilizing a solid target results in significantly higher yields. However, the target needs manipulating for the production, including for transferring the solid target into the target holder in the cyclotron. Also, after the bombardment, the solid target has to be removed manually or removed via an automated target transfer system to be dissolved in a hot cell. This manipulating and post-processing can put the personnel at a higher risk of radioactive exposure above the risk they already experience in the cyclotron facility, besides being time-consuming during short half-life ^{68}Ga production. On the other hand, the solution in the liquid target approach can be conveniently loaded into the target holder in the same way as done in ^{18}F production. Also, similar to the solid-target approach, ^{68}Ga must be purified from the remaining ^{68}Zn contaminants in the solution, which leads to a lower yield of ^{68}Ga production.

To overcome these limitations, the ^{68}Ge/^{68}Ga generator is used as an alternative approach and indeed is the most common method to produce ^{68}Ga in clinical use, especially in non-cyclotron medical centers. Commercially available, compact-sized ^{68}Ge/^{68}Ga generators, which reflect the efforts of six decades of development[22], can provide an acidic solution of $^{68}GaCl_3$ that is suitable for routine labeling with BFCA through forming an octahedral coordination complex. A typical generator consists of a small chromatographic column, where ^{68}Ge is immobilized with selected absorbents, such as TiO_2, SnO_2, pyrogallol-derivatized SiO_2, and a mixed matrix, situated in a shielding lead container. ^{68}Ge, a parent radionuclide, spontaneously decays in the column to give ^{68}Ga, with typical yields of 70%–80% in the elution. Secular equilibrium, where both ^{68}Ge and ^{68}Ga have equal radioactivity, in the ^{68}Ge/^{68}Ga generator occurs due to the half-life of ^{68}Ge (270 d) being over 100 times longer than that of ^{68}Ga (68 min). Theoretically, ^{68}Ga accumulated from previous elutions means the system can reach secular equilibrium in around 14 h. Almost 100% ^{68}Ga can be produced after 6 h post elution. Most manufacturers suggest that the ^{68}Ga production cycle for clinical use can be repeated up to 2–3 times a day depending on the generator-loaded radioactivity and the age of the generator.

The first ^{68}Ge/^{68}Ga generator was launched worldwide beginning in the late 1990s. Some of its many advantages that deserve mentioning include the stable column matrices, easy elution, long shelf-life of 1–2 years, effective shielding container, and compact size. Each ^{68}Ge/^{68}Ga generator manufacturer offers various parameters in terms of different types of column matrix, molarity of the HCl eluent, ^{68}Ga volume of elution, ^{68}Ge breakthrough and impurity amount, and weight of the generator, as shown in Table 1.

Although it is necessary to replace a new ^{68}Ge/^{68}Ga generator for clinical use after its recommended shelf-life, the "expired" ^{68}Ge/^{68}Ga generator can actually continue to be employed to elute ^{68}Ga to label certain ^{68}Ga-based radiopharmaceuticals for research purposes, especially for animal experimentation. In the present study, the essential parameters of an over-lifespan ITM ^{68}Ge/^{68}Ga generator (i.e., used past its recommended lifespan) were evaluated to ensure its efficacy and safety for continuing ^{68}Ga elution.

MATERIALS AND METHODS

A SiO_2-based ^{68}Ge/^{68}Ga generator was purchased from Isotope Technologies München (ITM) Medical Isotopes GmbH, Germany (previously, Isotope Technologies Garching (ITG)). All the solvents and reagents were purchased from commercial suppliers and used without further purification. 0.05 M HCl (GMP) was purchased from ABX Advanced Biochemical Compounds.

The ^{68}Ga activity was measured with a dose calibrator (CRC25R, Capintec, USA). The ^{68}Ge activity was measured by gamma-ray spectrometry using a multichannel analyzer, A multichannel analyzer (MCA) integrated gamma spectrometer system (Ortec DSPEC jr 2.0) coupled with a high-purity germanium probe (HPGe probe, Ortec Gem20P4-70) was used in the experiments. The

TABLE 1. Characteristics of some commercially available $^{68}Ge/^{68}Ga$ generators.

Company	Generator specifications					
	Column material	Eluent	^{68}Ge breakthrough	Elution volume	Metallic impurities	Weight of generator
Eckert & Ziegler Cyclotron Co. Ltd. (Obninsk)[23]	TiO_2	0.1 M HCl	< 0.005%	5 ml	Ga < 1 µg/mCi Ni < 1 µg/mCi	11.7 kg
Eckert & Ziegler IGG100 and IGG101 GMP (Gallia Pharm)[23]	TiO_2	0.1 M HCl	< 0.001%	5 ml	Fe < 10 µg/mCi Zn < 10 µg/mCi	IGG100 = 10 kg IGG101 = 14 kg
iThemba LABS, South Africa[23]	SnO_2	0.6 M HCl	< 0.002%	5 ml	1–20 ppm for Sn, Fe, Cu, Mn, and Al	
Pars Isotope (PARS-GalluGEN®), Tehran, Iran[23]	SnO_2	0.6 M HCl	< 0.00002%		>1 ppm for Fe, Sn and Zn	
IRE EliT (Galli Eo®), Fleurus, Belgium[23]	Unspecified	0.1 M HCl	< 0.001%		< 10 µg/GBq of ^{68}Ga for Fe, Cu, Ni, Zn, Pb, and Al	
Isotope Technologies Garching, GmbH, Germany[23]	Silica gel modified with dodecayl gallate	Sterile 0.05 M HCl	< 0.005%	3–4 ml	< µg/GBq of ^{68}Ga for (Ni, Zn, Nb, Pb, Fe, and Cu)	
Isotope ROSATOM[24]	TiO_2	0.1 M HCl	< 0.005%	5 ml		11.7 kg
I.D.B. Holland B.V.[25]	SnO_2	0.6 M HCl	< 0.002%	6 ml	< 10 ppm (Ga, Ge, Zn, Ti, Sn, Fe, Al, and Cu)	26 kg

metal-ion impurities in the ^{68}Ga eluates were analyzed by inductively coupled plasma-mass spectrometry (ICP-MS).

Evaluation of 68Ga elution

A 21-months-old $^{68}Ge/^{68}Ga$ generator (Isotope Technologies München (ITM) Medical Isotopes GmbH, Germany) loaded at the manufacturer site with ^{68}Ge 50 mCi was used for the study evaluation. Before starting the experiments, the generator was eluted with 30 ml of 0.05 M HCl to wash away ^{68}Ge breakthrough and other impurities accumulated in the pyrogallol-formaldehyde resin column as recommended by the manufacturer because the system had not been used for several months. The ITM $^{68}Ge/^{68}Ga$ generator was manually eluted with 4.0 ml of 0.05 M HCl. Subsequently, the elution profile was studied by collecting the eluates in fractions of 1 ml for 4 fractions. The elution yield of ^{68}Ga activity in each fraction was immediately determined in a dose calibrator.

^{68}Ge breakthrough measurement

^{68}Ge breakthrough was measured after the separated ^{68}Ga eluates were allowed to decay for at least 48 h to a level where the ^{68}Ge activity could be indirectly detected as a decay product. All the eluates were measured under the following conditions: constant geometry using 1.5 ml, placed at a distance of 10 cm from the detector, and then all the decayed samples were counted to determine ^{68}Ge breakthrough with a measuring time of 1,000 sec per fraction and with a dead time of less than 10%. Due to the half-life of ^{68}Ge being much longer than that of ^{68}Ga, the activity of ^{68}Ga was theoretically calculated by using the secular equilibrium equation[26] (Equation 1):

$$A^t_{Ga} = A^0_{Ge} = (1\text{-}e^{(\ln 2/t_{1/2})t}) \quad \text{(Equation 1)}$$

where A^t_{Ga} and A^0_{Ge} are ^{68}Ga activity at time points t after elution and ^{68}Ge activity when co-eluted (i.e., at breakthrough), and $\lambda = \ln 2/t_{1/2}$

The percentage of ^{68}Ge-breakthrough in all the samples should be lower than 0.005%. (According to the generator specification and $^{68}GaCl_3$ monograph.)

Metal impurities measurement

The potential metal-ion impurities in the ^{68}Ga eluates were analyzed by inductively coupled plasma-mass spectrometry (ICP-MS) after the fractionated ^{68}Ga eluates had been allowed to decay for at least 48 h. The trace metals of interest were ^{57}Fe, ^{60}Ni, ^{63}Cu, ^{66}Zn, and ^{208}Pb measured as contaminants per elution and per fraction. The operating conditions for the ICP-MS during the measurements were as follows: plasma power, 1550 W; cool flow, 14 L/min; auxiliary flow, 0.8 L/min; nebulizer flow, 1.043 L/min; helium flow, 0 ml/min; sampling depth, 5 mm; spray chamber temp, 2.7 °C; and pump speed, 40 rpm.

To determine the contents of these metals, calibration standards containing these elements in the following concentration were prepared to obtain a concentration series for the calibration curve: 1, 10, 50, and 100 ppb. The generator eluent was diluted by a factor of 5 with 0.05 M HCl. The 0.05 M HCl was further measured as the blank sample.

Results and Discussion

Generator elution and elution yield

At 21 months after its last calibration date, the GMP-certified ITM ^{68}Ge/^{68}Ga generator contained 10.643 mCi of ^{68}Ga. The elution yield of ^{68}Ga was 35.2 ± 8.1%; n = 5 (decay corrected), ranging from 28.6% to 44.3%. The elution yield decreased with a linear trend in a similar pattern to in a previous report (R2 = 0.957)[27] over the course of the study. The majority of the ^{68}Ga activity was found in fractions 2 to 4. The elution profiles of each eluate are shown in Fig 1. Slightly different elution profiles were observed with the activity eluted in fractions 2–3 compared to in fractions 2–4 at the beginning time of the generator operation.

^{68}Ge breakthrough measurement

^{68}Ge breakthrough is expressed as a percentage of ^{68}Ge activity on the elution day relative to ^{68}Ga activity at calibration time. In this study, ^{68}Ge breakthrough from the ITM ^{68}Ge/^{68}Ga generator could not be detected as the minimal sensitivity of the HPGe probe was 10-5%. However, a previous report by Chakravarty et al mentioned that the ^{68}Ge breakthrough of a SiO_2-based ^{68}Ge/^{68}Ga generator was always <10^{-3}% over the period of 1 year.[27]

^{68}Ge was strongly absorbed on the pyrogallol-formaldehyde resin column. The breakthrough of ^{68}Ge in all the samples was below the detectable level over the extended periods of generator usage (lower than 0.005% according to the generator specification and $^{68}GaCl_3$ monograph). According to the recommendation of a monograph of the European Pharmacopeia, the limitation for ^{68}Ge breakthrough could be high as >100 times the safety level for patients.[28] The decreased percentage ^{68}Ge breakthrough (down to 0.0012%) showed the beneficial characteristics of the ITM generator, which could be extrapolated to an overall decrease in radiolysis.[29] Therefore, the level of ^{68}Ge breakthrough from the ITM ^{68}Ge/^{68}Ga generator after its recommended shelf-life was considered acceptable for both basic research as well as animal imaging research.

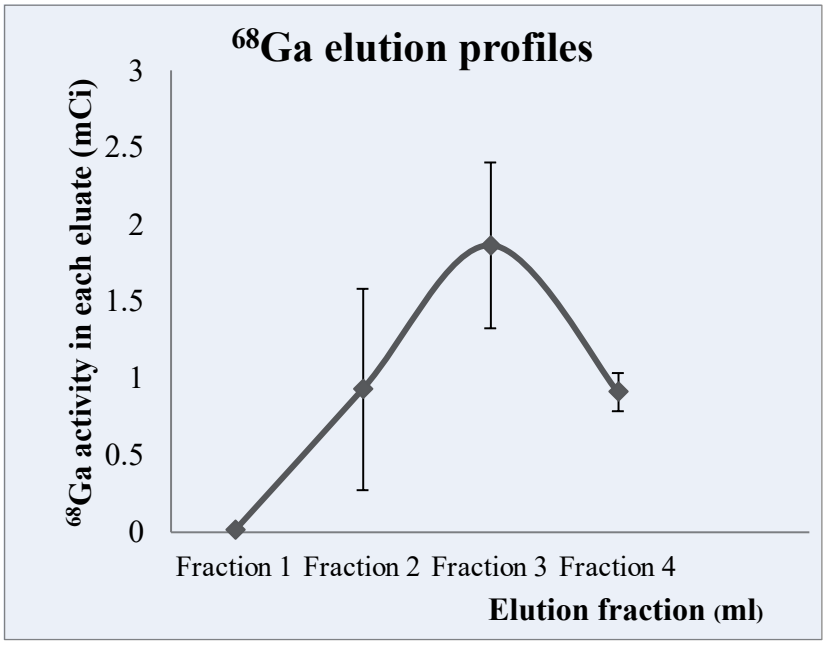

Fig 1. ^{68}Ga elution profiles of a 21-month-old ITM ^{68}Ge/^{68}Ga generator after its recommended shelf-life.

Metal impurities

The common chemical impurities of concern in ^{68}Ga elution are the metallic ions Fe, Zn, Pb, Ni, and Cu. These metal impurities are generally expressed in mg/l (ppm). The average amounts of the metallic ions Fe, Zn, Pb, Ni, and Cu found in this study were 18.60, 9.86, 2.42, 0.52, and 0.47 µg/GBq, respectively. The analysis results for the metal impurities are shown in Table 2. Although the excess amount of Fe^{3+} (approximately 8 µg/GBq) in the eluent from the over-lifespan ITM ^{68}Ge/^{68}Ga generator could potentially compete with ^{68}Ga during complex formation[30,31] to reduce the radiochemical yield (RCY), the calculated radioactivity of the final product here was more than 0.3 mCi (1.1 MBq), which was still enough for use in animal experiments and studies.[32] Moreover, the Fe^{3+} residue can be removed in a purification step by reversed-phase Sep-Pak (C-18). Therefore, the radiochemical purity (RCP) of the final product can be obtained in the same quality as required for use in clinical practice.

Other metallic ions, such as Pb, Cu, and Ni, were found in amounts of less than 10 µg/GBq according to the eluate specification. Since the ITM generator employed a modified dodecyl-3,4,5-trihydroxybenzoate hydrophobically bound to an octadecyl-modified silica resin, which allows its authorized marketing in Europe as a pharmaceutical-grade generator[29], the other metallic contents of the eluate were found to be extremely low.

TABLE 2. Analysis of the metal impurities in the ^{68}Ga eluate using inductively coupled plasma-mass spectrometry (ICP-MS)

	^{57}Fe (ppm)	^{60}Ni (ppm)	^{63}Cu (ppm)	^{66}Zn (ppm)	^{208}Pb (ppm)
1	5.893	0.198	0.027	4.173	1.274
	4.463	0.070	0.096	7.920	1.944
	4.390	0.060	0.086	0.969	0.206
	4.294	0.064	0.057	1.015	0.434
2	5.682	0.189	0.234	13.343	0.403
	4.955	0.111	0.130	1.159	0.369
	4.627	0.085	0.109	0.996	0.328
	4.326	0.068	0.093	0.941	0.465
3	4.435	0.167	0.114	2.910	0.258
	4.413	0.076	0.082	1.042	0.245
	4.213	0.072	0.118	0.973	0.332
	4.227	0.123	0.114	1.246	0.247
4	4.525	0.177	0.145	1.622	0.759
	4.540	0.152	0.107	1.138	0.326
	3.932	0.148	0.114	1.115	0.221
	4.347	0.123	0.133	0.990	0.180
5	5.415	0.276	0.129	3.184	0.251
	5.850	0.192	0.174	2.286	3.679
	4.261	0.124	0.168	1.090	0.074
	4.178	0.136	0.114	1.207	0.106

CONCLUSION

The manufacturer's recommended lifespan for the pyrogallol-formaldehyde resin-based $^{68}Ge/^{68}Ga$ generator produced by ITM GmbH Germany is 12 months or 250 elutions; however, it still provides an adequate amount of ^{68}Ga eluent that could be effectively used to prepare ^{68}Ga-radiopharmaceuticals for basic research after 21 months, long past its recommended shelf-life. The ITM $^{68}Ge/^{68}Ga$ generator demonstrated consistent and reliable ^{68}Ga elution profiles with the absence of ^{68}Ge breakthrough in the eluant samples as verified by the manufacturer. Even though free Fe ions were found in an excess amount of 18 μg/GBq, which can affect the RCY, the radioactivity in the final product was still enough for animal experiments and studies. The other metallic ions Zn, Pb, Ni, and Cu, except Fe, were all less than 10 μg/GBq as indicated in the manufacturer's specification. Therefore, the ITM $^{68}Ge/^{68}Ga$ generator has enhanced use beyond its recommended shelf-life to prepare ^{68}Ga radiopharmaceuticals that are considered safe and suitable for further animal experiments and studies.

ACKNOWLEDGEMENTS

The dissertation was financially supported under Grant no. DO2875 of Liam Tuntawiroon, Siriraj Foundation.

Conflict of interest: All authors declare that they have no conflicts of interest.

REFERENCES

1. Sarko D, Eisenhut M, Haberkorn U, Mier W. Bifunctional chelators in the design and application of radiopharmaceuticals for oncological diseases. Curr Med Chem. 2012;19(17):2667-88.
2. Schuhmacher J, Zhang H, Doll J, Mäcke HR, Matys R, Hauser H, et al. GRP receptor-targeted PET of a rat pancreas carcinoma xenograft in nude mice with a 68Ga-labeled bombesin(6-14) analog. J Nucl Med. 2005;46(4):691-9.
3. Jeong JM, Hong MK, Chang YS, Lee Y-S, Kim YJ, Cheon GJ, et al. Preparation of a promising angiogenesis PET imaging agent: 68Ga-labeled c(RGDyK)-isothiocyanatobenzyl-1,4,7-triazacyclononane-1,4,7-triacetic acid and feasibility studies in mice. J Nucl Med. 2008;49(5):830.
4. Mier W, Hoffend J, Krämer S, Schuhmacher J, Hull WE, Eisenhut M, et al. Conjugation of DOTA Using Isolated Phenolic Active Esters: The Labeling and Biodistribution of Albumin as Blood Pool Marker. Bioconjug Chem. 2005;16(1):237-40.
5. Hoffend J, Mier W, Schuhmacher J, Schmidt K, Dimitrakopoulou-Strauss A, Strauss LG, et al. Gallium-68-DOTA-albumin as a PET blood-pool marker: experimental evaluation in vivo. Nucl Med Biol. 2005;32(3):287-92.
6. Baum RP, Prasad V, Müller D, Schuchardt C, Orlova A, Wennborg A, et al. Molecular imaging of HER2-expressing malignant tumors in breast cancer patients using synthetic 111In- or 68Ga-labeled affibody molecules. J Nucl Med. 2010;51(6):892-7.
7. Werner RA, Bluemel C, Allen-Auerbach MS, Higuchi T, Herrmann K. 68Gallium- and 90Yttrium-/ 177Lutetium: "theranostic twins" for diagnosis and treatment of NETs. Ann Nucl Med. 2015;29(1):1-7.
8. Eiber M, Weirich G, Holzapfel K, Souvatzoglou M, Haller B, Rauscher I, et al. Simultaneous (68)Ga-PSMA HBED-CC PET/MRI Improves the Localization of Primary Prostate Cancer. Eur Urol. 2016;70(5):829-36.
9. Prasad V, Steffen IG, Diederichs G, Makowski MR, Wust P, Brenner W. Biodistribution of [(68)Ga]PSMA-HBED-CC in Patients with Prostate Cancer: Characterization of Uptake in Normal Organs and Tumour Lesions. Mol Imaging Biol. 2016;18(3):428-36.
10. Cytawa W, Seitz AK, Kircher S, Fukushima K, Tran-Gia J, Schirbel A, et al. (68)Ga-PSMA I&T PET/CT for primary staging of prostate cancer. Eur J Nucl Med Mol Imaging. 2020;47(1):168-77.
11. Derlin T, Weiberg D, von Klot C, Wester HJ, Henkenberens C, Ross TL, et al. (68)Ga-PSMA I&T PET/CT for assessment of prostate cancer: evaluation of image quality after forced diuresis and delayed imaging. Eur Radiol. 2016;26(12):4345-53.
12. Antunes P, Ginj M, Zhang H, Waser B, Baum RP, Reubi JC, et al. Are radiogallium-labelled DOTA-conjugated somatostatin analogues superior to those labelled with other radiometals? Eur J Nucl Med Mol Imaging. 2007;34(7):982-93.
13. Reubi JC, Schär JC, Waser B, Wenger S, Heppeler A, Schmitt JS, et al. Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med. 2000;27(3):273-82.
14. Hofmann M, Maecke H, Börner R, Weckesser E, Schöffski P, Oei L, et al. Biokinetics and imaging with the somatostatin receptor PET radioligand (68)Ga-DOTATOC: preliminary data. Eur J Nucl Med. 2001;28(12):1751-7.
15. Kowalski J, Henze M, Schuhmacher J, Mäcke HR, Hofmann M, Haberkorn U. Evaluation of positron emission tomography imaging using [68Ga]-DOTA-D Phe(1)-Tyr(3)-Octreotide in comparison to [111In]-DTPAOC SPECT. First results in patients with neuroendocrine tumors. Mol Imaging Biol. 2003;5(1):42-8.
16. Wild D, Mäcke HR, Waser B, Reubi JC, Ginj M, Rasch H, et al. 68Ga-DOTANOC: a first compound for PET imaging with high affinity for somatostatin receptor subtypes 2 and 5. Eur J Nucl Med Mol Imaging. 2005;32(6):724.
17. Wild D, Schmitt JS, Ginj M, Mäcke HR, Bernard BF, Krenning E, et al. DOTA-NOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 for labelling with various radiometals. Eur J Nucl Med Mol Imaging. 2003;30(10):1338-47.
18. Kratochwil C, Flechsig P, Lindner T, Abderrahim L, Altmann A, Mier W, et al. (68)Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. J Nucl Med. 2019;60(6):801-5.
19. Spreckelmeyer S, Balzer M, Poetzsch S, Brenner W. Fully-automated production of [68Ga]Ga-FAPI-46 for clinical application. EJNMMI Radiopharmacy and Chemistry. 2020;5(1):31.
20. Lin M, Waligorski GJ, Lepera CG. Production of curie quantities of (68)Ga with a medical cyclotron via the (68)Zn(p,n)(68)Ga reaction. Appl Radiat Isot. 2018;133:1-3.
21. Rodnick ME, Sollert C, Stark D, Clark M, Katsifis A, Hockley BG, et al. Cyclotron-based production of (68)Ga, [(68)Ga]

GaCl(3), and [(68)Ga]Ga-PSMA-11 from a liquid target. EJNMMI Radiopharm Chem. 2020;5(1):25.
22. Velikyan I. 68Ga-Based radiopharmaceuticals: production and application relationship. Molecules. 2015;20(7):12913-43.
23. Romero E, Martínez A, Oteo M, Ibañez M, Santos M, Morcillo MÁ. Development and long-term evaluation of a new 68Ge/68Ga generator based on nano-SnO2 for PET imaging. Sci Rep. 2020;10(1):12756.
24. https://rusatom-energy.com/media/rosatom-news/rosatom-facility-gains-record-revenues-from-stable-isotopes-sales/
25. M. Harfensteller, R. Henkelmann, J. Moreno, O. Leib, T. August, O. Buck, T. Nikula. Gallium-68 a candidate for use in clinical routine. February 3, 2010, CERN.
26. Eppard E, Loktionova NS, Rösch F. Quantitative online isolation of 68Ge from 68Ge/68Ga generator eluates for purification and immediate quality control of breakthrough. Appl Radiat Isot 2013;82:45-48.
27. Chakravarty R, Chakraborty S, Ram R, Vatsa R, Bhusari P, Shukla J, et al. Detailed evaluation of different (68)Ge/(68)Ga generators: an attempt toward achieving efficient (68)Ga radiopharmacy. J Labelled Comp Radiopharm. 2016;59(3):87-94.
28. Uğur A, Yaylali O, Yüksel D. Examination of metallic impurities of 68Ge/68Ga generators used for radioactive labeling of peptides in clinical PET applications. Nucl Med Commun. 2021;42(1):81-85.
29. Amor-Coarasa A, Kelly JM, Gruca M, Nikolopoulou A, Vallabhajosula S, Babich JW. Continuation of comprehensive quality control of the itG 68Ge/68Ga generator and production of 68Ga-DOTATOC and 68Ga-PSMA-HBED-CC for clinical research studies. Nucl Med Biol. 2017;53:37-39.
30. Asti M, De Pietri G, Fraternali A, Grassi E, Sghedoni R, Fioroni F, et al. Validation of 68Ge/68Ga generator processing by chemical purification for routine clinical application of 68Ga-DOTATOC. Nucl Med Biol. 2008;35:721-4.
31. Amor-Coarasa A, Milera A, Carvajal D, Gulec S, McGoron AJ. Lyophilized Kit for the Preparation of the PET Perfusion Agent [(68)Ga]-MAA. Int J Mol Imaging. 2014;2014:269365.
32. Lückerath K, Stuparu AD, Wei L, Kim W, Radu CG, Mona CE, et al. Detection Threshold and Reproducibility of 68Ga-PSMA11 PET/CT in a Mouse Model of Prostate Cancer. J Nucl Med. 2018;59(9):1392-7.