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Reduce, reuse and recycle: A green solution to Canada's medical isotope shortage

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HIGHLIGHTS

- Commercial power electron accelerators are realistic option to produce ^{99}Mo.
- Could cover national demand of Canada.
- Demonstrate LINAC-^{99}Mo as environmental and economical solution to isotope crisis.
- Demonstrate LINAC-^{99m}Tc to be clinically equivalent to current fission-^{99m}Tc supply.

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ABSTRACT

Due to the unforeseen maintenance issues at the National Research Universal (NRU) reactor at Chalk River and coincidental shutdowns of other international reactors, a global shortage of medical isotopes (in particular technetium-99m, Tc-99m) occurred in 2009. The operation of these research reactors is expensive, their age creates concerns about their continued maintenance and the process results in a large amount of long-lived nuclear waste, whose storage cost has been subsidized by governments. While the NRU has since revived its operations, it is scheduled to cease isotope production in 2016. The Canadian government created the Non-reactor based medical Isotope Supply Program (NISP) to promote research into alternative methods for producing medical isotopes. The NRC was a member of a collaboration looking into the use of electron linear accelerators (LINAC) to produce molybdenum-99 (Mo-99), the parent isotope of Tc-99m. This paper outlines NRC's involvement in every step of this process, from the production, chemical processing, recycling and preliminary animal studies to demonstrate the equivalence of LINAC Tc-99m with the existing supply. This process stems from reusing an old idea, reduces the nuclear waste to virtually zero and recycles material to create a green solution to Canada's medical isotope shortage.

1. Introduction

The most widely used isotope for medical imaging is Tc-99m. Currently, commercial Tc-99m (half-life ~6 h) is derived from the decay of the parent isotope Mo-99. Because the half-life of Mo-99 is about 66 h, the time scale during which Tc-99m can be stored and shipped is extended by an order of magnitude as compared to the direct production of Tc-99m. The source of the commercial Mo-99 is primarily fission of U-235 in research reactors. Due to the nature of this process, many longer lived isotopes are also created which need to be separated and stored. This radioactive waste management cost has to date been subsidized by the country hosting the reactor. Moreover, the targets for some of these production reactors have been High Enriched Uranium (HEU) which has security issues. While reactors can be made to operate with Low Enriched Uranium (LEU) this creates less of the desired isotope and more of the undesirable waste. The NRC has investigated the use of electron linear accelerators (LINAC) to produce Mo-99 via the Mo-100 (γ,n) reaction. This work built upon work carried out at Idaho National Laboratory in the 1990s (Bennett et al., 1999). The Canadian government committed to finding a cleaner and more secure source of medical isotopes through the Non-reactor based medical Isotope Supply Program (NISP) which would replace the Canadian NRU reactor after 2016, at which point the NRU reactor will cease medical isotope production.

2. Production

Mo-99 can be produced via the Mo-100(γ,n) reaction. The bremsstrahlung process, whereby a high-energy electron is scattered by an atomic nucleus, can be used to produce a beam of

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high-energy photons. The giant dipole resonance in the (γ,n) reaction results in photo-induced reactions in the molybdenum isotopes. Estimates of required production rates (Ross et al., 2010) indicate that two 100 kW machines could meet the demand of the Canadian public for Tc-99m. The NRC 35 MeV, 2 kW LINAC was used to demonstrate all the steps in the production process.

While the NRC LINAC cannot produce clinically relevant quantities of Tc-99m, it can produce enough material for a robust test of all the steps from irradiation through to the elution of Tc-99 m solution. Using the NRC LINAC, disks were irradiated for about 1 h at a beam power of 1.5 kW and an electron energy of 35 MeV, in order to determine the approximate yields one could expect from an irradiation. The measured and calculated yields of Mo-99 for two disks (each with a diameter of 2 cm) separated by 1.8 cm are summarized in Table 1. Calculations were carried out using the MCNP5 Monte Carlo code. The (γ,n) cross section for Mo-100 was taken from Beil et al. (1974). The measurements were performed using a calibrated germanium solid state gamma spectrometer. The radioactive disks were placed 30 cm from the detector head and measured count rates were such that the deadtime was consistently below 1%. The measurements were corrected for self attenuation, geometric and detector efficiency and systematic effects of source position were included in the uncertainty determination. This experiment indicated that calculated yields were about 25% larger than the measured value, although results with smaller uncertainties are needed for a definitive conclusion.

3. Separation

Once the disks have been irradiated they must be dissolved so that the Tc-99m, which is continually being formed as a result of the Mo-99 decay, can be extracted. The molybdenum disks were dissolved in hydrogen peroxide to form molybdenum-trioxide (MoO_3). An alkaline solution of sodium hydroxide (NaOH) was prepared by neutralizing the acidic peroxide solution with NaOH which also converts the MoO_3 into a sodium molybdate (Na_2MoO_4) compound. A new efficient radiochemistry is required for LINAC based Mo-99 production as the specific activity is at least four orders of magnitude smaller than that acquired through fission of U-235. A wide range of techniques have been developed to separate the technetium from the low specific activity molybdenum oxide. The NRC utilized the NorthStar automated radionuclide separator (ARSII) (McAlister and Horwitz, 2009). The ARSII uses a column that selectively retains the technetium as the parent solution passes over it. Thus the technetium can be extracted from a relatively large volume of parent solution. Once the column is cleared of the parent solution, a saline rinse of the column removes the technetium as sodium pertechnetate, meeting the specifications of that obtained from a conventional fission-Mo-99 generator.

Table 1
Comparison of the measured and calculated Mo-99 yields for two disks. Upstream and downstream correspond to locations closer and farther from the LINAC beam target window, respectively.

	Upstream disk	Downstream disk
Measured (MBq)	21 (+/−10%)	12 (+/−10%)
Calculated (MBq)	27 (+/−10%)	14 (+/−16%)
Differences	25%	20%

4. Animal study

Disks of enriched Mo-100 were irradiated with the NRC LINAC to generate about 1110 MBq of Mo-99. After target dissolution and separation of the Tc-99m using the ARSII, about 1000 MBq was sent to the Ottawa Heart Institute. There the Tc-99m was chelated to pharmaceuticals suitable for cardiac and bone uptake. While the radionuclidic and radiochemical quality of the Tc-99m could be evaluated without imaging, effects of potential non-radioactive impurities resulting from the separation process could be immediately observed in a diagnostic image. Hence, Single Photon Emission Computed Tomography (SPECT) images were acquired for three rats and compared to images for the same three rats obtained using Tc-99m derived from a standard reactor Mo-99 generator. Each rat acted as its own control. An individual would be injected with the fission-Tc-99m first and then with the LINAC-Tc-99m after three days to ensure the previous radioisotope was completely biologically cleared. The injected activity was measured in an ionization chamber at the University of Ottawa Heart Institute immediately before injection and all the animals received the same amount of Tc-99m. The details of this study are outlined in a paper published in the journal Physics in Medicine and Biology (Galea et al., 2013).

The activity of the Mo-99 parent solution and the activity of the daughter Tc-99m were measured using the NRC ionization chambers, which were calibrated from solutions standardized by primary methods. The Mo-99 parent activity allowed for the calculation of the theoretical amount of Tc-99m in the parent solution at the time of separation. The ratio between the daughter Tc-99m activity and the Tc-99m parent solution, decay corrected to a common reference time of separation, results in the efficiency of the separation process. The efficiency of the separation was typically greater than 90%. This study demonstrated delivery of Tc-99m from end of beam irradiation to the end user of approximately 30 h. Both cardiac and bone imaging reconstituted pharmaceuticals passed the requirements for radionuclide and radiochemical purity, acidity, and aluminum breakthrough according to the regulations outlined by Health Canada for existing Tc-99m-tagged pharmaceuticals. Images obtained using the heart and bone scanning agents using reactor and LINAC produced Tc-99m

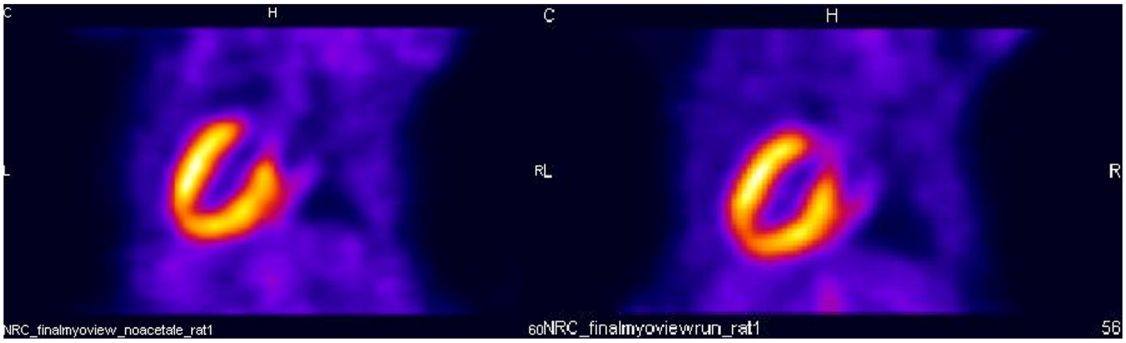

Fig. 1. Cardiac SPECT images of a rat injected with LINAC-Tc-99m (left) and fission-Tc-99m (right) for the same rat.