JRMP Journal of Radiopharmaceuticals and Molecular Probes Vol. 5, No.1, 2019
J Radiopharm Mol Prob 2019;5(1): 3-10
ISSN 2384-1583(Print) / ISSN 2508-3848(Online)

ORIGINAL ARTICLE

https://doi.org/10.22643/ JRMP.2019.5.1.3

The development of a portable MO_4^- (M = ^{188}Re or ^{99m}Tc) concentration device for extending the lifetime of RI generators

Kang-Hyuk Choi[1], Ul Jae Park[1], Jong Bum Kim[1], Beom-Su Jang[2]

[1] Neutron and Radioisotope Application Research Division, Korea Atomic Energy Research Institute, 111 Daedeok-Daero 989 beon-gil, Yuseong Gu, Daejeon, Korea.
[2] Research Division for Biotechnology, Korea Atomic Energy Research Institute, 29 Geumgu-gil, Jeongeup-Si, Jeollabuk-Do, Korea.

ABSTRACT

The activities per volume of ^{188}Re and ^{99m}Tc from their generators are dependent on the specific activity of their mother nuclides ^{188}W and ^{99}Mo respectively. After a particular lapse of time, the eluted RI activity is exponentially reduced and thus cannot satisfy the needs of clinical application. The purpose of this study is to develop a ^{188}Re and ^{99m}Tc concentration device with a compact size that can extend the period of use as well as conveniently concentrate the RI. We designed the concentration module by including two-different check valves that do not required any manual on-off operations. In these concentration process, cation exchange resin embedded with Ag and anion exchange resins were used. After completing the concentrating step, the recovering yield was identified to be more than 93% for ^{188}Re generators and 88% for ^{99m}Tc generators. Moreover, all these procedures were done within 5 min.

Key Word: RI concentration, Concentration device, Technetium-99m (Tc-99m), Rhenium-188 (Re-188), Validity period,

Introduction

Radioisotope (RI) generator contains an ion chromatography system in which mother nuclides are attached onto adsorbents, such as Al_2O_3, and the daughter nuclides are eluted from the generator. The most widely used generator throughout the world is the ^{99}Mo/^{99m}Tc generator. The clinical use of ^{99m}Tc has been mainly for the diagnosis of cancers in bone, brain, heart and other organs. Because of the proper half-life (6 h) and diagnostic imaging capacity of ^{99m}Tc which comprises 70% of all medical isotopes, ^{99m}Tc is the daughter nuclide of ^{99}Mo that can be obtained either by thermal neutron-irradiation of pure ^{98}Mo or from fission product of Uranium-235 in a nuclear reactor. In general, most ^{99m}Tc generators are prepared by using fission-^{99}Mo since it doesn't require large amount of adsorbent to attach ^{99}Mo with high specificity.

The longer the generator is used, the smaller amount of the desired radioisotope is attained due to the half-life of mother nuclide. Even though the permissible period of a ^{99}Mo/^{99m}Tc generator application is two weeks, but the actual lifetime of the generator is less than a week. At the second week, the activity of $^{99m}TcO_4^-$ is approximately a quarter of that at the first week. Therefore, increasing the concentration of $^{99m}TcO_4^-$ would be useful to extend the lifetime of the ^{99}Mo/^{99m}Tc generators.

Received: June 17, 2019 / Revised: July 2, 2018 / Accepted: July 9, 2018

Correspnding author : Dr. Kang-Hyuk Choi, Radioisotope Research Division, Korea Atomic Energy Research Institute, 111 Daedeok-Daero 989 beon-gil, Yuseong Gu, Daejeon, Korea.
E-mail: khchoi@kaeri.re.kr Tel: +82-42-868-4643

Copyright©2019 The Korean Society of Radiopharmaceuticals and Molecular Probes

Recently, many researchers have been focused on ^{188}Re in that it has similar chemical and physical characteristics to ^{99m}Tc. ^{188}Re is one of the prominent therapeutic radioisotopes for various medical applications such as bone pain palliation and synovectomy. Additionally, ^{188}Re is also an attractive agent for simultaneous diagnosis and therapy of cancer, as it emits both beta (β_{max} = 2.12 MeV) and gamma (γ = 155 KeV) rays with proper half-life (16.9 h). ^{188}Re is obtained by the ^{188}W/^{188}Re generator that contains an alumina adsorbent embedded ^{188}W ($T_{1/2}$ = 69.4 days). ^{188}Re, a daughter nuclide of ^{188}W, is produced by a double n-γ reaction from ^{186}W. Since ^{188}W has low specific activity, relatively large column and therefore large eluate volumes are required to get a highly purified ^{188}Re. Therefore, it is required to be more enriched in order to extend the permissible period of ^{188}W/^{188}Re generator. Recently, some ^{188}W/^{188}Re generators are commercially available for research and medical purposes. To label reasonable amount of ^{188}Re with cold-kit, large volume of eluate was needed and its labeling yield was not satisfactory. To solve this problem, high performance ^{188}W/^{188}Re generator with a small column was established by using newly developed adsorbent (7).

Numerous studies have focused on the concentration of $^{99m}TcO_4^-$ and $^{188}ReO_4^-$ to improve the labeling yield. For example, it has been reported simple concentration system of $^{99m}TcO_4^-$ and $^{188}ReO_4^-$ with post-elution tandem cation/anion exchange column (11, 1, 5, 6). Chattopadhyayet al. (2, 3) showed a new concept for concentrating ^{99m}Tc from (n, γ)^{99}Mo by using strong ion exchange resin (Dowex 1X8) and AgCl column. Mushtaq et al. (10) reported that acetone was a good eluent for ^{99m}Tc and ^{188}Re generators and it can be easily vaporized to form concentrated RI. Mansur et al. (9) reported the concentration of ^{99m}Tc and ^{188}Re using silver cation exchange and alumina column after primary elution. Luo et al. (8) reported the automatic concentration apparatus for extending the permissible period of ^{188}Re generator. Despite substantial concentration systems have been developed to extend lifetime of radioisotopes, it still remains to be investigated portable devices for convenient concentration.

We describe herein the development of the RI concentration system with ion exchange column to get high activity of ^{188}Re and ^{99m}Tc per unit volume. We also investigated the concentration process with this device and animal studies demonstrating efficacy of the concentrated radioisotopes.

Materials and methods

1.1. Materials

All chemicals and reagents used were analytical grade (AR) purchased from Sigma-Aldrich Co. and most are of GR/AR grade. The parts, fittings and check valves, of device were obtained from Upchurch Scientific®. Cation exchange resins (AG 50W-X8, AG50W-X12) were obtained from BioRad. An anion exchange column (Sep-Pak Light QMA) and IC-Ag column were purchased from Waters. Sodium pertechnetate ([^{99m}Tc] $NaTcO_4$) was obtained from a ^{99}Mo/^{99m}Tc generator produced by Sam Young Unitech,Co. Sodium perrhenate ([^{188}Re] $NaReO_4$) was used from the ^{188}W/^{188}Re generators developed at KAERI. The endotoxin test vial was purchased from ENDOSAFE®. Radioactivities were measured using an ionizing chamber (Atomlab 200, Biodex), radionuclide purity was checked by a HPGe γ-ray detector, and radiolabeling yield was determined by an ITLC scanner. The inveon SPECT/CT system (Siemens Medical Solutions, Knoxville, TN, USA) was used for the anatomical and molecular imaging of mice.

1.2. Preparation of Ag-cation exchange column

10 g of cation exchange resins (AG 50W-X8, AG50W-X12) were washed with 100 ml of deionized water and 0.1 M HNO_3 in sequence. An empty SPE tube was filled with 1-1.5 g of resin and then 0.5 N $AgNO_3$ in 0.1 M HNO_3 solution was passed through the SPE tube at a flow rate of 2 ml/min. After filling Ag ions into the SPE tube, the total adsorbed amounts were 6 ml and 4 ml of 0.5 M $AgNO_3$ when using AG50W-X12 and AG 50W-X8 resin, respectively. These adsorption capacities were calculated using the relation given below.

Adsorption amount of Ag = 3.0 mmol/1g of wet AG50W-X12 resin

Adsorption amount of Ag = 2.25mmol/1g of wet AG50W-X8 resin

1.3. Shield design and analysis

For calculating the radioactivity shield, simulation geometries were constituted as shown in Fig.1. For the beta source (^{188}Re), the shield was made in the order of Teflon and lead. The diameter of the shield is 5.03 cm and the inner constitutions were 1.3 × 0.4 cm RI source in the middle of a 1.91 cm length of air, X cm of Teflon, and Y cm of lead (X + Y = 1.56) shields. For ^{99m}Tc, all the geometries were the same, only difference of lead and Teflon sequence. Calculation was done using MCNPx 2.6 and dose conversion factor was used in ICRP21-1971.

1.4. Preparation of portable concentration device

A rough outline of the concentration system of the radioisotopes is as follows (Fig. 2). Two-different check valves were connected to a T-connector to protect the backward flow. One was opened with a cracking pressure of 1 psi and the other with 15 psi. When a vacuum vial was connected to the retrieval region in the same

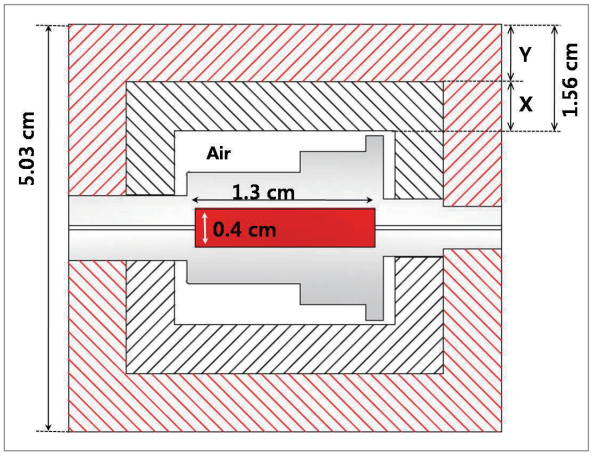

Figure 1. Geometry for calculating the radiation shield
Total length is 5.03 cm and shielding region is 1.56 cm. RI source core is 0.4 x 1.3 cm cylinder form. (Shielding of ^{99m}Tc : X= lead, Y= Teflon, Shielding of ^{188}Re : X = Teflon, Y =lead)

constitution, only the check valve (B) was opened, and RI (^{188}Re or ^{99m}Tc) was adsorbed into the anion exchange resin. Another empty vial was changed with a vacuum vial and 1ml of saline was allowed to flow through the check valve (A). Concentrated RI was collected in an empty vial. There were two different concentration systems. I-type and L-type. These were used same concept as shown in Fig. 3. Each type was also divided by two categories, one for ^{188}Re and the other for ^{99m}Tc.

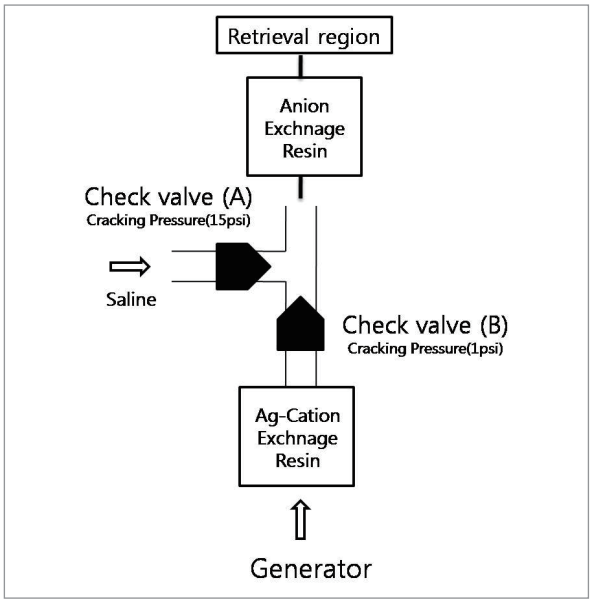

Figure 2. The arrangement of components for RI concentration system

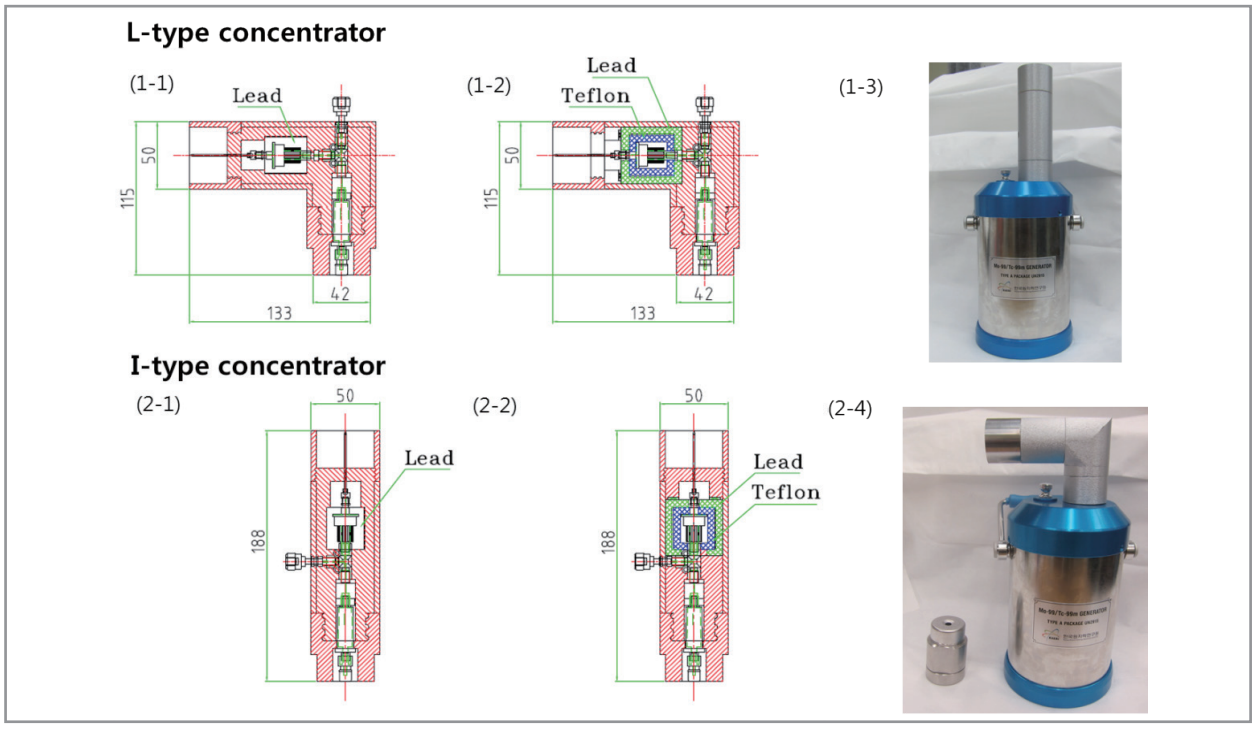

Figure 3. RI concentration systems for ^{99m}Tc and ^{188}Re (L-type : (1-1) ^{99m}Tc concentration system shielding with lead, (1-2) ^{188}Re concentration system shielding with Teflon and lead in order, (1-3) The profile of I type concentration system connected with a generator, I-type: (2-1) ^{99m}Tc concentration system shielding with lead, (2-2) ^{188}Re concentration system shielding with Teflon and lead in order, (2-3) The profile of I type concentration system connected with a generator)

1.5. Quality Analysis

With the concentrated ^{99m}Tc and ^{188}Re, quality control was done on the basis of a 'standard and test method' regulated by the KFDA (Korea Food & Drug Administration) and KAERI regulations. To determine the radiochemical purity of $^{188}ReO_4^-$ and $^{99m}TcO_4^-$, the samples were chromatographed on ITLC-SG using 75% MeOH and HPLC. The metal ions content of the RI solution was checked using a spot test and ICP-AES. In addition, clarity, pH, and endotoxin tests were performed.

1.6. The preparation of labeled compound

After concentration was performed, 1 ml of $^{99m}TcO_4^-$ containing 740 MBq (20 mCi) was added to the MDP kit vial, gently mixed for 2 min, and allowed to stand for 10 min at room temperature. One drop of labeled compound was placed over a 15 cm SG/ITLC strip at a position 2 cm from the lower end. The strip was developed in 75% methanol, dried in air and scanned with TLC scanner.

1.7. Animal study

37 MBq of ^{99m}Tc-MDP was intravenously administrated to ICR mouse. The micro SPECT image was acquired at 3 hrs after injection. The mice were scanned with an Inveon SPECT/CT system, equipped with a 1-pinhole mouse high-sensitivity collimator.

Results and Discussion

The principle of the concentration device to obtain a high specific activity of MO_4^- (M = ^{188}Re or ^{99m}Tc) and to extend the lifetime of the generator was based on

the previous report by Singh et al. (11), Guhlke et al. (5) and Knapp et al. (6). The technological principle of concentrating ^{99m}Tc and ^{188}Re are as follows (Fig. 4). First, by passing 5 ml of saline solution containing radioisotopes through a cation exchange resin embedding Ag ion and the salt within the solution was removed. In this mechanism, Na^+ from a saline was exchanged with Ag^+ and adsorbed cation exchange resin, and then Cl^- ions reacted with Ag^+ to form AgCl precipitation. At this point, the radioisotope ($^{188}ReO_4^-$ or $^{99m}TcO_4^-$) was in the state of dissolving in pure water. While an RI solution was passed through an anion exchange resin, where only RI was attached to the anion exchange resin (Sep-Pak Light QMA) since there were no other interfering ions. Then, $^{188}ReO_4^-$or $^{99m}TcO_4^-$ attached to the anion exchange resin can be easily extracted by passing 0.5-1 ml of the saline solution because Na^+ and Cl^- in the saline interfere with the ionic bond between isotope and resin. Using the above method, total volume of RI solution can be reduced from 5-10 ml to 0.5-1 ml.

This principle was used to develop a compact-sized enhancing system.

To determine the desalination capacity in 0.9% NaCl solution, Lab made Ag-cation exchange resin was comparatively studied with commercially available IC-Ag Sep-Pak. The titration point was checked when the AgCl precipitation formed within the 0.1 M $AgNO_3$ solution. IC-Ag Seppak, AG50W-X12 (1 g) containing maximum Ag^+ (3 mmol), and AG 50W-X8 (1 g) with Ag^+ (2.25 mmol) can eliminate 14, 15 and 11 ml of saline, respectively. Although AG 50W-C12 and IC-Ag have good characteristics in terms of desalting effect, they have a drawback in that internal pressure within a column and T-connector increases when saline was allowed to flow. Thus, it is difficult to get a concentrated RI, and even takes a long time when a vacuum vial was used to extract the RI solution. For this reason, AG 50W-X8 is preferable as the desalting column material. The shelf stability lasts for one month in a dark bottle and lasts for 2 month in a refrigerator. Sep-Pak Light QMA was used to adsorb $^{188}ReO_4^-$ and $^{99m}TcO_4^-$, and can be recycled at least five times just washing with 1 ml of pure water.

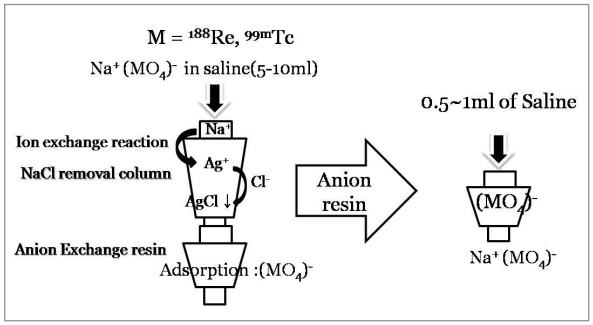

Figure 4. Basic principle for RI concentration

^{188}Re simultaneously emits gamma and beta rays, and primarily emits beta rays with maximum beta energy of 2.12 MeV. Lead reduces Bremsstrahlung X-ray from beta ray as well as gamma ray and Teflon reduce the generation of X-ray. For the calculation of the shielding thickness, the beta energy spectrum of ^{188}Re was referred to RSICC DATA LIBRARY DLC-172 (4). These data have been designed to address the need for medical, environmental, and occupational radiation protection. To calculate the dose rate of the outer side of a ^{188}Re concentrator, 'F5 tally' and 'Fluence to Dose conversion factor from ICRP21-1971' were used for computing the dose rate with the variable length of the inner (Teflon) and outer shields (Lead). The computing results of MCNPx revealed the units of (Sv/h)/(particles/cm^2-sec) and converted into the dose rate per hour. With assumption of a maximum amount used (50 mCi for ^{188}Re or ^{99m}Tc), the computed results of the surface dose rates are shown in Table 1 and 2. All these data satisfy the regulations of RI-package and transportation (activity at a 10 cm distance from the surface: below 2 mSv/h).

In this portable concentration device, a key characteristic is that two separate check valves with different opening pressures were used instead of a 3-way valve. The cracking pressure of check valve (B) is lower than the other one (A), as Fig. 2. It is the reason why two resins in the middle of passing through the retrieval region from generator to concentrator induce the high internal pressure.

Table 1. The surface dose rates of 50 mCi ^{99m}Tc for different X and Y value

X cm (Lead)	Y cm (Teflon)	Surface (Sv/h)	10 cm from surface (Sv/h)
0.05	1.51	1.15E-12	4.28E-14
0.5	1.06	1.46E-12	5.85E-14
1.0	0.56	2.22E-12	8.83E-13
1.5	0.06	4.69E-12	1.85E-13

Table 2. The surface dose rates of 50 mCi ^{188}Re for different X and Y value

X cm (Lead)	Y cm (Teflon)	Surface (Sv/h)	10 cm from surface (Sv/h)
0.05	1.51	2.36E-3	6.53E-5
0.5	1.06	3.27E-3	8.90E-5
1.0	0.56	5.0E-3	1.35E-4
1.5	0.06	1.05E-2	2.82E-4

Generally, when the 3-way valve system is used, the valve opening and closing operations must be done manually or automatic with electronic device. But, this present concentration device do not required any such manual or automatic operations, making it more convenient to use. Moreover, we constructed two different types of system (I-type and L-type) considering the user convenience. The I-type is recommended for usage in spacious places equipped with a large shield, and the L-type for the confined places. The lengths of I and L types are 16.5 cm and 9.5 cm, respectively. The concentration steps of ^{99m}Tc and ^{188}Re were performed using the aforementioned technical principle with the equipped concentration device. First, the concentration device was placed on the generator and saline vial and vacuum vial were orderly placed at the specified location. 5 ml of saline in the vial was passed through a vacuum vial. After the vacuum vial was exchanged for another empty vial, 1 ml of saline was injected into the side inlet part. During this process, almost all of the eluted RI was conveniently recovered. The average recovery yield of ^{99m}Tc was 87.6%. In the same manner above, ^{188}Re was also concentrated, and the average yield was 92.5%. Table 3 summarizes the results of concentration of ^{99m}Tc and Table 4 represents the results for ^{188}Re. In this study, the anion exchange column (QMA Light) has been repeatedly used for the concentration process up to 5 times by simply washing with 1ml of pure water. The cation column is disposable and was easily detached by simply twisting the lower position of the concentrator.

The resultant concentrated ^{99m}Tc and ^{188}Re showed a clear solution with pH 6-7 and were checked for radiochemical and nuclide purity using ITLC/HPLC and MCA, respectively. The radiochemical purity was consistently over 99%. Metal impurities were also checked using a colorimetric spot test and ICP AES. No metals were identified, except trace of silver ions (lower than 0.1 ppm) were appeared. As a result of an endotoxin test, all of the concentrated RI was revealed as negative. All processes were compared with pre-concentrated RI, and we found that the results were consistent with as the KFDA regulations, even concentrated RI showed a better quality.

The animal studies were performed using approved protocols under KAERI Institutional Animal Care and Use Committee. During the concentration process, ^{99m}Tc

Table 3. Concentration of ^{99m}Tc form expired generator using a concentration device

X cm (Lead)	1st	2nd	3rd	4th	5th	6th	7th	8th
^{99m}Tc, 5 mL (MBq)	573	851	659	370	175	877	755	417
Concentration, 1mL (MBq)	488	740	577	318	159	762	652	379
Recovery Yield	85.2%	86.9%	87.6%	86.0%	90.9%	86.9%	86.4%	90.9%
Average Yield	87.6% (after 5 fold concentration)							

Table 4. Concentration of ^{188}Re from a generator after 1 year using a concentration device

	1	2	3	4	5
^{188}Re, 5 mL (MBq)	363	339	315	333	307
Concentration, 1mL (MBq)	327	315	292	308	289
Recovery Yield	90.1%	92.9%	92.7%	92.5%	94.1%
Average Yield	92.5% (after 5 fold concentration)				

generator produced by Sam Young Unictech Co. and an RI concentrator were comparatively studied. Single photon emission computed tomography (SPECT) imaging study of ^{99m}Tc-MDP using ^{99m}Tc obtained from above concentration process was carried out in normal ICR mice. The mice were anesthetized with 2% isoflurane in 100% oxygen (prone positioned in the cradle). SPECT images were acquired with Inveon Multimodality (SIEMENS, Germany), at 3 hrs after intravenous administration of radiotracer. The images were obtained with a multipinhole collimator using a 10% window centered over the 140 KeV photopeak. The CT scans were used for anatomical reference. For the CT scans, the X-ray sources were used at 300 μA and 60 kV. The number of acquired projections was 180 (one shot per projection) for 15 min and CT resolution was 200 μm. The SPECT and CT images were reconstructed and resultant images are shown in Fig 5. A large amount of ^{99m}Tc-MDP was accumulated in the backbone, especially in the cartilage and cavity, and a small amount was revealed in liver area. These images pattern are not distinguishably different from the ^{99m}Tc-MDP with $^{99m}TcO_4^-$ from the commercial ^{99m}Tc generator (Sam Young Unitech Co, Korea).

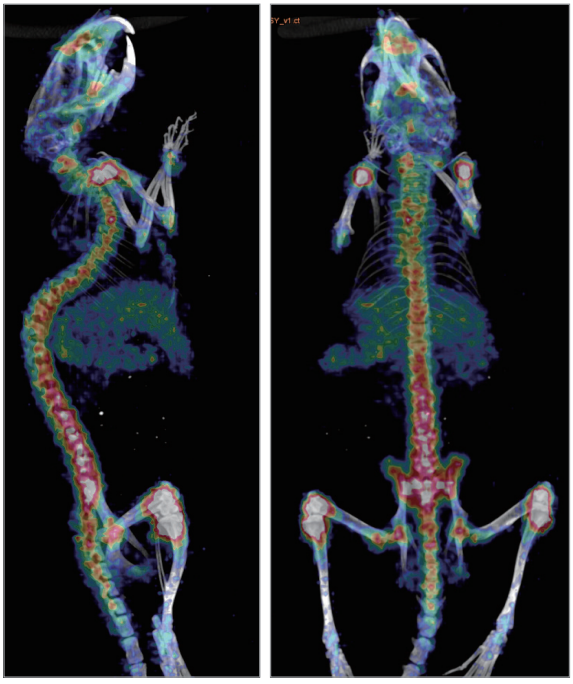

Figure 5. Animal SPECT-CT image profiles of ^{99m}Tc-MDP using with $^{99m}TcO_4^-$ from the concentrator in ICR mice at 3 hrs after i.v. administration.

Conclusion

Since 2007, there have often been cases in which the world's major research reactors for producing ^{99}Mo, the mother nuclide of ^{99m}Tc, have stopped functioning due to deterioration. In this situation, there have been major

setbacks in supply and demand within and outside the country, and cases have emerged in which hospital emergency patients cannot receive nuclear imaging examinations.

To alleviate this state which may occur in the near future, we studied and developed a RI concentration device for extending the lifetime of generators. According to the description of the results disclosed above, a portable RI concentration device will offer a new paradigm for the re-usage of expired generators and partially resolve the international problem of radioisotope supply and demand. In addition, it can aid in providing hospital care during emergency times when the isotope supply is low.

Acknowledgment

This study was supported by Nuclear R&D program of MSIP (Ministry of Science, ICT and Future Planning) in KOREA and KAERI (Korea Atomic Energy Research Institute) R&D program.

Reference

1. Blower PJ, Extending the life of a ^{99m}Tc generator: a simple and convenient method for concentrating generator eluate for clinical use. *Nucl Med Commun* 1993;14: 995-997.
2. Chattopadhyay S, Das MK, Sarkar PK, Sraswathy P, Ramamoorthy N, A novel ^{99m}Tc delivery system using (n, γ)^{99}Mo adsorbed on a large alumina column in tandem with Dowex-1 and AgCl columns. *Appl Radiat Isot* 2002;57:7-16.
3. Chattopadhyay S, Das MK, A novel technique for the effective concentration of ^{99m}Tc from a large alumina column loaded with low specific-activity (n, γ)-produced ^{99}Mo. *Appl Radiat Isot* 2008;66:1295-1299.
4. Eckerman KF, Westfal1 RJ, Ryman JC, Cristy M, NUCDECAY: Nuclear decay data for radiation dosimetry calculations for ICRP and MIRD. Radiation Safety Information Computational Center, *Oak Ridge National Laboratory* 1995: DLC-172
5. Guhlke S, Beets AL, Oetjen K, Mizadeh S, Biersack HJ, Knapp Jr. FF, Simple new method for effective concentration of ^{188}Re solutions from alumnina-based ^{188}W-^{188}Re generator. *J Nucl Med* 2000 ;41:1271-1278.
6. Knapp Jr. FF, Beets AL, MMirzadeh S, Guhlke S, Use of a new tandem cation/ anion exchange system with clinical-scale generators provides high specific volume solutions of technetium-99m and rehenium-188. 1998; IAEA-TECDOC 1029: 419-425.
7. Lee JS, Lee JS, Park UJ, Son KJ, Han HS, Development of a high performance ^{188}W/ ^{88}Re generator by using a synthetic alumina. *Appl Radiat Isot* 2009;67:1162-1166.
8. Luo TY, Lo AR, Hsieh BT, Lin WJ, A design for automatic preparation of highly concentrated ^{188}Re-perrhenate solutions. *Appl Radiat Isot* 2007;65: 21-25.
9. Mansur MS, Mushtaq A, Jehangir M, Concentration of ^{99m}Tc-pertechnetate and ^{188}Re-perrhenate. *Radiochim Acta* 2006;94:107-111
10. Mushtaq A, Preparation of high specific-volume solutions of technetium-99m and rhenium-188 *Appl Radiat Isot* 2003;58: 309-314
11. Singh J, Reghebi K, Lazarus CR, Clark SE, Callaham AP, Knapp Jr. FF, Blower PJ, Studies on the Preparation and isomeric composition of ^{186}Re and ^{188}Re-pentavalent rhenium dimercaptosuccinic acid complex. *Nucl Med Commmun* 1993;14:197-203.