Feasibility studies towards future self-sufficient supply of the $^{99}$Mo-$^{99m}$Tc isotopes with Japanese accelerators

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Abstract: In order to establish a self-sufficient supply of $^{99m}$Tc, we studied feasibilities to produce its parent nucleus, $^{99}$Mo, using Japanese accelerators. The daughter nucleus, $^{99m}$Tc, is indispensable for medical diagnosis. $^{99}$Mo has so far been imported from abroad, which is separated from fission products generated in nuclear reactors using enriched $^{235}$U fuel. We investigated $^{99m}$Tc production possibilities based on the following three scenarios: (1) $^{99}$Mo production by the (n, 2n) reaction by spallation neutrons at the J-PARC injector, LINAC; (2) $^{99}$Mo production by the (p, pn) reaction at $E_p = 50$–$80$ MeV proton at the RCNP cyclotron; (3) $^{99m}$Tc direct production with a $20$ MeV proton beam from the PET cyclotron. Among these three scenarios, scenario (1) is for a scheme on a global scale, scenario (2) works in a local area, and both cases take a long time for negotiations. Scenario (3) is attractive because we can use nearly 50 PET cyclotrons in Japan for $^{99m}$Tc production. We here consider both the advantages and disadvantages among the three scenarios by taking account of the Japanese accelerator situation.

Keywords: $^{99}$Mo-$^{99m}$Tc, Accelerator production, J-PARC, PET-cyclotron, Tc generator

1. Introduction

The radioisotope $^{99m}$Tc has long been used for medical diagnostic imaging with the SPECT (Single Photon Emission Computed Tomography) in many hospitals and medical facilities (as many as 1,200). Throughout the long history of radio-medical applications, various chemicals labeled by $^{99m}$Tc radioactive isotopes have been developed for medical examination (e.g. blood flow, bone metastasis, etc.; see Table 1).

The isotope supply in Japan is mostly from abroad, which may possibly have catastrophic impacts on medical activities when some difficulties might occur concerning the import of $^{99}$Mo isotopes from abroad in the future. In this paper, we discuss the feasibility for the self-sufficient supply of the $^{99m}$Tc isotope in Japan.

The short half-life of $^{99m}$Tc ($T_{1/2} = 6.02$ hr) makes a convenient delivering system impossible. However, the $^{99m}$Tc isotope is generated through the radioactive decay of $^{99}$Mo ($T_{1/2} = 66.0$ hr), which can be easily transported over long distances to hospitals.

The $^{99}$Mo isotope has been mostly generated in nuclear reactors using highly enriched $^{235}$U fuel (HEU). However, presently, the use of HEU tends to be prohibited due to PTBT (Partial Test Ban Treaty, 1963) and NPT (Treaty on the Non-Proliferation of Nuclear Weapons, 1968), so that the only 5 HEU reactors are in operation world-wide. All of them are more than 50 years old, and are now suffering from various problems. Therefore, we are now encountering a serious problem: that the supply of $^{99}$Mo isotopes may often become unstable, and that any $^{99}$Mo isotope shortage will reach a crisis level in medical diagnosis.2)

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Since the present $^{99}$Mo production scheme using HEU violates the regulations of PTBT and NPT, we need to develop alternative methods. Together with world-wide efforts, new methods to produce the $^{99}$Mo isotopes have been explored and proposed using Japanese accelerator facilities through photonuclear reactions ($\gamma, n$), neutron-induced reactions ($n, 2n$) and ($n, \alpha$), as well as proton-incident reactions ($p, pn$) and ($p, 2n$).

We started feasibility tests in generating neutrons from the high-energy, high-intensity proton beam of the injector LINAC of J-PARC (Japan-Proton Accelerator Research Complex). In this paper, we report on a series of feasibility-test experiments at the Ring-Cyclotron facility of RCNP (Research Center of Nuclear Physics). While the J-PARC injector LINAC could provide a 400 MeV, 300 µA beam, a proton beam of 400 MeV, 1 µA is available at the RCNP Ring-Cyclotron. The latter has been a nice playground to test the basic ideas and various feasibilities because of easier access and convenience for experimental designs. We also studied the possibilities of using lower energy proton beams for $^{99}$Mo production as well as $^{99m}$Tc direct production by using the AVF (Azimuthally Varying Field) cyclotron.

### 2. Production of $^{99m}$Tc isotopes with spallation neutrons

In nuclear reactions using projectiles above 100 MeV/nucleon, the collision speed becomes faster than the nucleon Fermi motion in nuclei, or above the sound velocity of nuclear matter. Therefore, the neutron yield increases dramatically through the spallation process (see Fig. 1). We expect to increase the $^{99}$Mo yield via the $^{100}$Mo($n, 2n$)$^{99}$Mo reaction. For producing medical isotopes, however, the specific activity is an additional factor to optimize the proton energy. We used a 400 MeV proton beam on a heavy-metal target to produce spallation neutrons, so that the $^{99}$Mo isotope would be produced via the $^{100}$Mo($n, 2n$)$^{99}$Mo reaction on a natural Mo target.

### Table 1. $^{99m}$Tc Radioactive medicines (from Ref. 1)

| Location            | $^{99m}$Tc Radioactive medicines |
|---------------------|----------------------------------|
| Brain               | $^{99m}$Tc-DTPA, $^{99m}$TcO$_4$, $^{99m}$Tc-HMPAO, $^{99m}$Tc-ECD |
| Thyroid gland       | $^{99m}$TcO$_4$                  |
| Lungs               | $^{99m}$Tc-MAA*, $^{99m}$Tc-colloid, $^{99m}$Tc-HAS (* added by present authors) |
| Heart               | $^{99m}$Tc-sestamibi, $^{99m}$Tc-tetrofosmin, $^{99m}$Tc-pyrophosphate, $^{99m}$Tc-red blood cell |
| Vein                | $^{99m}$Tc-MAA                   |
| Liver               | $^{99m}$Tc-phytate, $^{99m}$Tc-Sn colloid, $^{99m}$Tc-HIDA, $^{99m}$Tc-PMT |
| Salivary gland      | $^{99m}$TcO$_4$                 |
| Meckel diverticule  | $^{99m}$TcO$_4$                 |
| Gastrointestinal tract | $^{99m}$TcO$_4$            |
| Kidney              | $^{99m}$Tc-MAA, $^{99m}$Tc-MAG3, $^{99m}$Tc-DTPA |
| Testicles           | $^{99m}$Tc-HSA                  |
| Placenta            | $^{99m}$Tc-HSA                  |
| Spleen              | $^{99m}$Tc-Sn colloid           |
| Bone                | $^{99m}$Tc-MDP, $^{99m}$Tc-HMDP |
| Lymph node          | $^{99m}$Tc-Re colloid, $^{99m}$Tc-Sn colloid |

![Image of spallation neutrons](image-url)
3. Feasibility studies at RCNP for proposing the project at J-PARC

In order to propose a $^{99}$Mo-$^{99m}$Tc production project at J-PARC, we carried out a series of experiments using the 400 MeV proton beam at the Ring cyclotron of RCNP. With the target configuration set to use the cylindrically distributed spallation neutrons, as shown in Fig. 2, experiments were carried out to test $^{99}$Mo production. A 400 MeV 35 nA proton beam was incident on a neutron-production target of a natural Mo rod with 15 mm diameter and 150 mm length. The range of 400 MeV protons in a metallic Mo target was calculated to be 128 mm. Neutrons were emitted sideways along the beam axis in the Mo target. For determining the $^{99}$Mo production rate, we used natural Mo pellets of 10 mm diameter and 1 mm thickness set along the side of the neutron production target. The irradiation time was 0.5 hr with a beam intensity of 35 nA, i.e. 1/10,000 of the J-PARC beam. The next day, after cooling any background activities, $\gamma$-ray analyses were performed to determine the yield. The result showed that the $^{99}$Mo yield obtained by bombarding the 400 MeV 35 nA proton beam for 0.5 hr on a natural Mo target was at least 10 kBq/g. As shown in Fig. 4, the $^{99}$Mo yield expected in the case of J-PARC using the 400 MeV 330 µA proton beam for 10 hr is given by

\[
10 \text{ kBq/g} \times \frac{330 \text{ µA}}{35 \text{ nA}} \times \frac{10 \text{ hr}}{0.5 \text{ hr}} \approx 2 \text{ GBq/g/10 hr}
\]

If a 500 g natural Mo target is used, we expect to obtain 1 TBq/10 hr. We propose to add this function to the J-PARC/injector-LINAC as a parasite job to be operated independently from the major activities at the 3 GeV and 50 GeV synchrotron rings. As a result, we expect to use nearly 100% of the operating
time of the injector LINAC. We also expect that J-PARC can operate for 50 weeks over one year, and that the parasitic beam time for 10 hours of irradiation will be scheduled three times a week. Then, the total production time would be $(52 \times 3 \times 10 \text{ hr}) = 156 \times 10 \text{ hr}$ over one year. The total production of $^{99}$Tc would amount to $150 \text{ TBq/year}$. This is about the half of the total amounts of $^{99}$Tc supply (314 TBq in 2013, and 326 TBq in 2012).

Note that the yield estimation given here is based on an experiment using natural Mo with a $^{100}$Mo natural abundance of 9.63%. Using a highly enriched $^{100}$Mo (>90%), $^{99}$Mo yield is enhanced by almost a factor of 10, so that the $^{99}$Mo yield will reach to cover the total Japanese consumption.

### 4. Chemical separation and purification of $^{99m}$Mo-$^{99}$Tc for $^{99m}$Tc generation

Any chemical handling of $^{99m}$Mo-$^{99}$Tc isotopes at the production target has to be done under an extremely high radiation level with minimum disturbance to the main J-PARC activities.

We use MoO$_3$ powder as the target material. We can dissolve it by infusing a 4 mol-NaOH solvent after irradiation. Then, the $^{99}$Mo isotopes are transferred from the target vessel in the hot area to a carrier of radioactive liquid located outside of the accelerator room.

![Fig. 4. Results of feasibility test experiments at the RCNP/ cyclotron, and an experimental estimation of the $^{99}$Mo yields for the proposed J-PARC mission.](https://example.com/fig4.png)

We built a new chemical apparatus, named ‘Tc generator’ for the chemical separation of $^{99m}$Tc from a MoO$_3$ target. The MoO$_3$ is dissolved in 4nNaOH, and mixed with Methyl ethyl Kepton (MEK) for solvent extraction. Since the first product of extraction contains not only $^{99m}$Tc, but also other Tc isopes as well as other elements, it is thrown away from Exhaust-(I). Then, after waiting for about 10 hours for the accumulation of $^{99m}$Tc, 2nd and 3rd extractions are repeated to obtain $^{99m}$Tc until the $^{99}$Mo in the NaOH aqueous solution decays. In the case an enriched $^{100}$Mo is used for $^{99}$Mo production, the residue of $^{100}$Mo is recovered for later use.

![Fig. 5. ‘Tc generator’ for the chemical separation of $^{99m}$Tc from a MoO$_3$ target. The MoO$_3$ is dissolved in 4nNaOH, and mixed with Methyl ethyl Kepton (MEK) for solvent extraction.](https://example.com/fig5.png)

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![Fig. 6. Performance of chemical separation and purification through the Tc-generator is monitored by $\gamma$-ray measurements.](https://example.com/fig6.png)

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"Test exp.@ RCNP/ring cyclo. Beam : 400 MeV 35 nA Irradiation : 10 hours"
The (MEK) extraction is carried out in two stages:

(I) A NaOH solution of the Mo target includes $^{99m}$Tc together with any impurities as well as other Tc isotopes. Those are extracted in the first extraction after production, and the MEK solution is thrown away.

(II) After waiting for about the half-life necessary for building up $^{99m}$Tc in the NaOH solution, a second (MEK) extraction generates $^{99m}$Tc in the MEK solution exclusively. Then, the $^{99m}$Tc are further purified by passing through an aluminum column. This process (II) is repeated several times with intervals of about the half-life of $^{99m}$Tc, until the $^{99m}$Mo is phased out by decay.

In order to examine the performance of the $^{99m}$Tc produced by (n, 2n) reaction on a Mo target, we compared the quality of the $^{99m}$Tc samples using the present $^{99m}$Tc source from Mo target with that using the conventional commercial source separated from fission products. The latter was made by adding commercially available $^{99m}$Tc (60 MBq) into a solution of natMoO$_3$ (40 g) dissolved in NaOH (4 mol in 120 ml). The $^{99m}$Tc isotope was extracted with 15 ml of MEK from a solution containing a macro amount of natural Mo. After the evaporation of MEK, the dried sample was dissolved in a few ml of saline, and the solution was purified by passing through a neutral aluminum column to remove any possible residue of Mo. The amounts of impurities, and the extraction efficiency, etc. were measured by using inductivity coupled plasma mass spectroscopy (ICP-MS) and $\gamma$-ray spectroscopy with a Ge detector. The yield of $^{99m}$Tc was 75–90%. The impurities of Mo and Al were less than 10 ppb.

The labeling efficiency of $^{99m}$Tc-MDP was higher than 99%. All of these numbers were found to satisfy the requirement of USP (United States Pharmacopeia). The requirement is to keep the impurity at less than 0.01% of the $^{99m}$Tc.

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Fig. 7. Proposed layout at the J-PARC injector LINAC. The proton beam line for the ADS/TEF-T project is used so that produced neutrons are used parasitically. The MoO$_3$ target is used, which is soluble in 4nNaOH, so that any hot isotopes in the solution can be transferred to a liquid RI bottle outside the accelerator room. Chemical process for separation and purification can be done in local hot-laboratories.
5. Design and planning of the neutron source at the J-PARC/TEF-T facility

We propose a parasitic use of spallation neutrons from a target of the 400 MeV proton beam in the ADS/TEF-T (Accelerator-Driven System/Transmutation Experimental Facility-T) beam line with minimum disturbance. Figure 7 shows a preliminary proposal of a layout for $^{99}$Mo-$^{99m}$Tc production, which must be a subject to be improved in practical use. The parasitic use of the beam was emphasized because a radioisotope production for medical use requires a stable supply independently of other activities. Further detailed design work for construction must be completed in collaboration with J-PARC staff members.

6. Test experiments at the RCNP AVF cyclotron to produce $^{99}$Mo isotopes through the (p, pn) reaction with a 80 MeV proton beam

When we had completed the feasibility studies discussed in the previous sections (Sections 2 to 4), and had designed the preliminary scheme discussed in Section 5, we learned that the ADS/TEF-T project might take more time than we had expected. We started to explore other possibilities of using a proton beam with the RCNP AVF (Azimuthally Varying Field) cyclotron.

Shown in Fig. 8 is the excitation function of the $^{99}$Mo production through the (p, pn) reaction.

We studied the contributions of the background reactions, and concluded that the optimum beam energy would be 50 to 80 MeV. Although the thick target yield increases at higher energy, it is by not more than 100 MeV because of background reactions, such as (p, p2n), (p, p3n), increase.

The 80 MeV 1 µA proton beam from the AVF-cyclotron was used to bombard a Mo pellet of 10 mmφ, 8.6 mm thick (the proton range is 8.55 mm) to test the $^{99}$Mo yield through the (p, pn) reaction. The experimentally obtained $^{99}$Mo yield was 40 MBq/µA/hour. With a 10 hours bombardment of a 10 µA proton beam, we can produce 4 GBq $^{99}$Mo isotopes that are sufficient to satisfy the weekly demand of Osaka University hospital.

7. Test of the direct production of $^{99m}$Tc via the Mo(p, 2n) reaction with a 20-MeV proton beam from the RCNP cyclotron

The direct production of $^{99m}$Tc isotopes via the $^{100}$Mo(p, 2n) reaction was beyond our scope when we started the present project. We thought that the half-life of $^{99m}$Tc ($T_{1/2} = 6$ hours) is too short to make a delivering system to cover a wide area. However, we noticed that about 50 PET cyclotrons ($E_p = 18$ or 20 MeV) are in operation at various locations in Japan to produce isotopes for PET (see red marks in Fig. 9). Each PET cyclotron can produce $^{99m}$Tc isotopes for in-hospital use.

In order to test the feasibility of the method using the 20 MeV PET cyclotron for the direct production of $^{99m}$Tc isotopes via the Mo(p, 2n) reaction, we bombarded a 20 MeV 50 nA proton beam on a natural
MoO₃ pellet target having a thickness of 0.4 g/cm². Although the irradiation time was only 10 min, we were able to obtain ⁹⁹ᵐTc of about 5.6 × 10⁴ Bq, which led us to conclude that the ⁹⁹ᵐTc production yield is 21 MBq/µA/hour (at EOB).

The direct production of ⁹⁹ᵐTc isotopes through the ¹⁰⁰Mo(p, 2n) reaction using a medical cyclotron has been investigated since the early 1970’s as an alternative candidate of the HEU nuclear reactors. Measurements of the excitation function of the (p, 2n) reaction have been reported by three groups. Although the absolute cross sections are not quite in good agreement, their proton energy dependences are similar, showing a broad peak from 15 to 20 MeV (see Fig. 8(b)).

We compared our data of yield measurements with the calculated yield by integrating their excitation data. Our data were in agreement with a calculation based on data obtained by Scholten et al. ⁹⁹mTc Background ATc Isotopes (A = 93, 94, 95, 96) β+

We estimated that by using a 1 µA proton beam on a 96% enriched ¹⁰⁰Mo target with a thickness of 0.5 g/cm² for 10 hours, the yield of ⁹⁹mTc isotopes would be 3.5 GBq. This amount should be sufficient for typical hospitals. Through the test experiment with only 10 minutes of proton bombardment on a natural Mo target, we concluded that PET cyclotrons are useful for direct ⁹⁹mTc production. However, the γ-ray spectra showed not only the ⁹⁹mTc isotope, but also many γ-rays from other Tc isotopes (Fig. 10). The Tc isotope contaminations were ⁵⁸Tc (T₁/₂ = 2.8 h), ⁹⁴Tc (T₁/₂ = 4.9 h), ⁵⁵Tc (T₁/₂ = 20 h) and ⁹⁶Tc (T₁/₂ = 4.3 d). Those are difficult to separate through chemical processes. Obviously, we need to use highly enriched ¹⁰⁰Mo (higher than 99.5%). In order to reduce the production cost, we started to design a new target system for multiple use of the expensive ¹⁰⁰Mo.

8. Summary of feasibility research at RCNP, and concluding remarks

Through the series of RCNP experiments discussed above concerning the feasibility study of the ⁹⁹Mo-⁹⁹mTc production by the J-PARC injector beam, we were able to show that sufficient amounts of ⁹⁹Mo isotopes could be produced to cover the total Japanese consumption. Through this work, we are convinced that the method of producing ⁹⁹mTc isotopes from a Mo target by the accelerator is good despite the fact that the specific activity of ⁹⁹Mo is very low. It makes a contrast to the method hitherto well established for Mo chemical separation from fission products generated in nuclear reactors using enriched ²³⁵U fuel.

Hence, the alternative work would also contribute to reduce the use of enriched ²³⁵U fuel.

In Table 2, we summarize our efforts in three scenarios.

We established a Japanese style solution using the world top-level high-power accelerator facility, J-PARC. Through the feasibility study using the
400 MeV proton beam from the RCNP/RING-cyclotron, it has been shown that a sufficient amount of $^{99}$Mo can be produced at the J-PARC TEF-T beam line. We realized, however, that even though the total amount of the isotope production is sufficient, there still remain serious difficulties. For instance, after we achieved full confidence about $^{99}$Mo-$^{99m}$Tc production using the J-PARC, a serious question has arisen. The question is: “what can we do during the period while the J-PARC is not in operation?” The most important factor in serving such medical radioactive isotopes, like $^{99}$Mo, is stable supply. The solution for the requirement to assure stable supply of isotopes is to have a plural number of production sources.

Among the three scenarios in Table 2, while scenario (1) is a scheme of global scope, scenario (3) would work in domestic hospitals.

$^{99}$Mo isotope production at the J-PARC (Scenario (1)). In order to respond to the worldwide crisis of the $^{99}$Mo isotope supply with accelerators in lieu of nuclear reactors, the high-energy, high-intensity accelerator, J-PARC is the most suitable facility. Indeed, we have shown through experiments at RCNP that a sufficient amount of $^{99}$Mo isotope production is feasible at J-PARC using the spallation neutrons. Since we are considering to use the ADS/TEF-T beam line, we have to wait a few more years for the TEF-T facility.

$^{99m}$Tc direct production at the PET cyclotrons (Scenario (3)). We learned that in Japan there exist 50 PET cyclotrons that cover the best energy for the direct production of the $^{99m}$Tc isotope. A series of test experiments at the RCNP cyclotron have shown the feasibility of direct production. We thought this to be most promising and practical, being an exclusive medical project.

We found, however, the following two weak points: (1) An expensive enriched $^{100}$Mo target has to be used; otherwise, contaminations due to other Tc isotopes can not be separated. (2) In the case of an emergency, the production of the $^{99m}$Tc isotope takes at least a couple of hours for preparation before an examination. Therefore, the conventional Mo generation must be kept, and we must continue efforts towards a self-sufficient supply of the $^{99}$Mo isotopes in parallel.

The $^{99}$Mo isotope production network (Scenario (2)). As mentioned in Section 6, beside J-PARC, we have powerful cyclotrons that accelerate proton beams with an intensity of 100 to 300 µA, and with an energy of up to 70 or 80 MeV. Those cyclotrons in Japan are all constructed by SHI (Sumitomo Heavy Industry) at Sendai (CYRIC/Tohoku U.), Takasaki (JA EA), and Chiba (NIRS). If these machines provide 200 µA beam on 90% enriched $^{100}$Mo targets for 10 hours, each machine could produce 400 GBq $^{99}$Mo. Total amounts of

\[
\begin{array}{|c|c|c|}
\hline
\text{Scenario(1) [Section-3, 4, 5]} & \text{Scenario(2) [Section-6]} & \text{Scenario(3) [Section-7]} \\
\hline
\text{Production of }^{99}\text{Mo (for Milking)} & \text{Production of }^{99}\text{Mo (for Milking)} & \text{Direct Production of }^{99m}\text{Tc} \\
\text{$^{100}\text{Mo(n,2n)}^{99}\text{Mo}$ with spallation neutron} & \text{$^{100}\text{Mo(p,pn)}^{99}\text{Mo}$} & \text{$^{100}\text{Mo(p,2n)}^{99m}\text{Tc}$} \\
\hline
\end{array}
\]
3 \times 0.4 = 1.2 \text{ TBq} \text{ of } ^{99}\text{Mo}/\text{day} \text{ are expected to be produced. If the production could be continued for 54 weeks in total during each year, the yield of 65 \text{ TBq} ^{99}\text{Mo} \text{ isotopes is available. This amount is sufficient to cover the } ^{99}\text{Tc} \text{ direct production program at the PET cyclotrons (discussed in Scenario (3)) to establish a self-sufficient supply. We will have to start negotiation with the nuclear physics community.}

The Tc-generator. In all of the cases using the \((n, 2n)\), \((n, \gamma)\), \((\gamma, n)\), \((p, pn)\) and \((p, 2n)\) reactions on a Mo target, the ‘Tc-generator’ discussed in Section 4 is useful for the separation of \(^{99m}\text{Tc}\) from \(^{99}\text{Mo}\) isotopes produced with very low specific activities. The new method has overcome the difficulty in the chemical separation of the \(^{99}\text{Mo}\) radioactive isotopes. It is also contributing greatly to stop using the highly enriched \(^{235}\text{U}\) (HEU).

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