Middle East Journal of Scientific Publishing
Vol. (6) Issue (1)
Edition 18th
2023 (169 - 193)

ADVANTAGES AND LIMITATIONS OF ALTERNATIVE ISOTOPES TO TECHNETIUM 99-m IN NUCLEAR MEDICINE

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Published on: 6 Mar. 2023

ABSTRACT

The recent unexpected closure of the Chalk River, Canada, reactor and the high flux reactor, The Netherlands, at the same period in 2010 as the main supplier of radionuclides in the world lead to major interruption in the supply of the most important radionuclide used in medicine nowadays, Molybdenum-99 (Mo-99). In addition to this period, another shortage of Mo-99 supply occurred during the last decade resulting from maintenance of some other smaller reactors. Mo-99 is the source (parent) of Technetium-99m (Tc-99m) (daughter) which is used in about 80% of all nuclear medicine imaging procedures. Tc-99m has many characteristics which make it the preferable radionuclide in clinical applications. For example, it can be produced easily from a small onsite generator containing Mo-99 in a few minutes. Then, the decay of the source's activity (half-life) is approximately 6 hours, which is a short time and suitable for most diagnostic examinations, resulting in low patient dose and good image quality. In addition, decay of product is an important factor for imaging; hence Tc-99m producing pure gamma radiation at 140 kilo electron Volts (keV) is an ideal radionuclide. However, when this crisis occurred in 2010, some alternative radionuclides were applied in most of the nuclear medicine procedures, such as Rubidium-82 (Rb-82) and Thalium-201 (Tl-201). The difference in the physical and biological properties of these alternatives must be considered and studied, then compared with Tc-

99m properties for accurate images and lower patient doses. For example, with the myocardial perfusion test, Rb-82 characteristics are more useful than Tl-201 for better imaging results, a shorter physical half-life at 78 seconds and 73 hours respectively, lower radiation dose to the patient and an onsite generator for production. However, despite these advantages of Rb-82, Tl-201 is the most available technique nowadays and can be applied by classical imaging methods (planar) without a computer to process the image. Then, the cost of installation of an Rb-82 facility is high. In addition, imaging techniques are another reason to be considered because Rb-82 has a detection process of positron emissions, while Tl-201 has the detection of single gamma photon emission (the same as Tc-99m) and each technique has its effect on the imaging process. Recently, there is another trend to produce Tc-99m by accelerators instead of reactors to cover any expected shortage. Tc-99m production by accelerator is in the development level and is not yet the perfect way for Tc-99m supply. Hence, as new reactors in the world are planned, still most rely on those reactors' production of the isotopes and supply. On the other hand, alteration of work schedules (extended work time) might be a short-term solution in this crisis of supply shortage. However, the challenge that faces this idea is connected with the decay of the Mo-99 depending upon the half-life.

Chapter1: Introduction: Impact of Mo-99/Tc-99m Shortage

**** Introduction.***

During the 58th IAEA general conference on 25 September 2014, a paper called "*Medical radioisotopes Mo-99: Supply Challenges, Crisis Mitigation Effort and Alternatives"* was introduced [1]. The aim of this announcement was to prevent the expected shortage of one of the mostly used worldwide radioisotopes in nuclear medicine and to seek alternative methods for production or substitute isotopes. This crisis in the shortage of radioisotopes' availability occurred especially in the production of Technetium-99m (Tc-99m) which is most used in nuclear medicine diagnostics [2]. Tc-99m is the decay product of Molybdenum-99 (Mo-99) which is one of the products of Uranium-235 (U-235) fission in the reactor. The concern about the expected shortage of Tc-99m around the world has increased during the last decade. Hence, in March 2010 there was a critical period when all these reactors were stopped. Then, in May and July of 2010 the worst

experience of Tc-99m shortage in the history of medical isotopes was registered. At that time, Canadian and Dutch reactors were out of service where they together provided two-thirds of the global supply of Mo-99. In fact, the impact of the number of radioisotopes' shortages has been appearing since 2007 as a lack of delivery to nuclear medicine.

Tc-99m has specified characteristics to be most preferable in nuclear medicine procedures. These include a short half-life (6 hours) and decay by isomeric transition to a more stable state leading to pure gamma emissions at 140 keV. Hence, a small quantity injected into the patient can be decayed within 24 hours at 94% and excreted from the body. Basically, 80% of all nuclear medicine procedures rely on the availability of Tc-99m, in relation to approximately 30 million procedures worldwide [1] [2]. The global importance of Tc-99m in medical applications lead to advanced research about alternative techniques or less suitable radioisotopes to Tc-99m to prevent the effect of this crisis on medical examinations.

**** Tc-99m shortage of supply***

There are five main reactors in the world responsible for the supply of 90% of the Mo-99 isotope. These facilities are: NRU reactor in Chalk River, Canada; HFR in Petten, The Netherlands; BR2 in Mol, Belgium; OSIRIS in Saclay, France, and SAFARI in Pelindaba, South Africa. Table 1 shows the approximate percentage of Mo-99 production for each reactor. Almost 40% of the world's supply of Mo-99 is produced in the NRU reactor. Then, from 40% to 45% is produced in the three European reactors and about 15% is produced in South Africa. All these reactors were established more than 40 years ago. Therefore, maintenance was due for some of them and suddenly breakdowns appeared for the expected end of life for some of them [2] [4] [5]. Moreover, there is increased concern within the next decade regarding the permanent closure of one or

more of the major five reactors. On the other hand, smaller reactors are producing Mo-99 for domestic or regional needs mostly and are not counted as a global supplier. Some of these local producers of Mo-99 are Australia, Argentina, Indonesia and Poland. Although there is a low level of Mo-99 production at these small reactors, some of them are expected to increase their production, such as the Argentina and Indonesia reactors, to accommodate global needs.

Reactor	Production rate (%)
Chalk River (NRU) (Canada)	30% to 40%
High Flux Reactor (HFR) (Netherlands)	30% to 40%
OSIRIS (FRANCE)	7%
BR2 (Belgium)	14%
SAFARI-1 (South Africa)	15%

Table 1: Worldwide production capacity of Mo-99 [4] [5].

Mo-99 nowadays can be firstly produced by fission of Highly-Enriched Uranium-235 (HEU) targets. Each target irradiated for many days in one of several old research reactors, and a crisis is approaching due to the predicted shutdown of one of the largest production resources at Chalk River in Canada. The NRU reactor there delivers almost 50% of the global supply of 12,000 Curies (Ci) per 6 days weekly of Mo-99 (half- life of Mo-99 is 67 hours) [2] [3]. In excess of 30 million procedures are carried out each year (53% in North America, 23% Europe, 20% Asia, 4% Rest of the World), and whereas the nuclear medicine community is testing alternative imaging methods, it is probable that Tc-99m running will be required for a minimum of twenty years;worldwide need is set to increase by between 1% and 2% per year over that period. For example, the UK currently carries out about 0.5 million Tc-99m procedures each year, and although PET, CT and MRI might replace Tc-99m for some applications, this could impact the existing capability of those alternative techniques to encounter the needs of other imaging procedures. The use of some of these alternatives also experiences higher patient radiation doses; the short Tc-99m half-life and pure gamma emissions means a standard given dose of up to 27 mCi (1 Giga Becquerel (GBq)) experiences a patient dose of about 2-4 milliSevert (mSv). Earlier unintended supply failure of the NRU and HFR Petten reactors in 2009/2010 lead to optimized practice of Tc-99m such that usage reduced to around 10,000 Curies per 6 days weekly; additional optimization might be done by changes such as weekend processing of Mo-99 to prevent loss of activity through decay. In addition to facing the global instability of sourcing supply, the UK has the extra trouble that it has no appropriate high-flux research reactors and hence no present local source either of Mo-99 or directly of Tc-99m, though it does have a large generator manufacturing plant at Amersham;disturbance to the needed weekly supply of Mo-99 generators might leave the UK with no supply at all. Some other reasons include the predicted US limit on HEU deliveries after 2020, and uncertainties as to when standby European reactors become ready (such as the Jules Horowitz reactor presently under construction,

France). As a result of these matters, a domestic working group has been launched to study how to produce a safer source of Tc-99m for domestic use.

**** History of Mo-99 production facilities***

The main reactors in the world responsible for the majority of Mo-99 supply include [2]:-

1- In Canada, the NRU reactor (figure 1) is one of the oldest reactors in the world; it has been operating since 1957. The NRU reactor was planned to be shut down in 2005 formandatory safety reasons. Therefore, there was a project to design and construct two new reactors, Maple 1 and 2. Those reactors were supposed to be in operation by 1999. However, errors had been discovered in the design and after many years of tests, the Maple project stopped in 2008. As a result, the NRU license was extended after 2011, although for safety rules, the NRU reactor needs to be shut down for a minimum of 1 year in the near future.

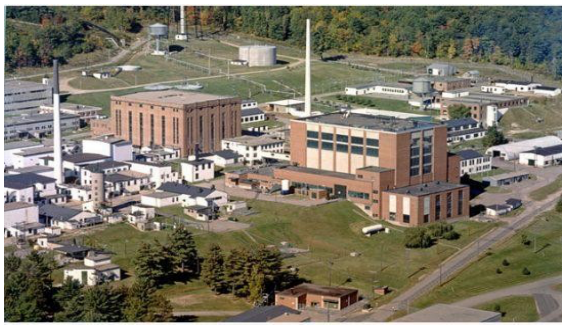

Figure 1: Chalk River Nuclear reactor-Canada [6].

2- In France, in 2014-2015, the OSIRIS reactor is expected to be shut down when the Jules Horowitz reactor (JHR) is completely ready for operation. Therefore, no gap in irradiation facility of U-235 in France leads to an acceptable price for irradiating processing of the U-235 target.

3- In Belgium, the BR2 reactor will still be operating at least until 2016, with the possibility to extend to 2020 or beyond, as there is no technical reason to stop. Otheruseful reasons for continuous operation of BR2 are suitable fuel is available and agreement from licensing authorities is valid. At that time, other irradiation facilities will provide the supply of Mo-99 such as MYRRHA, dedicated ADS and ADONIS.

4- In the Netherlands, because of a corrosion problem, HFR had been stopped for six months; then it was authorized by the Dutch regulating authority to operate again temporarily for a year until March 2010 to allow preparation of major maintenance. This temporary operation was expected to finish by February 2010 and the reactor operating again. Meanwhile, the PALLAS reactor was started to be designed to replaceHFR in 2016 as scheduled.

**** Main triggers for this crisis***

In August 2008, due to noticeable corrosion and a little leak at the main circuit of thefacility, the HFR reactor was not operated [2]. The closure of HFR as a supplier for about 40% of all Tc-99m in the world lead to a crisis in the supply of Tc-99m for nuclearmedicine. In addition, at BR2, OSIRIS and NRU, the

reactors' maintenance was not completed as scheduled, although it was in progress. Surprisingly, only the SAFARI irradiation facility was available and, unfortunately, two European reactors were stopped at the same time because of operating problems.

Moreover, HEU is a fission target for the production of Mo-99. Radioactive waste from the HEU target is a known problem and another security issue is being faced with weapons-grade HEU [4]. Therefore, the United States will phase-in an obstacle to stopthe supply of HEU in the next few years. Scientifically, Low Enriched Uranium-235 (LEU) target has no obstacle to be used; however, there are some technical problems which should be taken into account. A larger space is required as a larger number of targets are irradiated and a much higher quantity of waste is produced with LEU targets.

*** Nuclear Medicine Imaging Techniques**

**** Nuclear medicine imaging***

The idea behind nuclear medicine imaging is to detect radiation photons that are emitted from internal radiation sources, rather than external sources as used in X-rays and Computed Tomography (CT) scans [7] [8]. The construction of gamma camera images depends on the acquisition of gamma photons by the detection apparatus. For clarification, the radionuclide is inserted into the body (swallowed or injected) to be localized in the preferred organ due to labelling with certain drugs (pharmaceutical). Radiopharmaceuticals (radionuclide labelled to a drug) concentrate in certain organs and will decay with the time leading to gamma photons being emitted outside the body. Then, detection methods are related to the photons' emission principle, for the procedure intended and image quality required. For example, examinations for function assessment of the organ rely highly on counts rate (activity) observed.

The Gamma camera imaging system, or Anger camera, is designed to be used for diagnostic or therapy medical procedures which include evaluation of the function of some human organs as well as a little information about the human anatomy [7] [9]. For example, radioiodine is used to check thyroid function (uptake), Iodine-123 or Iodine-131 is used to study the function of the kidney after being labeled with Hippuran (pharmaceutical drug) and radioactive gases (e.g., Xenon-133) might be used for lung ventilation

imaging. The Gamma camera system consists of four basic components, which are: the collimator, a detection system, a computer system and the gantry system. In addition, there are two major groups of imaging techniques: the single photon emission computed tomography (SPECT) system and the positron emission tomography (PET) system. All previously mentioned components and major groups will be discussed next. Figure 2 below shows a schematic diagram of major gamma camera components, including image detection and construction.

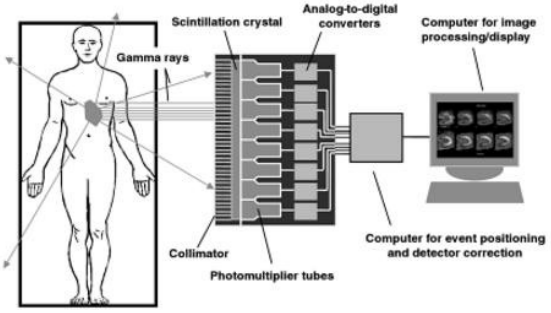

Figure 2: Major components of a gamma camera system including image acquisition [9]

**** Gamma camera components***

The four basic components (defined previously) are important factors in the detection of gamma ray photons initially, then for the reconstruction of the image. A brief explanation for each of these components will be provided [7] [8] [9].

**** Collimators***

The Collimator is made typically of holes and lead strips between them called septa. There are four types of collimators used in nuclear medicine: parallel hole, converging, diverging and pinhole. Collimators play the role of mechanical lens and select the direction of photons [7]. The organ to be imaged is composed of multiple radioactive points that emit photons isotropically, and therefore for a single image point there are several possible lines of response (LOR) leading to spatial localization ambiguity. To reduce this ambiguity, collimators select only one direction for the photons emanating from one radioactive point. Small hole collimators are characterized by good spatial resolution and low sensitivity, while large hole collimators have high sensitivity and reduced spatial resolution.

**** Scintillation crystals and solid-state detectors***

A nuclear medicine imaging system includes a large scintillation sodium iodide crystal doped with thallium NaI (Tl) [8]. The scintillation crystal in fact is the first element of the detection device. The NaI (Tl) scintillation crystal was first used about 60 years ago as a common detector for its physical properties, such as high atomic number (high probability of photoelectric

absorption). Photoelectric absorption is required in this case because all incident gamma photon energy needs to be absorbed in one interaction (a point on the detector represents another from the patient). Then, optical-wavelength photons will be produced and detected in the next step of detection by photomultiplier tubes (PMTs). Thickness of the crystal is an important factor in determination of intrinsic resolution and sensitivity.

In addition, high-purity Germanium (HPGe) is a solid-state detector developed for its great energy resolution (3-6 eV required to produce an electron-hole pair compared with about 30 eV for NaI (Tl)) and straight gamma radiation conversion [8]. The main advantage of this kind of detector is that PMTs are not used at the detection apparatus. Therefore, the weight of the detection head will be lighter and more compact than NaI (Tl). However, HPGe needs to be operated at very low temperatures and cooling must be provided, which is one of the drawbacks. Therefore, other detectors are suggested as an alternative to HPGe, such as Mercuric Iodide (HgI_2) and Cadmium Telluride (CdTe) and those might be operated at room temperature.

**** Photomultiplier tube array (PMTs)***

Optical light emitted by the crystal into the PMT will be converted into electrons. These electrons will be travelling within microchannel plates (MCP) for multiplication of electron flow [7]. The MCP has a channel diameter range of 5-50 μm and approximately 1mm thickness. The PMT window is a photocathode anode and MCPs are closely-filled hollow glass tubes. The PMT is evacuated and about 1000 Volts (V) are applied for electrons' acceleration. In fact, PM-MCP include two MCPs designed with close distance and 3000 V applied, resulting in a short path length of the electrons (with a few nanoseconds transit times).

**** Electronic and processing system***

Signals from the detection system are finally transferred to the computer system to be constructed into a readable image. There are specialized programs for this purpose, such as Monte Carlo.

**** Imaging techniques of gamma camera***

In nuclear medicine imaging, a conventional image acquisition technique called planar imaging is used for construction of the image in two dimensions [8]. This method might not be very accurate at determining small details such as a

tumour within normal tissue. However, advanced applications of imaging by using SPECT or PET techniques are more beneficial for different kinds of examinations. The introduction of CT with SPECT and PET systems is very supportive for more details about anatomy and accurate localization of intended tissue. SPECT and PET physics and applications will be discussed next for the main ideas.

**** Single Photon Emission Computed Tomography (SPECT and SPECT/CT)***

The Gamma camera technique represents the detection of single photon emission from an injected radionuclide by scintillation crystal (detector) and subsequent steps of the system before the acquisition of the image [9]. The major difference between the classical imaging technique (planar) and SPECT imaging is that 3-dimensional images will be acquired, in addition to improved image quality (resolution). SPECT images are improved as this system can rotate around the patient and construct the image from different angles.

In 1999, the first SPECT/CT technique was presented, although image combination techniques had been in clinical use for several years [10]. A low-power x-ray tube is used with the SPECT/CT system and includes separate gamma and X-ray detectors fixed on the same ring gantry. In addition, the X-ray machine is operated at 140 KV with only 2.5 mA for a tube current. A low patient dose will be provided by using this technique in comparison with conventional CT imaging practice. However, lesser image quality than state of art CT will be achieved. On the other hand, it is permitted for the calculations of patient attenuation to the fan beam shaped by the X-ray tube on the detectors along distinct paths, providing important higher quality attenuation charts than those provided with conventional Gadolinium-153 (Gd-153) scanning line sources.

**** SPECT and SPECT/CT in clinical practice***

Approximately 1:10,000 is the occurrence of well-differentiated thyroid cancer [10]. Total thyroidectomy and therapy with I-131-iodide is the traditional treatment in this case, with a survival rate of over 90 percent. Poorly differentiated thyroid cancer accounts for less than 20 percent of cases and are associated with high risk of local extension and metastases. The therapeutic effect of I-131 is ensured by emission of beta$^-$ (β^-) particles, while imaging is based on the emission of 364 KeV gamma

rays. Scanning is usually done by using planar scintigraphy, whereas SPECT is less frequentlyused.

In addition, Gallium Citrate-67 (Ga-67) scintigraphy is known as a useful procedure for assessment of patients with lymphoma, and an extra upgrade has been added with SPECT/CT to enhance diagnostic sensitivity as well as to identify sites with abnormal activity uptake [10]. SPECT/CT has special importance in classifying spinal lesions fromnearby nodal attachment. There is also another capability of SPECT/CT to identify the tracer uptake at the boundaries of the lower chest, launching over the hepatic dome,ribs or sternum. More information or diagnosis from CT-discovered tumours has been shown by SPECT/CT imaging leading to crucial changes in the patient's organization.

**** Positron Emission Tomography (PET and PET/CT)***

The idea behind PET techniques is the decay of one of the nucleus protons into a neutron leading to a positron being emitted (β^+) [11]. A positron is a positively chargedparticle and travels for a short distance (mm) inside the targeted organ and two annihilation photons will be emitted as a result of the positron interaction with one electron of the body's atoms. Emitted photons have an energy of 511 keV for each one. PET scanners use annihilation coincidence detection: these annihilation photonswill be detected in two opposite detectors of the PET ring at a time called the timing window.

**** PET and PET/CT in clinical practice***

One of the important applications of PET is the assessment of a range of cardiac diseases. Then, PET has produced great interest as it is a non-invasive procedure, andhas greatly improved the pathophysiological recognition of cardiac pathology [12]. By using dynamic acquisition and mathematical models of tracer kinetics, PET allows measurement of radiotracer uptake due to its exclusive physical and technical properties. In comparison, PET has better spatial and temporal resolution than the conventional nuclear technique. Moreover, PET's great detection sensitivity for radiotracer has allowed innovative insight into the technique of myocardial blood flow (MBF) quantification. Even though it has undoubted advantages, the widespread distribution of cardiac PET into clinical diagnostic services has been limited by the difficulties of production and short physical half-

lives of positron-emitting radionuclides, the requirement for an in-place cyclotron facility for the production of essential perfusion tracers, the restricted availability of PET equipment and the high prices of PET imaging. However, PET is gaining approval among cardiac diagnostic examinations.

On the other hand, PET might be involved in other procedures rather than cardiac imaging [12]. For example, detection of malignant diseases and their development stages such as head and neck cancer, lung cancer, breast cancer and prostate cancer. In addition, In the case of inflammation and infection, conventional nuclear medicine provides many tools permitting detection and follow-up of diseases, such as labelled white blood cell (WBC) scintigraphy and anti-granulocyte monoclonal antibody (MoAb) immunoscintigraphy. Within the last decade, PET/CT has become a usually approved technique in the detection of infection and inflammation, however, WBC scintigraphy continues to be the most accurate diagnostic method in certain cases.

*** Tc-99m production, properties and applications**

**** Introduction***

Nuclear medicine is known as one of the most regularly utilized diagnostic scanning techniques as about 38 million procedures were being globally performed annually [13]. This advanced technique is a non-invasive method that allows doctors to scan for several medical complications. Applications of radionuclides in medicine are increasing in the medical field due to their low radiation exposure to the patient.

Tc-99m is the most used radionuclide in nuclear scanning procedures with about 80 percent of all nuclear diagnostic procedures [13] [14] [15]. It is a metastable isomer of Tc-99m which emits its excess energy in the form of gamma-ray photons, and is used as a medical radionuclide. One of its properties is that it has a relatively short half-life which is about six hours. On the other hand, its parent isotope, Mo-99, is a radioactive isotope which undergoes beta$^+$ (β^+) decay with about 66 hours half-life (Figure 3). It is therefore commercially produced in the production facility and delivered to nuclear medicine departments where it will decay to Tc-99m. About 88% of Mo-99 decay results in the production of Tc-99m and this in turn decay to the ground state (Tc-99g) with about 211,000 years half-life (Figure 3).

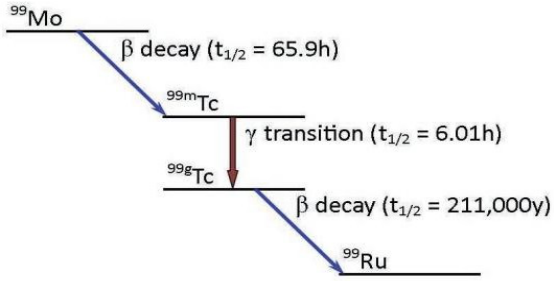

Figure 3: Mo-99 decay [14]

Mo-99 is purified according to the United States' Food and Drug Administration (FDA) standards and packaged in a radionuclide generator as "Tc-99m kit" after being taken from the production facility, usually a nuclear reactor or accelerator. Then, this kit willbe shipped to the customer (nuclear pharmacy) to be prepared before administration of the required dose to the patient. Tc-99m activity is extracted to be attached to tracer and finally administered to the patient according to the patient's specific needs and diagnostic purposes. This process of Mo-99/Tc-99m production and supply takesabout a week [13].

**** Production of Molybdenum-99 and Technetium-99m for Diagnostic Nuclear Medicine***

The parent isotope, Molybdenum-99, undergoes β^- decay which can be written in an equation, as below:-

$$^{99}_{42}Mo \rightarrow {}^{99m}_{43}Tc + {}^{0}_{-1}e + {}^{0}_{0}\overline{\nu_e}.$$

As previously mentioned, Tc-99m has a short half-life of about six hours, so it is preferable to be produced by the much longer-lived parent isotope, Mo-99. Mo-99 is a fission product of irradiation of U-235 targets the nuclear reactors [13] [14] [15]. Using these reactors is the normal worldwide technique to produce Mo-99 for diagnostic procedures at about 95%. The production efficiency of Mo-99 is dependent on the percent of U-235. So, reactors were designed to produce radionuclides in a way that they are able to utilize different levels of enriched U-235 targets. In cases of less than one percent of U-235, a process called enrichment will be established to improvethe fraction of U-235, leading to higher production efficiency of Mo-99 [16]. The percent of U-235 within the target's material is classified as presented in Table 2 below:-

Category of Uranium	U-235 Fraction
Depleted Uranium (DU)	< 0.711%
Natural Uranium (NU)	0.711%
Low Enriched Uranium (LEU)	0.711% < 20%
Highly Enriched Uranium (HEU)	20% - 100%

Table 2: Uranium classifications [13][18]

There are other methods to produce Mo-99 by using accelerators instead of nuclear reactors [18]. Firstly, a photo-nuclear reaction is applied to produce Mo-99. In this method, an electron beam striking a metal target result in *bremsstrahlung* radiation that bombards a molybdenum target enriched with Mo-100 target to produce Mo-99and neutrons will be released. Secondly, the bombardment of a Molybdenum-98 (Mo-98) target can also be used to

generate Mo-99. Accelerators are still seen as a recent development over the use of nuclear reactors for the production of Mo-99, yet the concept is currently attracting acceptance due to the increasing availability of designsof new production centers. In addition, more research for production techniques has been encouraged as a result of the viability of commercial production of Mo-99.

In addition, there are four main steps for the production-supply chain in order to assure the appropriate quality and integrity of the Tc-99m that is being administered to the patient (see Figure 6):-

1- Production of Mo-99.
2- Processing of Mo-99.
3- Preparation of Tc-99m.
4- Patient administration of Tc-99m.

It enables collection of Tc-99m after the decay of the Mo-99 unit and administration of individual activities for each patient as required. The various components of the production-delivery chain involve basic steps which are: the nuclear physics of production, the chemistry of processing, and medical injection into the patient.

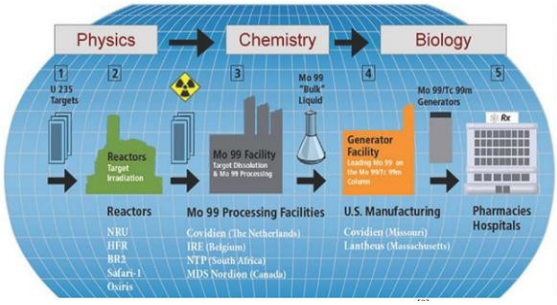

Figure 4: Global supply chain of Mo-99 and its following utilization [13] [15] [18]

As the Mo-99 is produced from the radionuclide reactors, it will be transported to theprocessing facilities to purify the Mo-99 from any other isotopes that might possibly be included by using a chemical wash of the radionuclide. Then, the ionized solution of Molybdate ($MoO4^{-2}$) will be prepared by the processing facility. Next, this solution will be checked and assured to follow current standards of the FDA and other international organizations. Finally, it will be delivered to the manufacturing centers which place the purified Mo-99 solution into the "Tc-99m generator kit". A unit size of one 6-day curie is obtained by placing 9.4 µg of Molybdate within an alumina chromatography column. The Tc-99m is harvested as a nuclear pharmacy during elution based on higher adsorption of Molybdate to the alumina column comparatively to Tc-99m. This eluted Tc-99m is used to label different tracers, according to the explored organs, and the obtained radiotracer will be administeredto the

patient.

As Tc-99m has an unstable nucleus, it decays to a stable Tc-99 by emitting gamma rays [20]. The emission of this gamma decay radiation can be equated as below:-

**** Thyroid Imaging***

The application of radiopharmaceuticals such as radioactive Iodine-131 (I-131), Iodine-123 (I-123), and Tc-99m in detecting thyroid functional parameters and imaging the gland has been known as the core of the development of the field of nuclear imaging [21]. Thyroid imaging techniques generally benefit from some phase of hormone synthesis within the thyroid gland. Basically, radiopharmaceuticals are actively transferred into the thyroid gland. This process is known as *trapping*. Depending on the properties of different radiopharmaceuticals, after some time, the thyroid gland is imaged using gamma cameras.

**** Iodine 131***

Iodine-131 has about 8 day's half-life and it undergoes beta decay with gamma emissions of 364 keV. Such properties are known as its major disadvantages in that it has a long physical half-life and β^- emissions, which can cause a significant radiation dose to be delivered to the thyroid (about 1 rad/μCi). As a result, I-131 is seen to be unfavorable for routine imaging of the thyroid. Nevertheless, it has a low price and ready availability.

**** Iodine 123***

On the other hand, I-123 has about 13 hours half-life and decays by electron capture, with a photon energy of 159 keV. Its lower gamma energy emission offers excellent imaging and the absence of β^- emissions allows significant lower radiation doses to the thyroid compared to I-131. While I-123 is the radiotracer of choice for thyroid imaging, this cyclotron-produced isotope has a high cost and limited availability.

**** Technetium-99m***

Another radionuclide that can be used in thyroid gland imaging is Tc-99m [21]. It is trapped by the thyroid in the same way as iodides but unlike iodides, it is eventually released and "washed" from the gland. It has a shorter half-life of 6 hours and gamma energy of 140 keV making it an ideal radiopharmaceutical for gamma camera imaging. Such physical properties and its ready availability make it superior to the iodides for thyroid scanning. Additionally, its lower absorbed radiation dose to the thyroid allows higher activities to be administered for the thyroid gland

therefore giving improved imaging of the gland.

**** Technetium Myocardial Perfusion Radiopharmaceuticals***

In myocardial perfusion imaging, Tl-201 was the first successful agent and is still generally used in various clinical cases. However, its low photo-peak energy, limit resolution, and its long half-life reduces the activity that can be administered [21]. The ideal solution to these restrictions is that several classes of Tc-99m-labelled radiopharmaceuticals are being developed with the imaging advantages of Technetium.

Unlike Tl-201, the Technetium label grants the promising properties of ready availability; larger inserted activity for the improved statistics, with lowered radiation dose to patients; and advantageous photon energy, thus permitting higher-resolution (image quality) gamma camera images using either SPECT or planar techniques. Tc- 99m with 140 keV photon energy can reduce attenuation artifacts from the breast or diaphragm therefore increasing the specificity of the examination. With the ability to be administered at higher doses, Tc-99m-labelled agents also enable first-pass radionuclide angiocardiography using multi-crystal cameras at the time of intravenous function at rest or stress. Also, Technetium radiopharmaceuticals with reasonably long retention in the myocardium permit gated SPECT acquisition for evaluation of left ventricular wall motion. As a result, the left ventricular function and perfusion can be assessed using a single tracer injection.

*** Advantages and limitations of alternative isotopes to Tc-99m**

**** General characteristics of alternatives***

As a result of the expected shortage in the supply of Technetium-99m, several isotopes have been used as alternative radionuclides in various nuclear medicine imaging techniques such as Oxygen-15, Nitrogen-13, Thallium-201 (Tl-201) and Rubidium-82 (Rb-82) [22] [23]. Table 3 shows some of the isotopes used as alternatives. These radionuclides should be studied and introduced to be convenient and acceptable in the use of particular nuclear medicine examinations as an alternative to Tc-99m. The alternative radionuclide's physical properties are a crucial factor in comparison with Tc-99m, which is then used as a radiopharmaceutical with a suitable marker (pharmaceutical) where this marker is a non-radioactive drug and has the

ability to concentrate in the organ of interest after labelling with radionuclide. The most important physical properties of these isotopes are physical half-life (T1/2), disintegration products either gamma ray or particulate radiation, including sufficient energy which must be emitted at a restricted range, and the production method of these alternative isotopes, which is a major reason for the choice of the isotope. On the other hand, physiological characteristics of different organs in the human body when an isotope is inserted are taken into account for the selection decision of the isotopes. For example, uptake and extraction percentage of the injected activity vary from one organ to another in the human body, resulting in a different count density being detected in the image detector, because an abnormal part of an imaged organ will show a different physiological output of detected radiation in comparison with a healthy one.

Several aspects should be taken into account when a radioactive tracer is chosen. Some of these aspects are [24]:-

1- Avoid a radioactive tracer that needs a long time for preparation or complicated procedures to use it.

2- The availability of storage space and suitability is important for safety purposes.

3- Expertise of those who deal with the tracer is necessary before the choice.

4- Cost of radioactive tracer should be acceptable in relation to its specifications.

ISOTOPE	ENERGY	DECAY	HALF-LIFE (physical)	PRODUCTION
Rubidium-82	Emax (β^+): 3.53 MeV Annihilation photons: 511 keV	β^+	78 seconds	Generator (Sr-82)
Thalium-201	X-ray: 70-80 keV gamma ray: 135, 167 keV	Electron capture	73 hours	Cyclotron
Oxygen-15water	Emax (β^+): 0.73 MeV Annihilation photons: 511 keV	β^+	2.4 minutes	Cyclotron
Nitrogen-13ammonia	Emax (β^+): 0.49 MeV Annihilation photons: 511 keV	β^+	9.8 minutes	Cyclotron

Table 3: Physical properties of some isotopes used as alternatives to Tc-99m [25] [26]

Two isotopes will be introduced in this chapter as they are the most used as alternative radionuclides to Tc-99m in myocardial perfusion imaging (MPI) tests because the patient dose from those isotopes is less than Tc-99m which is the main point in seeking an alternative. In addition, imaging accuracy is achieved with a high degree of accuracy with greater sensitivity and specificity [27]. These isotopes are Rb-82 PET and Tl-201 SPECT, although other isotopes were introduced.

**** Myocardial Perfusion Imaging (MPI) to detect coronary artery disease***

The Myocardial Perfusion Imaging (MPI) test is one of nuclear medicine's examinations which was established to assess coronary artery

blood flow through the heart muscle [24, 28]. MPI is a non-invasive imaging method and has the ability to identify regions of abnormalities of coronary blood flow. In fact, this test does not show arteries themselves; however, it shows function and the ability of the heart muscle to pump blood through the arteries. It is useful in the case of a previous heart attack and it can be done in the case of discomfort in the chest and to detect if the discomfort comes from lack of blood flow to the heart muscle caused by narrowed or blocked arteries. The MPI test is usually performed by two imaging techniques, Single- Photon Emission Computed Tomography (SPECT) or Positron Emission Tomography (PET). Hence, Tl-201 is applied with the SPECT imaging system, whereas Rb-82 is used for the PET imaging technique. Moreover, Oxygen-15 water and Nitrogen-13 are introduced as other tracers for the MPI test [26]. The importance of using a radioactive tracer for the MPI test is to diagnose abnormality of blood flow through heart arteries. However, this imaging technique does not give significant information about the anatomical structure of the targeted organ.

**** Use of Rubidium-82 for a myocardial perfusion imaging scan as alternative***

A high contrast is a crucial factor in the case of a myocardial perfusion imaging test, because regions of normal blood flow and abnormal perfusion (ischemia) should be identified clearly. Generally, high contrast is usually provided in nuclear medicine examinations, but in the case of a coronary artery disease (CAD) test, uptake and distribution of radioactive material in addition to source physical properties are important factors to satisfy this goal. Therefore, Rb-82 (PET) is used for the diagnosis of obstructive CAD with higher accuracy than Tl-201 (SPECT) [27].

Positron emission radionuclides have been used in nuclear medicine examinations for their physical and physiological characteristics. The commonest isotope that is used with positron emission is Rubidium-82 (Rb-82). This isotope is useful in the case of CAD detection using the MPI test [25].

**** Physical properties of Rb-82***

These include some advantages [26] [27] [29]:-

1- Instead of a cyclotron, Rb-82 is simply produced in an onsite generator and a small space is needed to house it, similar to a Tc-99m

generator. It is Potassium analog which is extracted by a Na^+/K^+ pump mechanism of the cell membrane. This represents the first-pass extraction (perfusion of blood through myocardium carrying tracer). Rb-82 production can be described easily, as follows [25]:-

Strontium-82 (Sr-82) (electron capture) →Rb-82 (positron emission) →Krypton-82 (Kr-82)

Where Sr-82 has a half-life of about 25 days and Kr-82 is a stable nucleus.

2- A very short physical half-life for Rb-82 of about 78 seconds leads to an effective half-life equal to approximately 77 seconds (biological T1/2=10 hour). Effective half-life is calculated by using the following equation [30]:-

$$T_{1/2,eff} = \frac{T_{1,phy} \cdot T_{1,bio}}{T_{1,phy} + T_{1,bio}} \quad (1)$$

The short effective half-life is one of the drawbacks of Rb-82 because imaging acquisition should last for about 10 minutes and be taken directly after injection. However, a short half-life achieves higher imaging accuracy with a lower radiation dose to the patient [26].

3- Rb-82 (Activity 1.1 – 2.22 GBq) is the most used PET tracer in clinical practice. Rb-82 is injected as a single bolus or short infusion (<30 s) [26].

**** Physiological properties of Rb-82***

These include [25] [26]:-

1- First-pass extraction of Rb-82 is approximately 85% through a Na^+/K^+ pump. Hence, most injected Rb-82 is washed from the first-pass of blood flow during myocardium.

2- Non-linearity of Rb-82 for first-pass extraction at high blood flow rate could be corrected with the use of proper correction models.

3- Uptake of Rb-82 in myocardium is variable; it might be high at high insulin level or low free fatty acid in the plasma. Patient preparation is usually aimed to increase myocardial uptake of radionuclide. Uptake is described as standard uptake value as[7]:-

Where:

1- Ci is either the mean (for SUV mean) or maximum (for SUV max) decay-corrected activity concentration (kBq/mL) within the defined region in the image (or tissue).

2- A is the injected activity (kBq).

3- And W is the patient weight (g).

**** Imaging protocols***

The acquisition of Rb-82 images is usually performed at rest and stress; it is combined typically with adenosine at pharmacological stress induction [26]. Stress imaging means the patient applies physical exercise to reach peak stress for higher blood flow achieved and then images will be taken at that level. Immediately after injection of the

tracer, image acquisition should be started because image acquisition will continue for about 10 minutes. Rb-82 is injected as a single bolus or it can be in the form of a short infusion. In general, the mechanism of image construction with PET techniques relies on the detection of two 511 keV photons with opposite travelling directions at 180^0 by two opposing detectors in the ring detectors.

**** Other considerations***

Rb-82 PET has greater specificity and sensitivity than the Tl-201 SPECT imaging technique for those patients with 50% stenosis [27]. Sensitivity and specificity are referring to the accuracy of producing useful images in addition to good localization resolution; they are defined by the following equations[31]:-

Importantly, for the whole 'rest and stress' Rb-82 PET scan, the total radiation dose is less than 2 mSv (lower by 5 to 10 times than Tc-99m and Tl-201) [3].

**** Use of Thallium-201 for a myocardial perfusion imaging (MPI) scan as alternative***

Tl-201 has been used as an effective agent for the myocardial perfusion imaging (MPI)test since the 1970s with a planar imaging system (non-computerized) before Tc-99m was used with its advanced preferred properties later in the 1990s [23] [28]. However,since the 1980s Tl-201 was used as a common radiopharmaceutical in the SPECT imaging technique, as it had been introduced to the MPI test for its physical and biological characteristics which are important for identifying myocardium function even with other non-favourable specifications.

**** Physiological properties of Tl-201***

Although there are some disadvantages of Tl-201's physical properties, several useful biological advantages were reported which are definitely necessary in the imaging process. These advantages are [24] [33]:-

1- First pass extraction in the myocardium is more than 88%, because Tl-201 is Potassium analog and extracted actively by cell membrane Na^+/K^+ pumps.

2- Blood clearance half-time is approximately 30 seconds, 92% of the injected dose is cleared within 5 minutes.

3- Uptake percentage of Tl-201 in the heart muscle is 3%-4% of the total administered activity, higher than the Tc-99m uptake percentage from 1%-1.4%.

4- The redistribution property of Tl-201 is an important factor for assessment of Tl- 201 viability in the heart muscle. It begins 10-15 minutes after the Tl-201 injection followed by

the redistribution imaging after 4 or even 24 hours.

This importance of biological characteristics of Tl-201 provides a higher contrast between a normal perfusion area and regions of abnormality (ischemia) and hence diagnostic results will be more accurate with confirmation of sensitivity and specificity of the results [22]. Moreover, as the tracer clears rapidly from normal myocardium than those with abnormal arteries blood flow and perfusion low rate, defective regions could be noticed clearly.

**** Physical properties of Tl-201 (disadvantages)***

There are some disadvantages of Tl-201 in the MPI test [22] [23]:-

1- A long effective half-life, T1/2eff=56 hours, hence, T1/2phy=73 hours and T1/2bio=10 hours, where T1/2 eff can be calculated by using equation 1. Long T1/2, eff allows extra time for image acquisition but a higher dose is expected to the patient than with Rb-82.

2- Tl-201 decays by the electron capture process and produces 70-80 keV X-ray (88%), 135 and 167 keV gamma ray (12%). Hence, predominant X-ray photons have low energy and are easily attenuated inside the patient.

3- As a result of localized tracer in many organs of the human body, such as the liver, testes, kidneys and myocardium as well as a targeted tracer, a high effective dose is calculated at 34.5 mSv/150 MBq. Therefore, radiation dosimetry is not a favourable part in this test. As a result of the high absorbed dose, limited activity of Tl-201 needs to be injected into the patient, usually 74-148 MBq (3-4 mCi), to avoid risks of excess radiation exposure limits. Limitation of the administered dose is the most challenging aspect related to the count density while the patient dose is kept within acceptable limits [29].

3- The production process is a crucial factor in the decision to use the Tl-201 radioisotope for its cost, space and time considerations, because Tl-201 is produced by a cyclotron as a Potassium analog radioisotope.

**** Tl-201 imaging protocols***

The imaging process is usually done by several methods. Firstly, stress imaging is performed 5-7 minutes after injection. Secondly, 4 to 24 hours delayed at rest (redistribution) imaging after injection to assess viability of Tl-201. Finally, the reinjection technique is used with little activity administered for a myocardial viability assessment.

*** Discussion**

**** Short and long-term responses***

Recently, many nuclear medicine studies have been replaced by other medical imaging techniques such as Computed Tomography (CT) scan, Magnetic Resonance Imaging

(MRI) and advanced Ultrasound applications [4] [5]. Bone scintigraphy and myocardial perfusion imaging (MPI) are the most techniques in nuclear medicine that consume Tc-99m, among others. Resulting from the Tc-99m shortage, many departments reverted to using Tl-201 for MPI. Tl-201 is produced by cyclotron instead of reactor, thus it is not affected by a reactor's closing. In addition to Tl-201, Rb-82 is another choice for the MPI procedure, but it has an installation difficulty for the Positron Emission Tomography (PET) camera with high costs required for it to be installed.

On the other hand, there are other important nuclear medicine studies where a practical alternative is not available nowadays. These include lung ventilation, sentinel lymph node localization and localization of parathyroid adenoma. In addition, the majority of these studies need a small amount of Tc-99m, therefore the priority can be for those procedures during shortage periods of Tc-99m supply. It is not easy to decide which procedure could be used to replace the nuclear medicine procedure, but the actual issue is if the capacity of alternative procedures is sufficient. Cost of procedures and radiation dose must be justified in many cases. For example, in the UK an additional 200,000 bone scan tests each year need higher capacity which is unlikely.

Technologically it is accepted that a nuclear reactor is the most reliable method for the production of Mo-99 worldwide. Therefore, new reactors are designed to be operational in the next few years in Europe, USA and the UK. Therefore, challenges will face any other proposal for different production techniques, for example, the Mo-100 (p, 2n) T-99m reaction which directly produces Tc-99m by using a medical cyclotron.

However, the plant for new reactors is very expensive and they are difficult projects to be established. For example, a study carried out on projected costs of electricity generation aims to compare various technologies and countries on a ranked playing field [34]. It uses similar ideas along with certain data collected in a survey of 181 plants in 22 countries, including 11 planned new nuclear plants. The results show that the UK has the highest cost for nuclear plant, reached as its government arranged to finalize a £24.5 bn deal to build Hinkley C, the country's first new nuclear reactor for a generation. Figure 7 shows the levelized cost of electricity (LCOE) required for operation of these plants.

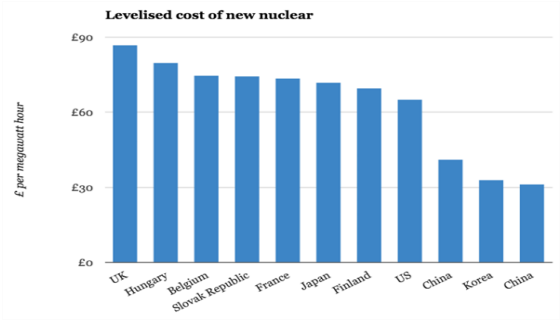

Figure 5: LCOE for new nuclear capacity for a range of countries, including two in China [34]

**** Rb-82 PET and Tl-201 SPECT statistics during Tc-99m crisis***

A study was presented in 2014 at the Society of Nuclear Medicine and Molecular Imaging (SNMMI), Ottawa Heart Institute [27]. There were 80 normal subjects (40 men and 40 women) examined with Rb-82 PET or Tl-201 SPECT Stress perfusion imaging with low likelihood of coronary artery diseases. In addition, 50 patients for Rb-82 PET and 74 patients for Tl-201 SPECT with normal left-ventricular ejection fraction (LVEF) at 40% or greater (no previous history of revascularization) were used for assessment of sensitivity and specificity for the stenosis detection at 50% and 70%. For stenosis of 50%, Rb-82 reading of sensitivity was 83% compared with 56% for Tl-201 and for specificity it was 94% and 85% for Rb-82 and Tl-201 respectively. For stenosis of 70%, the Rb-82 sensitivity reading reached 90% and only 57% was recorded for Tl-201; specificity was 93% for Rb-82 and 70% for Tl-201. Finally, both isotopes show nearly similar accuracy for the detection of stenosis at 50% or 70%.

**** Tc-99m and Tl-201 for MPI test comparison***

Radiopharmaceuticals for SPECT myocardial perfusion scintigraphy are Tl-201 and Tc-99m Sestamibi and Tetrofosmin. Sestamibi and Tetrofosmin are lipophilic monovalent cationic agents with a first pass extraction fraction of 65% and 54% respectively. These pharmaceuticals diffuse along the negative transmembrane potential gradient and accumulate inside the mitochondria with minimal redistribution. The relationship between coronary blood flow and extraction fraction of these radiopharmaceuticals has been analyzed extensively [35]. For Tl-201 there is a linear relationship between blood flow and uptake until 3 ml/min/g. On the other hand, at higher rate the uptake demonstrates a plateau called "roll-off" related to reduced first pass extraction fraction. Tc-99m labelled radiopharmaceuticals have lesser first pass extraction fraction than Tl-201 and their plateau is reached at about 2 ml/min/g. The consequence of this "roll-off" is decreased contrast

between high blood flow regions and those subtended by stenotic coronary arteries making it more difficult to diagnosemild stenosis.

*** Conclusion and recommendations**

**** Conclusion and recommendations***

In brief, most nuclear medicine procedures depend highly on Tc-99m as a radiopharmaceutical for diagnostic purposes because Tc-99m has advantageous characteristics that are useful in most nuclear medicine procedures. Nevertheless, some other radionuclides have been used recently as alternatives in certain procedures for the detection of diseases, such as Rb-82 and Tl-201 due to their own beneficial features. For some characteristics of alternatives, advantages and limitations cannot be directly indicated, as for certain examinations the total physical and biological properties of the alternative determine the possibility of using this alternative for best results in comparison with others. For example, the short half-life of Rb-82 can be useful to reduce the dose deposited in the patient, however, a short image acquisition time is not desired which appears in this case. In addition, an onsite generator and a simple method of production is a great advantage. On the other hand, Tl-201 has some physical disadvantages, such as a long half-life, high effective dose and complexity of production. However, other physiological advantages in the MPI test are required; for example, first pass extraction should be high with high coronary blood flow. Moreover, imaging techniques and simplicity of image construction shouldbe considered.

Further research is needed, however the plans for new nuclear reactors in some countries such as the UK and USA as the most effective way of Mo-99 production might be frustrating this research. Lessons should be learned from this crisis that reactors are not necessarily the only way of producing radionuclides for medical applications. Therefore, the variety of radionuclides and different methods of production should be taken into account as another solution for future supply of these isotopes. Local supply of radionuclides is required while most world supply is dependent on two reactors out of about only six main reactors. Moreover, the safety of the whole sites and the workers must be considered with the projects of new reactors, including nuclear weapons restrictions and prevention of accidents.

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