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Diversification of ^{99}Mo/^{99m}Tc separation: Non-fission reactor production of ^{99}Mo as a strategy for enhancing ^{99m}Tc availability

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Abstract

This paper discusses the benefits of obtaining ^{99m}Tc from non-fission reactor-produced low specific activity ^{99}Mo. This scenario is based on establishing a diversified chain of facilities for the distribution of ^{99m}Tc separated from reactor-produced ^{99}Mo by (n,γ) activation of natural/enriched Mo. Such facilities have expected lower investments than required for the proposed chain of cyclotrons for the production of ^{99m}Tc. Facilities can receive and process reactor-irradiated Mo targets then used for extraction of ^{99m}Tc over a period of two weeks; with three extractions on the same day. Estimates suggest that a center receiving 1.85 TBq (50 Ci) of ^{99}Mo once every four days can provide 1.3-3.3 TBq (40-90 Ci) of ^{99m}Tc daily. This model can use research reactors operating in the US to supply current ^{99}Mo needs by using natural ^{nat}Mo targets. Molybdenum-99 production capacity enhancement can be accomplished by using ^{98}Mo enriched targets. The proposed model reduces the loss of ^{99}Mo by decay and avoids proliferation as well as waste management issues associated with fission-produced ^{99}Mo.

Introduction

Several options are under consideration to ensure the uninterrupted supply of ^{99m}Tc for nuclear medicine applications (*1-3*). A recent article suggests the potential advantages of a "diversified" production approach using medium energy cyclotrons to enhance ^{99m}Tc availability (*4*). Highly enriched ^{100}Mo targets are irradiated with 18-25 MeV protons to yield ^{99m}Tc [^{100}Mo(p,2n)^{99m}Tc]. As an example, a 1.5 g ^{100}Mo solid target irradiated with 18 MeV protons at 240 μA beam current for 6 hours can provide ~ 333 GBq (9 Ci) of ^{99m}Tc at end of bombardment (EOB) (*5*). The possibility of such a strategy will depend on daily irradiations of ^{100}Mo targets and radiochemical processing to recover ^{99m}Tc as pertechnetate solution prior to distribution (Figure 1). A large network of new cyclotron facilities having compliance with 21 CFR 212 or USP <823> for ^{99m}Tc production similar to existing PET radiopharmaceutical production facilities would be needed for the success of this model.

In this communication, we propose a similar scheme of diversified radiochemical processing facilities for reactor produced low specific activity (LSA) ^{99}Mo for the preparation of ^{99m}Tc pertechnetate (*6*). The distinct advantage of this strategy is based on optimal use of reactor produced ^{99}Mo by minimizing decay loss. It is estimated that currently approximately 60-80% of ^{99}Mo is lost from radioactive decay prior to facility receipt of ^{99}Mo/^{99m}Tc generators (*7*). We estimate that by using only one or two of the existing US nuclear reactors, our model could provide sufficient ^{99m}Tc to meet the entire US requirements for ^{99m}Tc (Figure 2).

How much ^{99m}Tc is required?

Approximately 50,000 diagnostic procedures are estimated to be performed with ^{99m}Tc radiopharmaceuticals in the US daily (3). Patient doses vary from a few hundred MBq to a maximum of 1.1 GBq. The daily activity levels of ^{99m}Tc administered to all patients in the US can be as high as 55.5 TBq (1,500 Ci). The total available ^{99m}Tc activity is not used, since significant activity is lost due to radioactive decay, and the actual US ^{99m}Tc activity requirement could be ~111 TBq (3,000 Ci). If the proposed cyclotron route is used as the principal US source of ^{99m}Tc, it would be expected that more than 300 distributed cyclotrons may be required, whereas the use of a couple of existing nuclear reactors would be expected to suffice for our alternative strategy.

Diversified processing facilities for reactor produced LSA ^{99}Mo

The reactor production of ^{99}Mo by irradiating natural molybdenum trioxide was used earlier for the preparation of ^{99m}Tc; but mostly abandoned after the introduction and wide availability of the alumina based ^{99}Mo/^{99m}Tc column generator using fission-produced high specific activity ^{99}Mo. We propose to revive this earlier and accepted technology using a network of geographically diversified radiochemical processing facilities for the separation of ^{99m}Tc from ^{99}Mo. The irradiated Mo targets can be transported to these radiochemical processing facilities and the expected transportation time is less than 24 hours either by road or air. As an example, irradiation of 25 g of a ^{nat}Mo powder target (i.e. as the oxide; 24.13% ^{98}Mo) for 6-days in a reactor with an approximate neutron flux of 6 x 10^{14} neutrons/cm^2/sec would result in the production of ~ 1.85 TBq (50 Ci) of ^{99}Mo at EOB. Assuming a decay loss of ~25% during transport, 1.4 TBq (38 Ci) of ^{99}Mo will be available for radiochemical processing. Recovering the irradiated dry powder and simple dissolution in sodium hydroxide solution provides sodium (^{99}Mo) molybdate, the source of ^{99m}Tc. The separation of ^{99m}Tc can be accomplished using any one of the established methods (*8*). Solvent extraction using methyl ethyl ketone (MEK) is effective and simple and cost effective automated modules can be developed for the preparation of high concentration of no-carrier added ^{99m}Tc activity (*9*). Alternatively, solid phase extraction chromatographic separation also can be adapted (*10*).

Instead of a single ^{99m}Tc extraction from the irradiated target by the cyclotron route, the ^{99m}Tc can be extracted from ^{99}Mo stock solution at frequent intervals, for instance, every six hours beginning in the early morning, and transported to users either as pertechnetate or as finished radiopharmaceuticals. The 6-h ^{99m}Tc half life allows easy distribution of radiopharmaceutical products. If the ^{99}Mo processing facilities are established in the same location as cyclotron facilities used for ^{18}F production, the existing [^{18}F]FDG distribution network can be used for distribution of ^{99m}Tc products. Figure 3 shows the amount of ^{99m}Tc available from a single batch of 1.85 TBq (50 Ci) of ^{99}Mo at EOB over a period of 12 days, with three extractions on the same day at six hour intervals. About 9.62 TBq (260 Ci) of ^{99m}Tc can be obtained from a single 1.85 TBq (50 Ci) batch of ^{99}Mo. This is in contrast to a single separation possible from a cyclotron irradiated enriched ^{100}Mo target.

An important advantage and cost savings of using reactor-produced LSA ^{99}Mo is that usable quantities of ^{99m}Tc activity can be repeatedly extracted, for a period as long as two weeks. Fresh lots of ^{99}Mo could be supplied at 4 day intervals. Simultaneous operation of 3 batches of ^{99}Mo and multiple daily extractions could manage a sustained supply of ^{99m}Tc on a daily basis. Figure 4 illustrates the activity levels of ^{99}Mo available on each day and the activity of ^{99m}Tc extractable on a daily basis. If three batches of ^{99}Mo are available simultaneously in a processing centre, the ^{99m}Tc activity available is expected to vary from 1.48-3.33 TBq (40-90 Ci) of ^{99m}Tc. In such a scenario, 60 such processing facilities could produce 111 TBq (3,000 Ci) of ^{99m}Tc, which is sufficient to conduct an estimated current US demand of 50,000 daily investigations. Depending upon the capacity available for irradiation, participation of a limited number of reactors in the US could thus provide the entire US ^{99m}Tc requirements. Scaling up of such a ^{99}Mo production scenario by a factor of ~ 4 can be accomplished with the use of enriched ^{98}Mo targets (> 95 % ^{98}Mo), theoretically yielding up to 444 TBq (12,000 Ci) ^{99m}Tc daily. Enriched targets can be recovered for reuse, a scenario similar to the recovery and reuse of ^{100}Mo targets in the case of cyclotron production.

Investment needed at each processing facility

Only moderate investment would be expected for each processing facility, with the basic essential requirements based on the availability of licensed facilities equipped with the required shielding, ventilation and waste handling capabilities, which would also include one hot cell for processing the irradiated targets, and one or two hot cells for installation of ^{99m}Tc/^{99}Mo separation systems. Additional investment would be required for installation of automated modules for separation of ^{99m}Tc from ^{99}Mo. The hot cells used for placing the module for separation of ^{99m}Tc as well as the facility must be GMP compliant, since the pertechnetate will be used for the formulation of radiopharmaceuticals. Facility compliance with 21 CFR 210, 21 CFR 211, and USP<797> may in fact be expected to be easier with the reactor route versus processing of cyclotron targets, since both MEK extraction and solid phase chromatographic procedures had already received Food and Drug Administration (FDA) approval.

The expected costs for equipment to set up such a facility having 2-3 hot cells together with a couple of automated modules would be in the 2-4 million dollar range. The production capabilities of each ^{99m}Tc/^{99}Mo separation unit could be as high as 1.48-1.85 TBq (40-50 Ci) of ^{99m}Tc per day, which translates to ~ 555 TBq (15,000 Ci) of ^{99m}Tc annually, which is equivalent to 500,000 patient doses. In conjunction with existing central radiopharmacies and/or cyclotron centers, it could be possible that the ^{99}Mo/^{99m}Tc radiochemical processing units could be economically operated, since the additional operational and infrastructure costs would be minimized.

Advantages of the proposed model

Such a proposed production scenario would have several advantages which could improve the economics of the ^{99}Mo/^{99m}Tc supply chain since the HEU proliferation concern, waste generation and disposal issues from use of low enriched uranium (LEU) would be avoided. The irradiation capacity of existing US nuclear reactors would be used with no additional reactor facility investments and the inherently difficult local production challenges required for direct cyclotron production of ^{99m}Tc using enriched ^{100}Mo targets would also be avoided. Also, it remains to be seen if the combined use of medical cyclotrons for routine production of both ^{18}F and ^{99m}Tc will limit the available beam time required for PET tracer development, which would be expected to reduce the ability of these facilities to develop new agents which in turn may negatively impact patient care. The basic radiochemical processing concepts for ^{99}Mo from reactor production are simpler than for processing of cyclotron targets for ^{99m}Tc production. While cyclotron irradiated ^{100}Mo targets yield ^{99m}Tc only once, reactor irradiated ^{98}Mo targets provide ^{99m}Tc available from continuous in-growth over an extended time period. Although not required for ^{99}Mo production from ^{nat}Mo, use of more expensive ^{98}Mo enriched targets will scale up ^{99}Mo production by a factor of ~ four. With enriched ^{98}Mo targets, the unused ^{98}Mo target can be recovered for future use much similar to the necessary enriched ^{100}Mo recovery from cyclotron targets. There would be minimum expected loss (<25%) of ^{99}Mo in the proposed strategy from parent radioactive decay, since ^{99m}Tc can be extracted from the irradiated target within 24 hours after EOB. Whereas about 70-80% of ^{99}Mo produced at EOB occurs prior to the initiation of alumina based $^{99}Mo/^{99m}Tc$ column generator use.

Conclusion

We have suggested a model for enhancing the availability of ^{99m}Tc by having a diversified chain of radiochemical processing laboratories for processing LSA ^{99}Mo. The model can work with the cooperation of a couple of existing US reactors and with far lower investment than what is anticipated for evolving alternative models. We suggest that a serious effort is timely for the nuclear medicine community, reactor facilities, commercial radiopharmaceutical entities and policy makers to discuss the merit of the proposed model and implement the same to enhance the availability of ^{99m}Tc; as well as to address proliferation issues.

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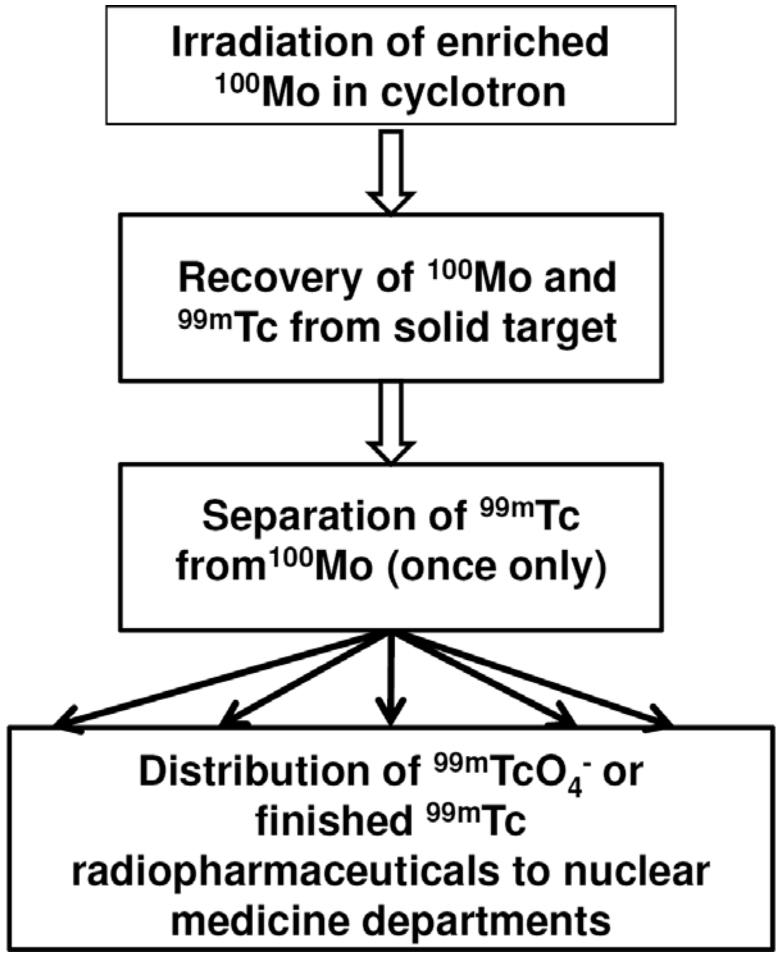

FIGURE 1. Production of ^{99m}Tc from cyclotron irradiated ^{100}Mo. After irradiation the target is processed by recovering irradiated ^{100}Mo from the solid target together with ^{99m}Tc. ^{99m}Tc is separated and purified to obtain pertechnetate solution for onward transfer to users. The separation process can be performed only once with the irradiated targets. Unused ^{100}Mo can be recovered, stored and reused for further irradiation.

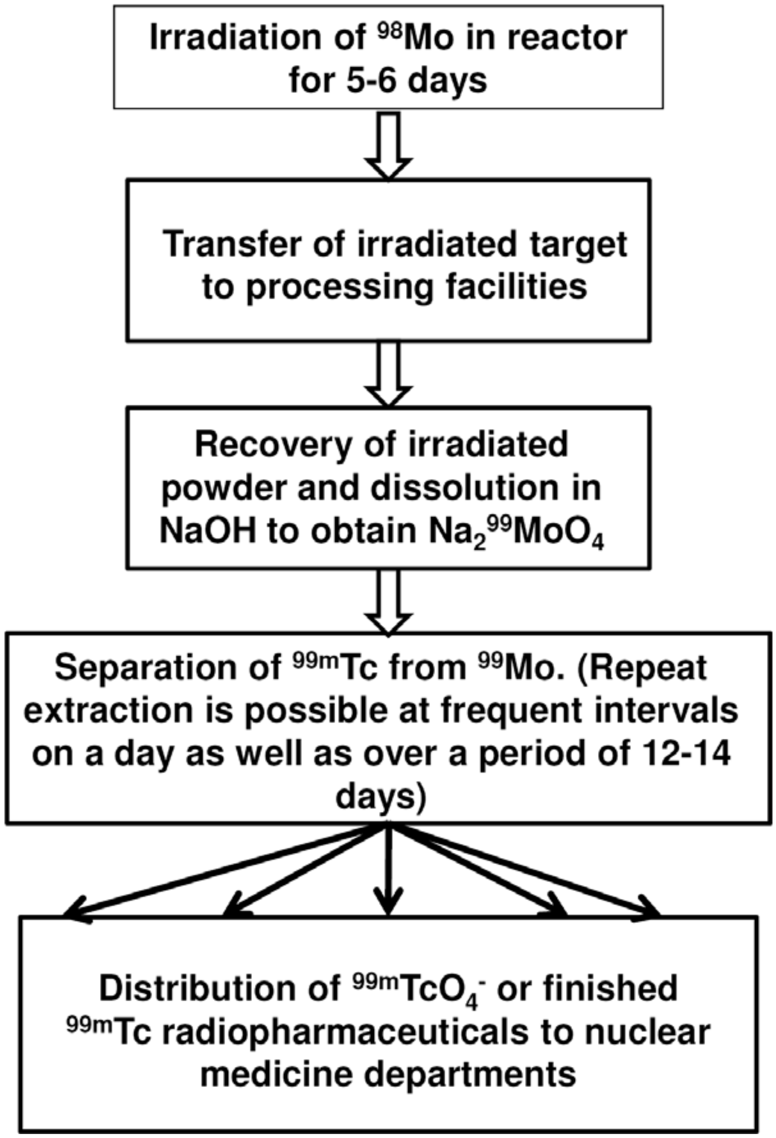

FIGURE 2. Production of ^{99m}Tc from reactor irradiated ^{nat}Mo targets. Irradiated targets are transferred to diversified radiochemical processing facilities. The target is dissolved in NaOH inside a hot cell to obtain Na_2MoO_4 solution. Multiple extractions can be performed on the same day as well as over a period of 12-14 days. The pertechnetate solution is distributed to user departments. Scaling up can be accomplished by using ^{98}Mo enriched target which can be recovered for re-use.

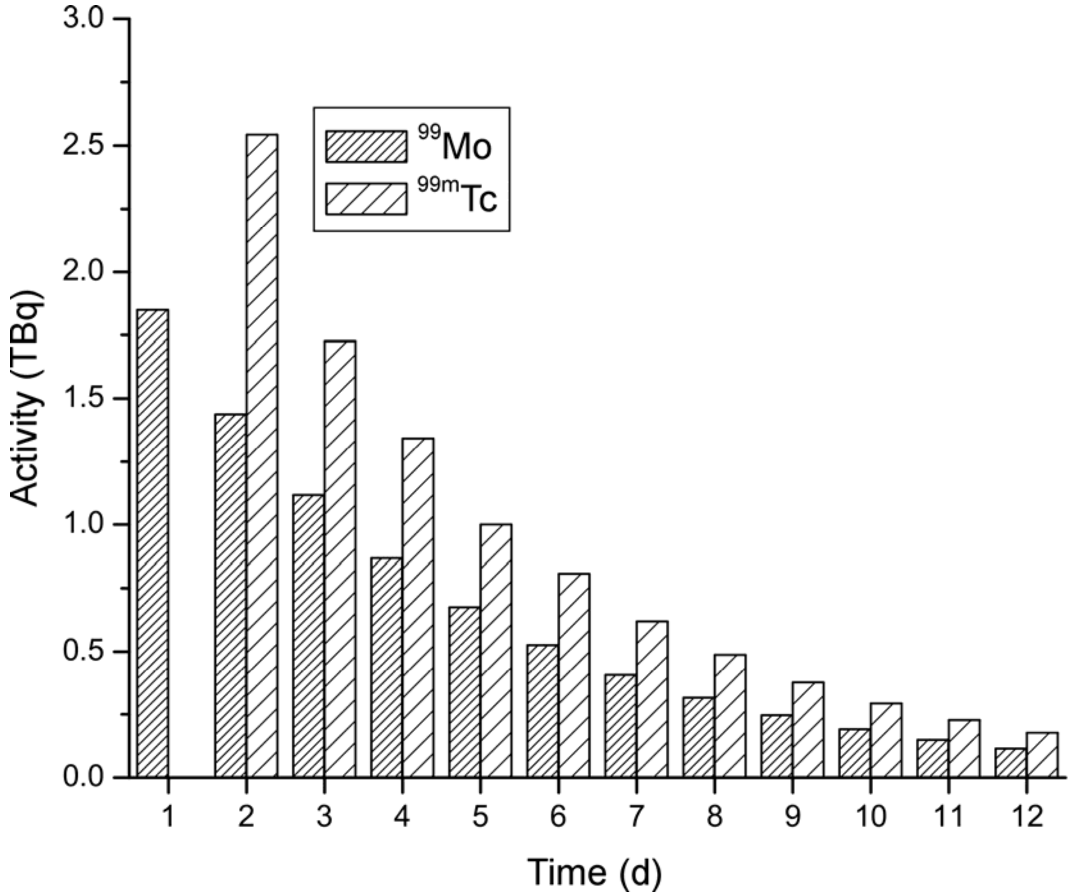

FIGURE 3. The decay of 1.85 TBq (50 Ci) of ^{99}Mo over a period of 11 days and ^{99m}Tc available on each day from a single batch of 1.85 TBq (50 Ci) ^{99}Mo. The ^{99m}Tc is eluted at three intervals starting from 400 hrs. with a gap of 6 hrs. Elution is not shown day 1, since this is the time required for transport of ^{99}Mo from reactor to the processing laboratories. About 9.62 TBq (260 Ci) ^{99m}Tc can be recovered from a single batch of 1.85 TBq (50 Ci) at EOB of ^{99}Mo supplied to a processing center.

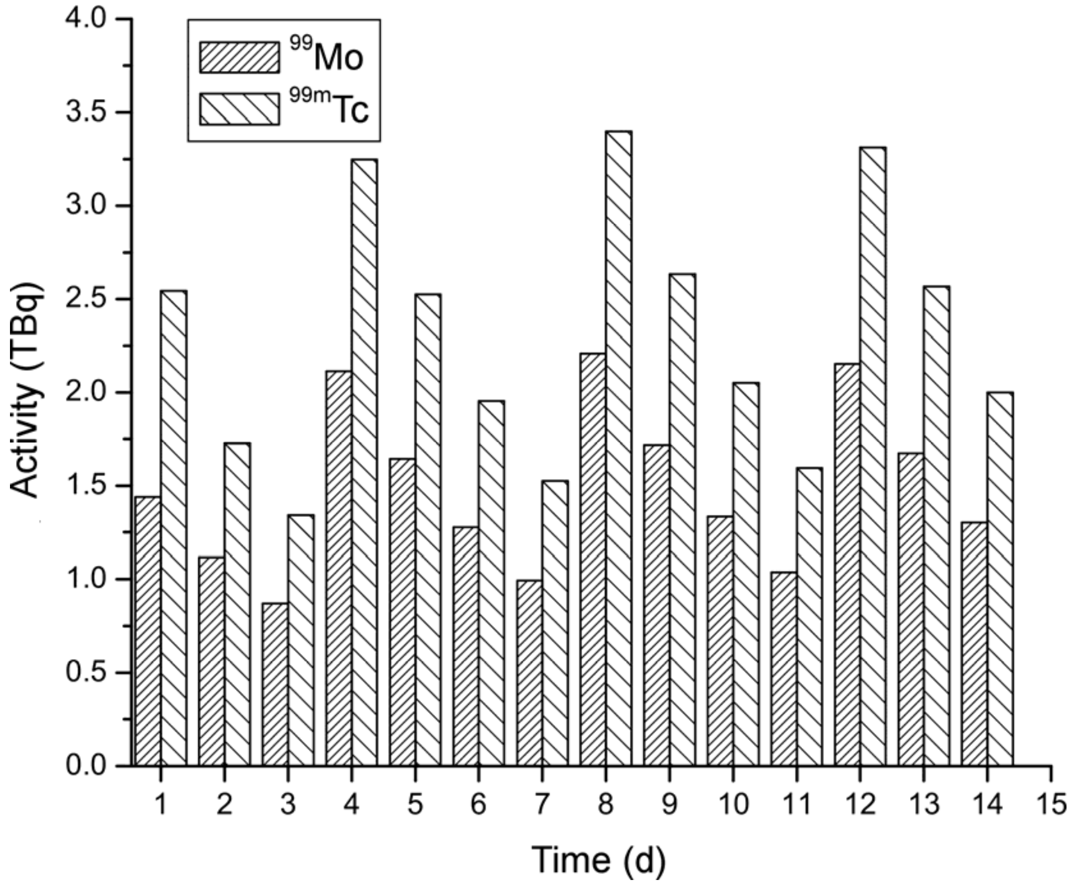

FIGURE 4. The ^{99}Mo and ^{99m}Tc availability in a central processing facility when 1.85 TBq (50 Ci) ^{99}Mo is shipped at an interval of 4 days. Assuming three elutions, the ^{99m}Tc availability at the center varies from 1.48-3.33 TBq (40-90 Ci) per day after 8th day when three batches of ^{99}Mo are simultaneously used.

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