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OPTIONS FOR UK TECHNETIUM-99M PRODUCTION USING ACCELERATORS*

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Abstract

Recent and ongoing shortages in reactor-based supplies of molybdenum-99 for hospital production of the important medical radioisotope Technetium-99m have prompted the re-examination of the alternative production methods using conventional and laser-based particle accelerators. At present the UK has no domestic source of molybdenum-99 and relies exclusively on overseas supply; the National Health Service, with professional partners, is therefore examining the options for domestic production of molybdenum-99 and/or technetium-99m to increase security of supply. In this paper we review the accelerator-based methods from a UK perspective, and outline the most promising methods for short- and medium-term supply, which include low-energy cyclotron and photonuclear reaction routes using enriched Molybdenum-100 targets.

THE MOLYBDENUM SUPPLY CRISIS

Technetium-99m (^{99m}Tc) is the most widely used radioisotope in nuclear medicine today, and accounts for over 80% of the present 3.2 billion dollar global market in radiopharmaceuticals; Fluorine-18 products for positron emission tomography (PET) account for most of the rest [1]. ^{99m}Tc is favoured due to its single 140 keV emission during decay, its short half-life of 6 hrs that minimise patient dose during imaging, and its normal production route whereby its ^{99}Mo precursor is distributed to hospitals in a generator which is then eluted to obtain the ^{99m}Tc built up from the ^{99}Mo decay (^{99}Mo half life is 66 hrs). ^{99}Mo is today primarily obtained via fission of HEU targets each irradiated for several days in one of several ageing research reactors, and a crisis is looming due to the foreseen shutdown of one of the largest production facilities at Chalk River in Canada; the NRU reactor there provides nearly 50% of the global weekly supply of 12,000 6-day Curies of ^{99}Mo, and after its shutdown in 2016 demand will outstrip supply by some margin [2–5]. More than 30M procedures are delivered each year (53% North America, 23% Europe, 20% Asia, 4% Rest of World), and whilst the nuclear medicine community is examining alternative imaging methods it is likely that ^{99m}Tc provision will be needed for at least twenty years; global demand is set to rise by between 1% and 2% per annum over that period. For example, the UK presently administers around 0.5M ^{99m}Tc procedures each year [1], and whilst PET, CT and MRI could replace ^{99m}Tc for some indications this would impact existing capacity of those alternative techniques to meet the needs of other imaging procedures. Use of some of these alternatives also incur greater patient radiation dose; the short ^{99m}Tc half life and pure gamma emission means a typical administered dose of up to 27 mCi (1000 MBq) incurs a patient dose of around 2-4 mSv. Previous unplanned outages of the NRU and HFR Petten reactors in 2009/2010 resulted in optimised usage of ^{99m}Tc such that demand reduced to around 10,000 6-day Curies per week; further optimisation could be achieved via changes such as weekend processing of ^{99}Mo to avoid loss of activity through decay [6].

As well as facing the global fragility of sourcing supply, the UK has the additional problem that it has no suitable high-flux research reactors and therefore no present domestic source either of ^{99}Mo or directly of ^{99m}Tc, although it does have a large generator manufacturing plant at Amersham; interruption to the required weekly supply of ^{99}Mo generators could leave the UK with no supply at all. Other factors include the likely US restriction on HEU shipments after 2020, and uncertainties as to when replacement European reactors become available (such as the Jules-Horowitz reactor currently under construction). Because of these issues, a national working group has been set up to examine how to obtain a more secure source of ^{99m}Tc for domestic use. Even with the introduction of full cost recovery at the nuclear reactor [7] it is unlikely that a commercial provider will build a UK-based reactor that processes ^{99}Mo, and in

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common with other countries the UK is therefore examining non-reactor approaches that utilise accelerator bombardment of targets.

ACCELERATOR-BASED APPROACHES

Similar to many other countries, ^{99m}Tc is presently mainly provided in the UK by processors utilising fission ^{99}Mo from the SAFARI, HFR and OSIRIS reactors; around 100 radiopharmacies receive generators which are then used in around 200 nuclear medicine departments [1]. Centralised production using accelerators is possible in principle but as yet no mechanism exists to bring this about; alternative methods must consider differences in issues such as specific activity, dose preparation and licensing of radiopharmaceuticals. A number of technical approaches are possible [8–10], which broadly divide into fission-based and transmutation-based methods; the four most prominent methods are now described.

Accelerator Fission Production

Photofission production of ^{99}Mo is most likely best achieved using a combination of a convertor target (e.g. W or Ta producing c.15 MeV γ-rays from c.30-50 MeV electrons) and a solid production target of depleted U, LEU or HEU [4, 9, 11]. Lower enrichment reduces licensing and proliferation issues, but use of uranium targets requires similar hot-cell processing and waste disposal to reactor ^{99}Mo production. Nevertheless, a single c.100 kW accelerator facility could provide sufficient ^{99}Mo for the UK [12], and suitable superconducting cavity technology has been developed at Daresbury Laboratory (and elsewhere) from which such an accelerator could be constructed [13]. An alternative is to use neutron-based fission in a subcritical assembly, utilising U either in solid or liquid form; the best-developed approach is SHINE, wherein photoneutrons drive fission in a reflected subcritical LEU solution in heavy water [14]. The disadvantage of subcritical systems is the relative difficulty in their licensing.

Neutron Capture

Transmutation via the ^{98}Mo(n,γ)^{99}Mo is achieved either with reactor or accelerator-derived neutrons, and in both cases shaping of the neutron spectrum into the epithermal resonance region can optimise the capture rate to a limited degree [15]; resonant capture is also utilised for production of other radioisotopes [16]. A variety of neutron-production target options exist, from 2.8 MeV p-Li, use of Be or C targets at 10s MeV, to spallation production at c.GeV energy [8, 9]. The primary disadvantages of neutron capture methods are the low specific activity of the resulting ^{99}Mo - which would mean that current generator technology would have to be adapted - and the requirement to use relatively large enriched ^{98}Mo targets to avoid co-production of unwanted products.

Photonuclear Transmutation

Photoneutron production from an intense electron source may also be used for transmutation via the ^{100}Mo(γ,n)^{99}Mo reaction. Again, due to the low specific activity the ^{99m}Tc must be extracted directly (see below). Several Canadian laboratories have explored this approach, following proof-of-principle at the 2 kW INMS (Ottawa) linac. At CLS (Saskatoon) a linac operated at 20 MeV/20 kW is used to bombard enriched ^{100}Mo targets over a 48 hour irradiation [17]. Dissolved targets are then to be shipped as Na_2MoO_4 solution from which ^{99m}Tc is extracted in an automated separator, prior to recovery of the enriched ^{100}Mo feed (which has a value around ~US$1000 per gram). Production rates are to be scaled from ~0.2 TBq/day to ~2 TBq/day, and the PIPE/NorthStar consortium is proposing the construction of 16 linacs to supply %50 of US requirements [18, 19].

Cyclotron Production

First proposed in 1971 [20], direct production of ^{99m}Tc may be achieved via the ^{100}Mo(p,2n)^{99m}Tc and ^{100}Mo(p,pn)^{99}Mo reactions [21–29]. Recent work has shown that 19 MeV bombardment onto a thin, enriched ^{100}Mo target optimises the tradeoff between ^{99m}Tc yield and radionuclidic purity; higher initial energy and degradation in the target below 10 MeV may give rise to increased patient doses (up to 30% more), which is also affected by the composition of the other Mo isotopes in the enriched target material [30, 31]. Since radionuclidic purity worsens with time after end of bombardment (EOB) it is proposed that extraction and administering of patient doses be done within 12 hours of target irradiation. Issues which have been recently resolved are the durability of the target (typically c.80 mg of ^{100}Mo sintered and pressed into a water-cooled Al target plate) and recovery of the ^{100}Mo feed (great than 90% efficiency); TRIUMF and University of Alberta have demonstrated yields approaching prior estimates that a 200 μA, 19 MeV cyclotron can produce c.0.4 TBq of ^{99m}Tc in a 6 hour bombardment [32,33]. Work remains to confirm the degree to which the generation of co-products ^{94}Tc, ^{95}Tc and ^{96}Tc affect patient dose.

UK APPROACH TO TECHNETIUM PRODUCTION

The high density of the UK's population is favourable to the direct production of ^{99m}Tc, and the cyclotron route is likely to hold the lowest risk in terms of accelerator development, development of associated chemistry, and licensing. To obtain the requisite 0.5M doses per year with a degree of over-capacity, development work in Canada indicates that two 19 MeV, c.300-500 μA cyclotrons would provide sufficient production. Whilst this could be implemented using commercial (normal-conducting) medical cyclotrons, it is worth noting that several novel compact accelerator technologies might also be capable of delivery the c.19 MeV output required. Compact superconducting cyclotrons have

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been developed by Ionetix at 11 MeV for hospital-based ^{13}N production for PET [34, 35], and upgrades of this design have been considered for 19 MeV output; their principal advantage is low-power operation in a small cryostat. Non-scaling FFAGs have been proposed for isotope production using an internal target, and if the necessary intensity is obtained could also in principle be applied to ^{99m}Tc [36]. The Siemens 'Oniac' - a magnet-free nested DC accelerator - has also been proposed for low-energy isotope production, and a prototype delivering protons up to several MeV is presently under development [37]. In the longer term, the use of laser-based proton acceleration may also be used for ^{99m}Tc production; proof-of-principle manufacture and extraction of ^{11}C, ^{18}F and ^{99m}Tc have been performed using single-shot irradiations. Scaled to tens of hertz repetition rates at c.50 J pulse energy would give clinically-relevant production.

DISCUSSION

The UK medical imaging community is presently considering how to address the future likely shortfall in ^{99m}Tc provision, and the national working group will produce a recommendation report later in 2014. The use of a direct cyclotron production of ^{99m}Tc has a number of advantages, but domestic developments are needed in extraction methods and their integration into the radiopharmaceutical supply chain. These include issues such as the presence of increased amounts of ^{99}Tc, or the presence of (unwanted) radioactive isotopes; licensing of new production routes and pharmaceuticals. Local production has the advantage of lower transportation times and logistical complexity, greater resilience to failure or contamination at any one production site, and more flexibility in scheduling production times. Production at a centralised radiopharmacy can achieve economies of scale using some production methods (for example fission-based methods) and may reduce licensing requirements, but direct ^{99m}Tc is produced at a single UK site would suffer from transportation issues. Whichever method is chosen it must be shown that the production cost of each dose can be made competitive with existing reactor-sourced material; recent economic analyses of cyclotron production show that production may be achieved at around £11 per dose [1]. Any future production will have to take account of the prevailing market conditions and must be based on commercial considerations.

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