In-house Cyclotron Production of High-purity Tc-99m and Tc-99m Radiopharmaceuticals

Petra Martini[1,2,*,§], Alessandra Boschi[2*,§], Gianfranco Cicoria[3], Federico Zagni[3], Andrea Corazza[3], Licia Uccelli[2], Micòl Pasquali[2], Gaia Pupillo[1], Mario Marengo[3], Massimo Loriggiola[1], Hanna Skliarova[1], Liliana Mou[1], Sara Cisternino[1], Sara Carturan[4], Laura Melendez-Alafort[5], Nikolay M. Uzunov[1], Michele Bello[4], Carlos Rossi Alvarez[1], Juan Esposito[1] and Adriano Duatti[1,6]

[1]Legnaro Laboratories, Italian National Institute for Nuclear Physics (INFN), Legnaro, Padua, ITALY,

[2]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Ferrara, ITALY,

[3]Nuclear Medicine S. Orsola Hospital, Bologna, ITALY,

[4]Department of Physics and Astronomy, University of Padua, ITALY

[5]Veneto Institute of Oncology IOV-IRSS, Padua, ITALY

[6]Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Ferrara, ITALY,

***** Corresponding authors: **Petra Martini** and **Alessandra Boschi** are to be contacted at Laboratory of Nuclear Medicine, University of Ferrara, Via Luigi Borsari, 46 - 44121 Ferrara, Italy; Tel.: +39 0532 455354; fax: +39 0532 455351. E-mail address: petra.martini@unife.it and alessandra.boschi@unife.it

§ **Author Contributions:** These authors contributed equally.

Codice campo modificato

ABSTRACT

In the last years, the technology for producing the important medical radionuclide technetium-99m by cyclotrons has become sufficiently mature to justify its introduction as an alternative source of the starting precursor $[^{99m}Tc][TcO_4]^-$ ubiquitously employed for the production of ^{99m}Tc-radiopharmaceuticals in hospitals. These technologies make use almost exclusively of the nuclear reaction $^{100}Mo(p,2n)^{99m}Tc$ that allows direct production of Tc-99m.

In this study, it is conjectured that this alternative production route will not replace the current supply chain based on the distribution of $^{99}Mo/^{99m}Tc$ generators, but could become a convenient emergency source of Tc-99m only for in-house hospitals equipped with a conventional, low-energy, medical cyclotron. On this ground, an outline of the essential steps that should be implemented for setting up a hospital radiopharmacy aimed at the occasional production of Tc-99m by a small cyclotron is discussed. These include (1) target production, (2) irradiation conditions, (3) separation/purification procedures, (4) terminal sterilization, (5) quality control, and (6) Mo-100 recovery. To address these issues, a comprehensive technology for cyclotron-production of Tc-99m, developed at the Legnaro National Laboratories of the Italian National Institute of Nuclear Physics (LNL-INFN), will be used as a reference example.

Keywords: Technetium-99m; Cyclotron; Generator; Molybdenum-100; ^{99m}Tc-radiopharmaceuticals; Hospital radiopharmacy; SPECT; European Pharmacopoeia.

Highlights

- Direct production of technetium-99m by cyclotrons through the ^{100}Mo(*p*,*2n*)^{99m}Tc nuclear reaction.
- Requisites for Mo-100 target production.
- Requisites for separation/purification of accelerator-produced [^{99m}Tc][TcO_4]$^-$.
- Quality requirements for cyclotron-produced [^{99m}Tc][TcO_4]$^-$ suitable for clinical use.

1. Introduction

The gamma-emitting radionuclide technetium-99m [$t_{1/2}$ = 6.06 h, Eγ = 140 keV (89%)] is still playing a major role in diagnostic nuclear medicine as it is commonly employed in nearly 85% of all diagnostic procedures carried out worldwide every year. Tc-99m is made easily available to hospitals through the transportable ^{99}Mo/^{99m}Tc generator system. The production of this generator is heavily dependent on the supply of the radionuclide ^{99}Mo ($t_{1/2}$ = 66 h), which in turn is produced in a few nuclear reactors around the world *via* neutron fission (Boyd, 1987; Molinski, 1982).

However, the shocking shortage of reactor-produced Mo-99 occurred a few years ago, prompted the scientific community to investigate alternative routes for Tc-99m production (Metello, 2015; NEA Nucelar development division, 2011; Pillai et al., 2013; Qaim, 2012; van der Marck et al., 2010; Ruth, 2014; Guerin et al., 2010). An attractive solution has already emerged, which is grounded on the direct cyclotron production of Tc-99m through the ^{100}Mo(*p*,*2n*)^{99m}Tc nuclear reaction. (Beaver and Hupf, 1971; Boschi et al., 2017; Boyd, 1987; Esposito et al., 2013; Manenti et al., 2014; Pillai et al., 2013; Qaim, 2015; Ruth, 2009, 2014; Scholten et al., 1999; Schaffer et al., 2015). Preliminary cross-section measurements and experimental studies have convincingly shown that this route is feasible and the optimal proton energy for Tc-99m production falls within the range 15–24 MeV (Esposito et al., 2013). This energy range is easily accessible by conventional medical cyclotrons, thus allowing direct production of Tc-99m to meet routine local demand (Bernard et al., 2014; Shaffer et al., 2015). It is important to note that quality specifications for the purity of the final [^{99m}Tc][TcO_4]$^-$ have been described in a monograph on accelerator-produced sodium ^{99m}Tc-pertechnetate for injection recently published in the European Pharmacopoeia (Ph. Eur., 2018). This document provides the necessary regulatory framework for the safe application of cyclotron-produced Tc-99m to the production of ^{99m}Tc-radiopharmaceuticals.

Depending on the irradiation conditions and other relevant parameters (see below), the activity produced in a single run can switch between 0.037 to 37 GBq or higher. Thus, two possible arrangements could be envisaged for the supply of cyclotron-produced Tc-99m: (a) centralized radiopharmacy producing high activities of Tc-99m (and, possibly, of Tc-99m radiopharmaceuticals) that are then distributed to hospitals nearby, or (b) in-house hospital radiopharmacy producing daily small amounts of Tc-99m according to its internal needs. We considered that in-house production

would be of higher interest for the nuclear medicine community since this could offer a convenient way out in the event of a temporary shortage of Tc-99m supply. For this reason, the purpose of this paper is to outline a possible set-up of a hospital radiopharmacy for pursuing cyclotron-production of $[^{99m}Tc][TcO_4]^-$ to be used as precursor for the preparation of injectable ^{99m}Tc-radiopharmaceuticals.

2. Experimental

2.1. Materials and methods

Technetium-99m, as $Na[^{99m}TcO_4]$ in physiological solution, was obtained from a Drytec™ $^{99}Mo/^{99m}Tc$ generator (GE Healthcare, UK).

Mo-100 enriched molybdenum powder was purchased from Isoflex (San Francisco, USA). The isotopic composition of the batch of the enriched material was: ^{100}Mo (99.86%), ^{98}Mo (0.115%), ^{97}Mo (0.005%), ^{96}Mo (0.005%), ^{95}Mo (0.005%), ^{94}Mo (0.005%), and ^{92}Mo (0.005%).

Gamma spectrometric measurements were performed using a High-Purity Germanium (HPGe) detector (Canberra, Meriden, USA) and traced back to the End-Of-Separation (EOS) time. Radionuclides were identified from the acquired spectra by Genie 2000 software (Canberra, Meriden, USA). The day before the experiment, efficiency calibration was carried out in the energy window 59−1836 keV, using a multipeak certified source (LEA SEARCH Areva, France) and according to IEC 61452 standards (IEC, 1995), using Genie 2000 software.

Thin-layer chromatography (TLC) was performed on paper strips (Whatman chr 1, Merck Sigma-Aldrich, Darmstadt, Germany) using both saline and methanol/water (80:20 v/v) as mobile phases.

2.2. Cyclotron

Any commercial cyclotron, commonly employed for the production of ^{18}F-radiopharmaceuticals, with proton energy ranging from 16.5 to 24.0 MeV, is suitable for in-house Tc-99m production. To accomplish irradiation of a solid target, the cyclotron should be equipped with an external beam line for extracting the proton current and a solid target station (irradiation unit).

In this study, a GE PETtrace cyclotron (E_{max} = 16.5 MeV, I_{max} = 100 μA) (GE Healthcare, USA) was equipped with an irradiation unit outfitted with a target holder consisting of two circular copper plates clumping the target (Fig. 1). A 15-mm hole was drilled through the plate standing in front of the beam line to allow exposure of the target to the proton current. A double cooling system flushed a stream of He gas and of water onto the front and the back of the target, respectively. After irradiation, the Mo-100 metallic foil was dropped automatically into a shielded container and transported to the hot laboratory. A detailed description of this irradiation unit was reported previously (Fig. 2) (Cicoria et al., 2006).

2.3. Target design and manufacturing

Mo-100 targets can be manufactured in different shapes depending on the geometrical requirements of the irradiation unit Hou et al., 2016a). Several methods can be employed for target preparation including (a) pressing and sintering of metallic Mo-100 powders (German, 1996), (b) physical vapor

deposition (PVD) of metallic Mo-100 foils (Kelly and Arnell, 2000), and (c) melting of metallic Mo-100 powders followed by high-pressure lamination.

In this work, thin circular metallic coins (∅ = 15.0 ± 0.2 mm) were obtained by hot isostatic pressing (100 MPa) of ^{100}Mo-enriched metallic powders followed by heating at 1700 °C (Atkinson, H. V., Davies, S., 2000). Coins were inserted into the target holder and then clamped. The two important parameters, thickness and total mass, were fixed at values 260 ± 11 µm and 450 ± 25 mg, covering the useful energy range (~~Ein~~E_{in} = 15.0 MeV,- ~~9.6~~E_{out} ~ 5.4 MeV) according to theoretical calculations of the ^{100}Mo(*p*,*2n*)^{99m}Tc nuclear reaction yield (Esposito, J., 2013). Another critical parameter was the percentage of ^{100}Mo-enrichment of the targets, which should not be lower than 99.50% and was fixed here at 99.86%.

ha formattato: Pedice

ha formattato: Pedice

2.4. Irradiation conditions

A broad range of experimental conditions has been reported for target irradiation depending on proton energy and beam current. However, using the experimental setup described above and taking into account the average daily request of Tc-99m activity of a conventional SPECT radiopharmacy, optimized irradiation conditions could be determined. These results indicated that the targets can be conveniently irradiated with a beam current of 80 µA, at proton energy of 15.0 MeV, over a period of 120 min. Under these conditions the expected yield of Tc-99m at the end of saturation bombardment is approximately 1.83 GBq/µA.

2.5. Chemical target processing

To complete the whole production process, a purification step should be accomplished. The most efficient approach was to make use of an automated module capable of receiving the irradiated target from the solid target transfer system and delivering a final vial containing the purified Tc-99m under the chemical form of pertechnetate anion, [^{99m}Tc][TcO_4]$^-$. Currently, a number of different purification procedures have been developed corresponding to just as many automated modules (Boschi et al., 2017). Interestingly, it is now possible to assemble a purification module for the chemical processing of the irradiated target in-house based on the selected separation procedure. Essentially, the purification process should involve the following steps: (a) target dissolution, (b) phase extraction/chromatographic separation of [^{99m}Tc][TcO_4]$^-$, (c) filtration/recovery of the final activity in a sterile vial. Each step can be conveniently accomplished using a commercially available, pre-fabricated module (or a combination of modules) that is finally assembled with the other modular components to yield a customized, fully complete separation apparatus.

In this study, a solvent extraction method was utilized for Tc-99m separation and purification by exploiting the well-known affinity of the pertechnetate anion for methyl-ethyl ketone (MEK). The resulting, remotely controlled apparatus (Fig. 3) was fabricated by assembling flexible modular units (ModularLab, Eckert&Ziegler, Berlin, Germany) connected with a hand-made, solvent extraction glass column (length=15 cm, ∅=1 cm), as previously described (Martini et al. 2016), and an especially designed reactor heater, having a bottom-opened vial and an air compressed cooling system, suited for the dissolution and separation process of the in-hospital high yield technetium-99m production. A block diagram of the complete extraction and purification procedure is shown in Fig. 4. All chemicals and reagents involved in the purification process were of analytical grade, unless otherwise specified. Hydrogen peroxide 30% w/w and sodium hydroxide pellets, 97+%, A.C.S. were purchased from Sigma-Aldrich (Milano, Italy). Methyl Ethyl Ketone (MEK) was purchased from Carlo Erba (Milano, Italy) and sodium chloride 0.9% from Fresenius Kabi (Isola della Scala, Verona,

Italy). Silica and acidic alumina SepPak Cartridges were obtained from Waters Corporation (Milford, MA, USA).

2.6. Quality control

Analytical methods for assessing radionuclidic (RP) and radiochemical purities (RCP) of the final $[^{99m}Tc][TcO_4]^-$ were selected according to the monograph on cyclotron produced Tc-99m published on the European Pharmacopoeia (European Pharmacopoeia 9.3, 2018). In this monograph, RP was assessed by gamma spectroscopy and should be not lower than 99.7%. RCP was determined by TLC using a physiological solution as eluent. In this system, Tc-99m colloidal impurities remained at the origin ((R_f = 0.0) whereas $[^{99m}Tc][TcO_4]^-$ migrated to the front (R_f = 0.9). A confirmatory quality control was performed using a methanol/water mixture (80:20 v/v) as mobile phase. Results showed again only the migration of $[^{99m}Tc][TcO_4]^-$ to the middle of the strip (R_f = 0.6) and retention of Tc-99m impurities at the origin (R_f = 0.0). It should be noted that these radioactive spots always ~~includes~~include tracer amount of the other technetium radioisotopes under the same chemical forms. According to Ph. Eur. requirements (95%), RCP was always found ≥ 99%.

As an additional quality control, comparison of the tomographic imaging performance of a conventional gamma camera (Siemens E.CAM dual-head gamma camera equipped with a low-energy high-resolution collimator, Siemens Healthcare, Milan, Italy) was undertaken with cyclotron- and generator-produced $[^{99m}Tc][TcO_4]^-$. Planar spatial resolution and tomographic performance was assessed with a 9 point-like sources planar grid and Jaszczak phantom (Jaszczak SPECT Phantom, Biodex Medical System, NY), respectively (IAEA, 2009).

The planar grid phantom, made of 9 small holes at a mutual distance of 5 cm in the cross points of a rectangular net, was filled with 185 kBq (5μCi, 1 μL) of ^{99m}Tc-pertechnetate and placed at a 10-cm distance from the detector head. Acquisitions were set at 30 minutes (1024 × 1024 matrix, pixel dimensions, 0.6 × 0.6 mm) and collected 8 and 12 h after EOB. Images were analyzed using the Sun-Java-based ImageJ software (Dougherty, 2009).

A Jaszczak phantom filled with 259 MBq (5650 mL, 7 mCi) of $[^{99m}Tc][TcO_4]^-$ was imaged using the following parameters: acquisition time, 60 minutes; angular step, 3°/frame; time 60 s/frame; angle of rotation 180°; matrix dimensions of reconstructed slices 128 × 128. The image reconstruction was performed using the filtered-back-projection method (FBP), considering a slice thickness of 4.795 mm, and was corrected for attenuation by using Chang method with linear attenuation value $\mu = 0.11$ cm^{-1}. The spatial uniformity and noise, calculated as standard deviation of counts, were evaluated by considering a region-of-interest (ROI) in the upper uniform section of the phantom. The contrast resolution was calculated by considering 6 different ROIs centered on the 6 spheres, located in the upper sector of the phantom.

2.7. Radiopharmacy setup

~~Likewise~~Likewise, conventional synthesis module for the preparation of PET radiopharmaceuticals, the Tc-99m purification module could be housed inside a hot cell with an internal controlled atmosphere (grade B). Sterilization of the final $[^{99m}Tc][TcO_4]^-$ solution was carried out preferably by autoclaving. For comparison, sterile filtration was conducted inside a grade A isolator (Tema Sinergie S.p.A., Faenza, Italy) by passing the final $[^{99m}Tc][TcO_4]^-$ solution through a 0.2-μm sterile filter (Millipore Express® SHF, Merck Millipore, US). A grade D laboratory environment is sufficient to ensure biological safety standards, particularly when terminal sterilization is applied.

2.8. Radiopharmaceuticals preparation

To check the labeling efficiency of the cyclotron produced [^{99m}Tc][TcO_4]$^-$, a number of ^{99m}Tc-radiopharmaceuticals have been prepared using the corresponding kit formulations and following the procedures described therein. For this purpose, representative ^{99m}Tc-radiocomplexes possessing a characteristic chemical motif were selected as follows: ^{99m}Tc-ECD (Neurolite®, Lantheus Medical Imaging, N. Billerica, MA), ^{99m}Tc-HMPAO (HMPAO Hexamethylpropyleneamine Oxime, CERETC™), ^{99m}Tc-Tetrofosmin (Myoview™, GE Healthcare, US), ^{99m}TcN-NOET [(NOET = *N,N'*-bis(ethoxyethyl)dithiocarbamato, Cisbio, Saclay, France], [$^{99m}Tc(CO)_3(H_2O)_3]^+$ (Isolink™, Covidien, Petten, The Netherlands) and ^{99m}Tc-HYNIC-TOC (^{99m}Tc-TEKTROTYD, Polatom, Otwock, Poland). Quality control (RCP) of the final radiopharmaceuticals was carried out strictly following supplier's instructions.

2.9. Target recovery

After removal of the organic phase, treatment of the alkaline aqueous fraction by refluxing excess HNO_3 (5 M) for 8 h, converted residual Mo-100 into molybdic acids and MoO_3 (main product). Evaporation of the solvent to dryness enabled to isolate molybdic acid and MoO_3 by repeated dissolution of the solid residue in small amount of water (5 mL) followed by centrifugation to separate mother liquors from $NaNO_3$ precipitate. When dried in vacuum at 40°C, the combined aqueous fractions yielded MoO_3 as a white powder.

3. Results and Discussion

Aim of the present work was to provide an outline of the experimental setup and operations that should be put in action for attaining in-house production of Tc-99m using a conventional (low energy) medical cyclotron. In the last years, a zealous experimental work has been pursued worldwide to demonstrate the practical feasibility of the direct production of Tc-99m through the nuclear reaction ^{100}Mo(*p*,*2n*)^{99m}Tc. This route employs highly enriched Mo-100 as solid target irradiated by a proton beam. The essential components for setting up of a cyclotron-production of Tc-99m are: (a) target manufacturing, (b) target irradiation, (c) target chemical processing and (d) quality control of the final Tc-99m.

A critical parameter for target production is the isotopic purity of the metallic Mo-100, the main substrate of the nuclear reaction (Hou et al. 2016a). To fulfill the requirements of the Ph. Eur. Monograph radionuclidic purity of the cyclotron produced Tc-99m (RP) must be ≥ 99.7%. It turns out that, to conform to this limit, isotopic purity of Mo-100 should not be less than 99.5%. This value ensures that RP will surely fit within Ph. Eur. requirements whatever proton energy between 15−24 MeV. At higher proton energies, the amount of radioactive contaminants, particularly other technetium radioisotopes, could dramatically increase because of the opening of additional reaction channels. In this study, an isotopic purity of 99.86% for Mo-100 was strictly preserved during target production.

Although a variety of methods for target manufacturing are available and provide quite satisfactory results, hot isostatic pressing was used in this study to fabricate circular Mo-100 targets (∅ = 15.0 ± 0.2 mm), weighing 450± 25 mg. In view of the emphasis here on in-house cyclotron production of Tc-99m, this technology has been deemed as sufficiently available also in laboratories not specifically

dedicated to manufacturing targets for nuclear physics and, thus, easily accessible. Target thickness had also a key impact on the yield of Tc-99m production. Using a beam current of 80 μA and a target thickness of 260 ± 11 μm, a final yield of approximately 30 ± 6 GBq (*ca.*, 1 Ci) was attained at EOB after 2-h irradiation at proton energy of 15.6 MeV. This amount of Tc-99m radioactivity is largely sufficient to satisfy the needs of a conventional nuclear medicine department equipped with one SPECT camera.

Chemical processing of the irradiated target is necessary to achieve efficient separation and purification of the final radionuclide. This can be obtained using different separation methods, but all of these technologies share the same common feature, namely that they can be accomplished by means of remotely-controlled, automated modular devices. The modular system utilized here was described elsewhere (Martini et al., 2016) and it was only slightly upgraded to optimize its performance. In particular, the dissolution procedure (Fig. 4) has been modified to deal with target masses up to 500 mg and different target configurations, such as multiple foils, single coin, or thick/thin film deposited on a backing material with different techniques. Target dissolution by hydrogen peroxide (H_2O_2), carried out at 90 °C under a helium stream, was improved by consecutively empting out and replenishing the reactor vessel three times by fresh H_2O_2 while collecting the three fractions in the phase-extraction column. This stepwise addition avoided surface passivation of the metallic foil. The whole procedure lasted approximately 60 ± 3 min, hence 10 min less than the previously described procedure (Martini et al., 2016). The recovery yield was about 93 ± 3% (decay corrected).

Quality control of the final $[^{99m}Tc][TcO_4]^-$ was performed according to analytical methods and procedures described in the Ph. Eur. monograph on accelerator-produced ^{99m}Tc-pertechnetate (European Pharmacopoeia, 9.3). RP was fully consistent with the proposed pharmaceutical requirements. Detailed analysis on radionuclidic impurities in the final product is described in Table 1. Similarly, radiochemical purity of $[^{99m}Tc][TcO_4]^-$ (RCP) was ≥ 99.95% and the specific activity of Tc-99m was estimated to be 4.1E+07 GBq/g at the EOS.

Since $[^{99m}Tc][TcO_4]^-$ is chemically stable also in boiling water, sterilization of the final ^{99m}Tc-pertechnetate was carried out by autoclaving (121 °C, 15 min).

To evaluate the labeling efficiency of accelerator-produced $[^{99m}Tc][TcO_4]^-$, labeling reactions have been conducted using commercial kit formulations and final RCP was determined according to instructions provided by the commercial supplier or following literature methods. Radiopharmaceuticals containing characteristic Tc-99m chemical motifs (^{99m}Tc-cores) were selected to cover the most common labeling procedures. More precisely, the following radiocompounds were prepared as representative examples of the corresponding ^{99m}Tc-cores: (*i*) ^{99m}Tc-ECD (^{99m}Tc-oxo, $[^{99m}Tc{\equiv}O]^{3+}$) , (*ii*) ^{99m}Tc-Tetrofosmin (^{99m}Tc-dioxo, $[O{=}Tc{=}O]^+$), (*iii*) ^{99m}TcN-NOET (^{99m}Tc-nitrido, $[^{99m}Tc{\equiv}N]^{2+}$), (*iv*) $[^{99m}Tc(CO)_3(H_2O)_3]^+$ (^{99m}Tc-*tris*-carbonyl, $[^{99m}Tc(CO)_3]^+$) and (*v*) ^{99m}Tc-HYNIC-Tyr^3-Octreotide (^{99m}Tc-hydrazido, [^{99m}Tc-HYNIC]) (Duatti, 2011; Boschi, 2013; Gabriel et al., 2003; Badar et al., 2014). Comparison of RCP values, as measured for both cyclotron- and generator-produced ^{99m}Tc-radiopharmaceuticals, did not reveal any substantial deviation from the expected quality requirements.

ha formattato: Apice

It should be noted that, in dealing with labeling reactions, the major difference between accelerator- and generator-produced Tc-99m might arise from the presence, in the former, of other technetium radioisotope impurities not affecting the generator eluate (Uccelli et al., 2013; Selivanova et al., 2015). These contaminants cannot be separated by chromatography, as they are chemically indistinguishable from Tc-99m itself. Therefore, it is not expected to observe any difference in the labeling yields of ^{99m}Tc-radiopharmaceuticals prepared with these two types of Tc-99m precursors when RCP is measured by conventional chromatographic methods (TLC and HPLC). Also the RCPs

of cyclotron and generator produced [^{99m}Tc]Tc-HMPAO (HMPAO Hexamethylpropyleneamine Oxime, CERETC^{TM}), that known to be particularly sensitive to the quality of ^{99m}Tc-pertechnetate, were comparable both at the end of the preparation, and at the expiry time. Imaging Tests with Accelerator-produced Tc-99m by Conventional Medical Cyclotron (G. Pupillo et al., 2016).

However, some evidence of the influence of other gamma-emitting technetium radioisotopes could be found by careful examination of the quality of SPECT images. For this reason, additional quality controls were accomplished to ascertain whether there exists any impact of the accelerator-produced starting material [^{99m}Tc][TcO_4]$^-$ over image's spatial resolution, contrast, noise and uniformity. Phantom studies have been carried out using a planar-grid and Jaszczak phantoms imaged by a conventional SPECT camera (Figs. 5 and 6). When these phantoms were filled with [^{99m}Tc][TcO_4]$^-$, no detectable discrepancies were observed between quality of images as obtained with both cyclotron-produced and generator-produced Tc-99m. More precisely, average FWHM spatial resolution, measured at 8 and 12 h after EOB, were 7.46 ± 0.17 (X axis) and 7.63 ± 0.20 (Y axis), and 7.67 ± 0.22 (X axis) and 7.81 ± 0.32 (Y axis), respectively. These values were in close agreement with those collected with generator-eluted Tc-99m, *i.e.*, 7.40 ± 0.29 (X axis) and 7.38 ± 0.16 (Y axis). In Table 2 tomographic imaging performance of the gamma camera obtained with Jaszczak phantom for generator-eluted and accelerator-produced ^{99m}Tc is reported.

Experimental findings clearly demonstrated that this approach can be efficiently used as a reliable alternative method for supplying [^{99m}Tc][TcO_4]$^-$ in high purity and, thus, usable for routine preparation of ^{99m}Tc-radiopharmaceuticals (IAEA 2017). Recently, the European Pharmacopoeia (Ph. Eur.) drafted a monograph, that will become effective in 2018, precisely addressing the quality requirements of accelerator-produced [^{99m}Tc][TcO_4]$^-$. Obviously, these quality standards will become mandatory for all Tc-99m productions carried out by cyclotrons within the European Union (EU) and, concomitantly, the published monograph will also constitute an authoritative reference globally.

It is worthy to point out here that replacement of the current supply chain of Tc-99m, based on ^{99}Mo/^{99m}Tc generators, is considered as highly unlikely owing to its well-established efficiency and worldwide acceptance. Therefore, cyclotron production of Tc-99m should be reasonably viewed as an emergency procedure that could easily take over the conventional generator approach in the event of some unexpected and disruptive failure of Mo-99 global production by nuclear reactors. This argument further supports the vision that accelerator-based methods might become more useful for local production in hospitals equipped with a medical cyclotron to meet an exceptional demand of Tc-99m originating from unpredictable shortages.

Furthermore, regarding the cyclotron-produced Tc-99m, we expect that the production cost, considering also the enriched target material recycle, could amount to nearly 2$/mCi. In 2008, before the Mo-99 shortage happened, the cost of Tc-99m sodium pertechnetate obtained from generator was estimated at around 0.36$/mCi (National Research Council, 2009) We have estimated, on our regional scale, that in the past ten years the price of Tc-99m sodium pertechnetate obtained from generator is doubled, about 0.77$/mCi. If considering that in 2018 is expected the permanent shutdown of the NRU reactor (Chalk River – Canada) (Osborne, 2016), that ensured about 2/3 of the Mo-99 world demand, the generator-produced Tc-99m price may further increase.

4. Conclusions

Cyclotron-produced Tc-99m has rapidly become an alternative approach that could guarantee a reliable source of this essential diagnostic radionuclide in the circumstance of any drawback and vulnerability of the conventional distribution network of ^{99}Mo/^{99m}Tc generators. However, it has not been demonstrated yet that this approach could fully replace the existing supply chain and, therefore, its usefulness seems currently limited to in-house production in a hospital radiopharmacy paralleling the production of other cyclotron-produced radionuclides. From this point of view, it is reasonable to figure that a production system easy to be installed into a conventional SPECT radiopharmacy, and that does not require any special equipment and material, would be greatly advantageous to enable in-situ implementation of this new route for producing Tc-99m.

Although small-cyclotron technology is well established, the design of a target station suitable for Mo-100 irradiation and of a modular unit for target chemical processing had to be fully envisioned.

In the present study, –emphasis was always given to in-house production carried out in a conventional hospital radiopharmacy considering highly desirable that the end user could easily reproduce the proposed technical solutions. In particular, the use of pressed metallic Mo-100 coins does not demand for a complex technology for target manufacturing. When combined with low beam currents and short irradiation times, this simplified technology can be easily fitted within the daily schedule of a radiopharmacy producing positron-emitting radionuclides when necessary. Similarly, the selected method of separation of Tc-99m from residual Mo-100 was inspired by illustrious results described decades ago when the first ^{99}Mo/^{99m}Tc generators were developed (Dash et al., 2013). The extraordinary affinity of the pertechnetate anion against MEK makes this extraction process extremely efficient and inexpensive. In summary, the production system described here might be suitable for sporadic, small-scale production of Tc-99m, thus weakening the dependence of this key radionuclide on the global supply chain and ensuring its constant availability.

Acknowledgement

This work was carried out within the framework of the TECHN-OSP research program and was financially supported by the CSN5 Committee of the Italian National Institute of Nuclear Physics (INFN).

References

Atkinson, H. V., Davies, S., 2000. Fundamental aspects of hot isostatic pressing: An overview. Metall and Mat Trans A, 31, 2981–3000.

Badar, A., Williams J., de Rosales, R.T., Tavaré, R., Kampmeier, F., Blower, P.J., Mullen, G.E., 2014. Optimising the radiolabelling properties of technetium tricarbonyl and His-tagged proteins. EJNMMI Res. 4, 14. doi: 10.1186/2191-219X-4-14.

Beaver, J.E., Hupf, H.B., 1971. Production of ^{99m}Tc on a medical cyclotron: a feasibility study. J. Nucl. Med. 12, 739–741.

Bénard, F., Buckley, K.R., Ruth, T.J., Zeisler, S.K., Klug, J., Hanemaayer, V., et al., 2014. Implementation of Multi-Curie Production of ^{99m}Tc by Conventional Medical Cyclotrons. J. Nucl. Med. 55, 1017–1022.

Boschi, A., Martini, P., Pasquali, M., Uccelli, L., 2017. Recent achievements in Tc-99m radiopharmaceutical direct production by medical cyclotrons. Drug. Dev. Ind. Pharm. 9, 1402−1412.

Boschi, A., Uccelli, L., Pasquali, M., Pasqualini, R., Guerrini, R., Duatti, A., 2013. Mixed tridentate p-donor and monodentate p-acceptor ligands as chelating systems for rhenium-188 and technetium-99m nitride radiopharmaceuticals. Curr. Radiopharm. 6, 137–145.

Boyd, R.E., 1987. Technetium Generators: Status and Prospects. Radiochim. Acta. 41, 59−64.

Chattopadhyay, S., Barua, L., De, A., Dasa, S.S., Kuniyil, R., Bhaskar, P., et al., 2012. A computerized compact module for separation of (^{99m})Tc-radionuclide from molybdenum. Appl. Radiat. Isot. 70, 2631–2637.

Cicoria, G., Pancaldi, D., Piancastelli, L., Giovaniello, G., Bianconi, D., Bollini, D., et al., 2006. Development and operational test of a solid target for the PETtrace cyclotron. Q. J. Nucl. Med. Mol. Imaging. Suppl. 1, 50, 3−4.

Dash, A., (Russ) Knapp Jr., F.F., Pillai, M.R.A., 2013. ^{99}Mo/^{99m}Tc separation: An assessment of separation technology options. Nucl. Med. Biol. 40, 167−176.

Dougherty G., 2009. Digital Image Processing for Medical Applications, Cambridge University Press, ISBN 978-0-521-86085-7.

Duatti, A. 2011. Fundamentals of technetium and rhenium chemistry. In Sampson's Textbook of Radiopharmacy, 4th Ed., London: Pharmaceutical Press, Chapter 8, pp. 101−124.

Esposito, J., Vecchi, G., Pupillo, G., Taibi, A., Uccelli, L., Boschi, A., et al., 2013. Evaluation of ^{99}Mo and ^{99m}Tc Productions Based on a High-Performance Cyclotron. Sci. Technol. Nucl. Ins. 2013, 1−14.

European Pharmacopoeia 9.3. Sodium pertechnetate (^{99m}Tc) injection (accelerator produced). 01/2018: 2891, 4801−4803 (published online at http://online6.edqm.eu/ep903/).

Gabriel, M., Decristoforo, C., Donnemiller, E., Ulmer, H., Rychlinski, C.W., Mather, S.J., Moncayo, R. 2003. An intrapatient comparison of ^{99m}Tc-EDDA/ HYNIC-TOC with ^{111}In-DTPA-octreotide for diagnosis of somatostatin receptor–expressing tumors. J. Nucl. Med. 44, 708–716.

German, R.M., 1996. Sintering Theory and Practice. John Wiley & Sons, Inc., ISBN 0-471-05786-X

Codice campo modificato
Codice campo modificato
Codice campo modificato
Codice campo modificato
Codice campo modificato

Guerin, B., Tremblay, S., Rodrigue, S., Rousseau, J.A., Dumulon-Perreault, V., Lecomte, R., et al., 2010. Cyclotron production of Tc-99m: an approach to the medical isotope crisis. J. Nucl. Med. 51, 13N-16N.

Hou, X., Tanguay, J., Buckley, K.R., Schaffer, P., Bénard, F., Ruth, T.J., et al., 2016a. Molybdenum target specifications for cyclotron production of ^{99m}Tc based on patient dose estimates. Phys. Med. Biol. 61, 542–553.

Hou, X., Tanguay, J., Vuckovic, M., Buckley, K., Schaffer, P., Bénard, et al., 2016b. Imaging study using radiopharmaceuticals labeled with cyclotron-produced ^{99m}Tc. Phys. Med. Biol. 61, 8199–8213.

IAEA, 2009. Quality Assurance for SPECT Systems, IAEA, Human Health Series 6, International Atomic Energy Agency, Vienna.

IAEA, 2017. Cyclotron based production of technetium-99m. Radioisotopes and Radiopharmaceuticals Reports, International Atomic Energy Agency, Vienna.

IEC61452:1995, Nuclear instrumentation – Measurement of gamma-ray emission rates of radionuclides – Calibration and use of germanium spectrometers. International Electrotechnical Commission, 1995.

Kelly, P.J., Arnell, R.D. 2000. Vacuum 56, 159−172.

Manenti, S., Holzwarth, U., Loriggiola, M., Gini, L., Esposito, J., Groppi, F., et al., 2014. The excitation functions of ^{100}Mo(p,x)^{99}Mo and ^{100}Mo(p,2n)^{99m}Tc. Appl. Radiat. Isot. 94, 344-348.

Martini, P., Boschi, A., Cicoria, G., Uccelli, L., Pasquali, M., Duatti, A., et al., 2016. A solvent-extraction module for cyclotron production of high-purity technetium-99m. Appl. Radiat. Isot. 118, 302–307.

Metello, L.F., 2015. ^{99m}Tc-tecnetium shortage: old problems asking for new solutions. J. Med. Imag. Radiat. Sci. 46, 256–261.

Molinski, V.J., 1982. A review of ^{99m}Tc generator technology. Int. J. Appl. Radiat. Isot. 33, 811−819.

National Research Council of the National Academies 2009. Chapter 6: Molybdenum-99/Technetium-99m production costs, in Medical Isotope Production Without Highly Enriched Uranium. The National Academies Press, Washington, DC, USA.

Nuclear Energy Agency (NEA) Nuclear development division. 2011.The supply of radioisotopes: the path to reliability. OECD; 8, Technologies for producing Molybdenum-99/Technetium-99m; pp. 101–106.

Osborne, J., 2016. NRU Mo-99 Production. Presentation to Mo-99 2016 Topical Meeting. s.l.:Atomic Energy of Canada Limited (AECL).

Pillai, M.R.A., Dash, A., Knapp, F.F.R. Jr., 2013. Sustained availability of ^{99m}Tc: possible paths forward. J. Nucl. Med. 54, 313–323.

Pupillo, G., Zagni, F., Corazza, A., Cicoria, G., Martini, P., Boschi, A., Uccelli, L., Pasquali, M., Duatti, A., Di Domenico, G., Marengo, M., Taibi, A., Loriggiola, M., Bello, M., Uzunov, N., Esposito, J. 2016. Imaging Tests with Accelerator-produced Tc-99m by Conventional Medical Cyclotron. Legnaro, Padova: INFN-LNL Annual Report 2015.

Qaim, S.M., 2012. The present and future of medical radionuclide production. Radiochim. Acta 100, 635–651.

Qaim, S.M., 2015. Nuclear data for medical radionuclides. J. Radioanal. Nucl. Chem. 305, 233–245.

Ruth, T.J., 2009. Accelerating production of medical radioisotopes. Nature 437, 536–537.

Ruth, T.J., 2014. The medical isotope crisis: how we got here and where we are going. J. Nucl. Med. Technol. 42, 245–248.

Schaffer, P., Bénard, F., Bernsteind, A., Buckley, K., Celler, A., Cockburn, N., et al., 2015. Direct production of ^{99m}Tc via ^{100}Mo(p,2n) on small medical cyclotrons. Physics Procedia 66, 383–395.

Scholten, B., Lambrecht, R.M., Cogneau, M., Vera Ruiz, H., Qaim, S.M., 1999. Excitation functions for the cyclotron production of ^{99m}Tc and ^{99}Mo. App. Radiat. Isot. 51, 69–80.

Selivanova, S.V., Lavallée, E., Senta, H., Caouette, L., Sader, J.A., Van Lier, E.J., et al., 2015. Radioisotopic purity of sodium pertechnetate ^{99m}Tc produced with a medium-energy cyclotron: implications for internal radiation dose, image quality, and release specifications. J. Nucl. Med. 56, 1600−1608.

Uccelli, L., Boschi, A., Pasquali, M., Duatti, A., Di Domenico, G., Pupillo, G., et al., 2013. Influence of the generator in-growth time on the final radiochemical purity and stability of Tc-99m radiopharmaceuticals. Sci. Technol. Nucl. Ins. 2013, 1−7.

van der Marck, S.C., Koning, A.J., Charlton, K.E., 2010. The options for the future production of the medical isotope ^{99}Mo. Eur. J. Nucl. Med. Mol. Imag. 37, 1817–1820.

Captions to Figures and Tables

Fig. 1. The solid target station assembled with the GE-PETtrace cyclotron used in this study

Fig. 2. Pictures and scheme of the essential components of the target unit: copper circular plates of the target holder (a), assembled target (b), back view of the target after inclusion in the solid target unit (c) and a schematic diagram of the target assembly (d) .

Fig. 3. On the left a schematic drawing of the extraction process; on the right picture of the automated solvent extraction and purification module. (1) dissolution reactor, (2) solvent-extraction column, (3) silica column, (4) alumina column, (5) waste, (6) final Tc-99m solution, (7) H_2O_2, (8) NaOH, (9/10) MEK, (11) H_2O, (12) saline.

Fig. 4. Flow chart for the solvent-extraction and purification process.

Fig. 5. Planar image of a grid phantom filled with cyclotron-produced ^{99m}Tc-pertechnetate at 8 h after EOB.

Fig. 6. SPECT images of two Jaszczak phantoms filled with generator- and accelerator-produced [^{99m}Tc]TcO_4^-, respectively. (A) Uniformity and noise. (B) Contrast. (C) Spatial resolution (rods'diameters, 4.8, 6.4, 7.9, 9.5, 11.1 and 12.7 mm).

Table 1. Radioisotopic impurities amount measured by γ-spectrometry in the final product Tc-99m pertechnetate at the EOS (decay corrected).

Table 2. Tomographic imaging performance of the gamma camera obtained with Jaszczak phantom for generator-eluted and accelerator-produced ^{99m}Tc.

Table 1

%	RP	Error (±)
^{99m}Tc	99.960	0.006
^{93m}Tc	1.60E-03	7E-05
^{93g}Tc	1.5E-02	3E-03
^{94m}Tc	7E-02	3E-02
^{94g}Tc	1.9E-01	4E-02
^{95g}Tc	6E-02	1E-02
^{96}Tc	1.5E-02	2E-03
^{95m}Tc	2.8E-04	6E-05
^{97}Tc	3.4E-03	2E-04

Table 2

	Generator-eluted ^{99m}Tc	Cyclotron-produced ^{99m}Tc
Tomographic Uniformity	15.2%	17.0%
Noise	9.7%	11.6%
Contrast sphere 31.8 mm	68.5%	67.0%
Contrast sphere 25.4 mm	57.0%	52.0%
Contrast sphere 19.1 mm	36.7%	37.9%
Contrast sphere 15.9 mm	30.0%	35.3%
Contrast sphere 12.7 mm	21.8%	19.5%
Contrast sphere 9.5 mm	8.3%	13.7%