

# Production review of accelerator-based medical isotopes

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**Abstract:** The production of reactor-based medical isotopes is prone to a supply shortage. This paper reviews the alternative accelerator-based medical isotopes production and common medical isotopes produced by cyclotrons, linear accelerators, and neutron generators. Lastly, it describes the present situation of medical isotopes production in China.

## Foreword

The use of medical isotopes in nuclear medicine for diagnosis and therapy has steadily increased over time [1-2], and so did the importance of their stable production and supply. Since the production of reactor-based medical isotopes is prone to supply shortages, this paper reviews the alternative accelerator-based medical isotopes production and the different medical isotopes produced by cyclotron, linear accelerator and neutron generator. Lastly, the present situation of medical isotopes production in China is also summarized.

## 1. Introduction

### 1.1. Definition of medical isotopes

Medical isotopes are all radioisotopes that emit radiation which can be used in Medicine [3].

### 1.2. Medical use

The application process of medical isotopes is depicted in Fig. 1 and can be summarized in four steps:

- (1) Irradiate a prepared target with the reactor or accelerator to occur nuclear reaction;
- (2) Separate and extract radioisotopes from the irradiated target;
- (3) Combine radioisotopes with the ligand to create radiopharmaceuticals;
- (4) Use radiopharmaceuticals in Medicine.

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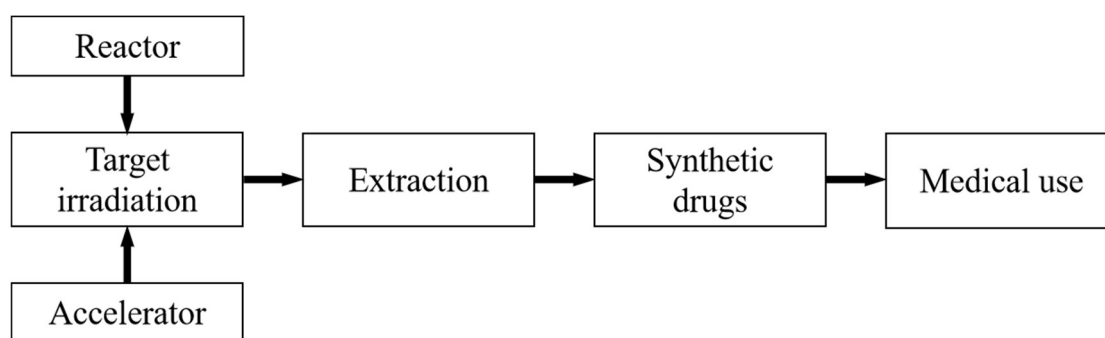


**Figure 1.** Process of the application of medical isotopes.

Radiopharmaceuticals combined with different radioisotopes have different medical uses in diagnosis, therapy, or both (theranostics) [4].

### 1.2.1. Radiopharmaceuticals for diagnosis

Radiopharmaceuticals for diagnosis are taken orally or injected into the body [5]. Then, they will be absorbed by a certain part of the body and emit  $\gamma$  rays which can be used in imaging. Abnormal tissues in the body tend to absorb radiopharmaceuticals abnormally and hence can be singled out using imaging techniques. Currently there are two main applications of radiopharmaceuticals for diagnosis in Medicine. They are Single Photon Emission Computed Tomography (SPECT) [6–8] and Positron Emission Tomography (PET) [9–11].

The main advantage of nuclear medicine diagnosis lies in its ability to find the lesions earlier since diseased tissue usually has functional changes at first, evolving into shape and structure changes. Another major feature of nuclear medicine diagnosis is that it can specifically show the tumors, their location and size.

### 1.2.2. Radiopharmaceuticals for therapy

Radiopharmaceuticals for therapy will accumulate in the diseased tissue after entering the human body. Then their cumulative radioactive emissions may be capable of producing biological effects, for instance in killing tumor cells, making these particularly suitable for cancer treatment [12]. The applications of radiopharmaceuticals for therapy include  $\alpha$  therapy,  $\beta$  therapy and Auger therapy. This review focuses on  $\alpha$  therapy and  $\beta$  therapy.

### 1.2.3. Radiopharmaceuticals for theranostics

Radiopharmaceuticals for theranostics can perform imaging diagnosis and medical treatment [13–15]. Imaging diagnosis can determine an optimal treatment plan, and also monitor and evaluate the medical treatment progress [14, 16–17]. Currently, radiopharmaceuticals for theranostics can use the same radiopharmaceutical which emits  $\gamma$  for diagnosis and  $\alpha$  or  $\beta$  for treatment [18–19] or two different radiopharmaceuticals (one for diagnosis and the other for treatment) [20].

Radiopharmaceuticals for theranostics have developed rapidly and made great progress in neuroendocrine tumors, thyroid cancer [16–17, 21–22], prostate cancer, breast cancer [23–24] and other diseases.

## 1.3. The status of medical isotopes production

Radioisotopes are divided into natural and artificial radioisotopes. Currently there are about 200 radioisotopes in use and most of them are produced artificially [25].

With the widespread usage of radiopharmaceuticals, the stable production and supply of medical isotopes become ever more important.

Presently medical isotopes are commonly produced in two ways: reactor and accelerator. Typically, reactor-based medical isotopes are neutron-rich isotopes and are characterized by a long half-life; while accelerator-based medical isotopes tend to feature shorter half-life and usually emit positrons or  $\gamma$  rays [26]. Except for a few radioisotopes that can be produced both via reactor and accelerator, these two different production methods complement each other [27].

Reactor irradiation is the most commonly used method to produce medical isotopes due to the wider inventory range, high yield, low cost, and ease of target preparation. However, this supply is sustained by reactors that were built in 1950-60's, and as shown in Table 1, the majority of these will gradually shut down before 2030.

**Table 1.** Information of world's reactors that can produce medical isotopes [28-30].

| Country      | Reactor name | Power[MW] | Critical time | Estimated retirement time |
|--------------|--------------|-----------|---------------|---------------------------|
| Belgium      | BR-2         | 100       | 1961          | 2026                      |
| Netherlands  | HFR          | 45        | 1961          | 2024                      |
| Czech        | LVR-15       | 10        | 1957          | 2028                      |
| Poland       | MARIA        | 20        | 1974          | 2030                      |
| South Africa | SAFARI-1     | 20        | 1965          | 2030                      |
| Russia       | WWR-TS       | 15        | 1964          | 2025                      |
| Australia    | OPAL         | 20        | 2006          | 2057                      |
| Germany      | FRM-II       | 20        | 2004          | 2054                      |

On top of that, owing to their age and as part of the decommission process, reactors are prone to either longer maintenance periods or unplanned shutdown events for safety or technical reasons [31]. Thus, the production of medical isotopes through the remaining reactors is unable to keep with global demand, increasing the risk of supply interruption or persistent shortage. Additionally, most targets irradiated by reactor may use highly enriched uranium (HEU) targets which are an important part of civilian HEU. They are difficult to control and may be made into a nuclear explosive device. At the same time radioactive waste produced by reactor is large and highly radioactive [32-33]. Therefore, reactor-based production of medical isotopes is accompanied by the risk of nuclear proliferation. All these factors strengthened the argument whether medical isotopes currently produced by reactors could be, not only complemented, but entirely replaced by accelerator production instead [34-35].

With the expanded interest and remarkable technological development of accelerator technology, some medical isotopes produced by reactors have already been replaced by accelerators. Furthermore, there are many advantages in having medical isotopes produced by accelerators:

- (1) Supervision is easier and it is safer [36];
- (2) The maintenance and decommissioning cost are low [25];
- (3) The amount of radioactive waste is less than 10% of the reactor, and the radioactive level is low [37];
- (4) It has no risk of nuclear proliferation [38].

## 2. Medical isotopes

This section reviews the medical isotopes produced by cyclotron, linear accelerator and neutron generator and will list some of the most common medical isotopes, their characteristics, application and production methods.

*2.1. Medical isotopes produced by cyclotron* **【1-6: PET radioisotopes, 7-8: SPECT radioisotopes, 9-11: therapeutic radioisotopes】**

A cyclotron is a particle accelerator that has charged particles accelerating through electromagnetic fields, spiraling outwards to ever increasing energies until they are ejected to irradiate the target and produce medical isotopes [39]. Compared with linear accelerator, the beam characteristic from the cyclotron is lower beam intensity due to the losses when deflecting, but its energy can be higher [40]. Cyclotron can be classified according to the particle energy. As shown in Table 2, different energy ranges of cyclotron can produce medical isotopes with different uses.

**Table 2.** Classification of cyclotron [41].

| Type                    | Energy of particles [MeV] | Application                                    |
|-------------------------|---------------------------|------------------------------------------------|
| Small medical cyclotron | <20                       | Short-lived radioisotopes for PET              |
| Medium-energy cyclotron | 20-35                     | Production of SPECT and some PET radioisotopes |
| High-energy cyclotron   | >35                       | Production of radioisotopes for therapy        |

### (1) $^{18}\text{F}$

$^{18}\text{F}$  ( $T_{1/2}=109.8$  min) will decay and emit positrons, with an average energy of 0.25 MeV, hence the distance travelled until the positron annihilation in tissue is short.  $^{18}\text{F}$  is one of the most commonly used PET radioisotopes. At present, FDA (Food and Drug Administration)-approved radiopharmaceuticals of  $^{18}\text{F}$  are used for the diagnosis of Alzheimer's disease, prostate cancer and other diseases, as well as in the diagnosis of central nervous system, myocardium. Moreover, it is also used in the evaluation of the treatment outcome [42-43].  $^{18}\text{F}$  usage in medical diagnosis is steadily increasing every year.

Most  $^{18}\text{F}$  is produced via cyclotrons, exploiting two nuclear reactions:

(1)  $^{18}\text{O}(p,n)^{18}\text{F}$  - Better yields [44], but it requires the use of expensive  $^{18}\text{O}$  water targets due to these targets need to be enriched with isotopes  $^{18}\text{O}$ ;

(2)  $^{20}\text{Ne}(d,\alpha)^{18}\text{F}$  - Characterized by lower yields and is gradually being replaced by the first production method. It can still be a viable alternative with production improvements [45].

### (2) $^{68}\text{Ga}$

$^{68}\text{Ga}$  ( $T_{1/2}=68$  min) is a positron emitter and a new metal PET radioisotope. The radiopharmaceuticals of  $^{68}\text{Ga}$  can be used for the diagnosis of neuroendocrine tumors and its sensitivity and specificity can reach more than 80% [46]. In addition,  $^{68}\text{Ga}$  and  $^{177}\text{Lu}$  ( $T_{1/2}=6.7$  d) have a similar property in coordination chemistry which are one of the most promising radiopharmaceuticals for theranostics. Both  $^{68}\text{Ga}$ -DOTA TATE and  $^{177}\text{Lu}$ -DOTA TATE have been approved by FDA to perform PET diagnosis and medical treatment of brain glioma [47]. For neuroendocrine tumors,  $^{68}\text{Ga}$  and  $^{177}\text{Lu}$  have been used clinically [48-49]. For castration-resistant prostate cancer,  $^{68}\text{Ga}$ -PSMA-11 is the first radiopharmaceuticals for PET imaging of the PSMA-positive prostate cancer approved by FDA;  $^{177}\text{Lu}$ -PSMA-617 is also effective for PSMA-targeted therapy [48, 50-51].

$^{68}\text{Ga}$  is generally produced by  $^{68}\text{Ge}/^{68}\text{Ga}$  generator which is relatively simple and convenient [52]. Alternatively, higher yields of  $^{68}\text{Ga}$  can also be obtained with the  $^{68}\text{Zn}(p,n)^{68}\text{Ga}$  reaction using a small cyclotron, using a solid target [53-54]. However, the solid target system is complex and the separation steps are lengthy. This production method also can use a solution target. The radiochemical and radionuclide purities are both >99.9% and the yield will improve by increasing the solution concentration and irradiation time [55].

### (3) $^{64}\text{Cu}$

$^{64}\text{Cu}$  ( $T_{1/2}=12.7$  h) will emit positrons and electrons upon decay, which can be utilized for PET diagnosis and also have the potential to be used for  $\beta$  therapy, thus making it

useful as a radiopharmaceutical for theranostics. Also,  $^{64}\text{Cu}$  can be combined with  $^{67}\text{Cu}$  ( $T_{1/2}=2.58$  d) as a radiopharmaceutical for theranostics, to conduct pre-targeted radioimmunotherapy [56]. At present, FDA has approved  $^{64}\text{Cu}$ -DOTA TATE to localize somatostatin receptor positive neuroendocrine tumors in adult patients.

$^{64}\text{Cu}$  can be produced by small medical cyclotrons, via  $^{64}\text{Ni}$  (p, n)  $^{64}\text{Cu}$ . It has a high specific activity and the yield and purity of the product are both high. However, this production method will need  $^{64}\text{Ni}$  enriched to a greater percent due to a low isotopic abundance of  $^{64}\text{Ni}$  in natural target (0.926%) [57]. So its cost will increase [58-59]. In addition,  $^{64}\text{Cu}$  can also be produced in deuteron-zinc reactions such as  $^{\text{nat}}\text{Zn}$  (d, x)  $^{64}\text{Cu}$  and  $^{66}\text{Zn}$  (d,  $\alpha$ )  $^{64}\text{Cu}$ . Though they have lower costs, their yields are lower and high-energy deuterons are required [60].

#### (4) $^{89}\text{Zr}$

$^{89}\text{Zr}$  ( $T_{1/2}=78.4$  h) is a positron emitter and a new metal PET radioisotope ideal for immunoimaging [61].

It is produced by cyclotrons involving the following nuclear reactions:

(1)  $^{89}\text{Y}$  (p, n)  $^{89}\text{Zr}$ - Requires low-energy protons (5-15 MeV) but the number of interference nuclear reactions is limited and hence one can obtain an high specific activity of  $^{89}\text{Zr}$  [62-64];

(2)  $^{89}\text{Y}$ (d,2n) $^{89}\text{Zr}$  - Needs low-energy deuteron (also 5-15 MeV) too but has the same advantages as the aforementioned production method [62-64] and even features a higher yield, albeit with caveats since one has to factor in the availability of the particle beams and the cost of these two production methods [65];

(3)  $^{\text{nat}}\text{Sr}(\alpha,\text{xn})^{89}\text{Zr}$  - Besides requiring  $\alpha$  beams, if enriched  $^{86}\text{Sr}$  targets are not used, abundant quantities of impurities such as  $^{88}\text{Zr}$  and  $^{86}\text{Zr}$  are easily produced when irradiating the  $^{\text{nat}}\text{Sr}$  targets [66].

#### (5) $^{124}\text{I}$

$^{124}\text{I}$  ( $T_{1/2}=4.2$  d) is a PET nuclide which can provide a higher quality diagnostic image [67]. Currently,  $^{124}\text{I}$  is used for diagnosis of thyroid cancer [68] and neuroblastoma [69].  $^{124}\text{I}$  and  $^{131}\text{I}$  can also be combined as a radiopharmaceutical for theranostics to treat thyroid cancer [16].

$^{124}\text{I}$  is produced via cyclotrons, in two different production methods:

(1)  $^{124}\text{Te}$  (p, n)  $^{124}\text{I}$  -The main production method currently employed, although it features a relatively low production rate, this production method can use a high current and enriched target thus improving the overall yield. Also this production method just needs a small medical cyclotron [67];

(2)  $^{124}\text{Te}$  (d, 2n)  $^{124}\text{I}$  - Despite its higher production yield it requires a deuteron beam and it leads to the production of impurities such as  $^{125}\text{I}$  [70].

#### (6) $^{76}\text{Br}$

$^{76}\text{Br}$  ( $T_{1/2} = 16.2$  h) is a new halogen PET nuclide with a good positron branching ratio and a longer half-life which yields significant advantage in PET diagnosis [71]. Presently, it can be used for tumor diagnosis of norepinephrine transporters (NET) [72].

$^{76}\text{Br}$  is usually produced via low-energy cyclotron through the  $^{76}\text{Se}$  (p, n)  $^{76}\text{Br}$  reaction. When an enriched target (>96%) is employed, high purity and yields of  $^{76}\text{Br}$  can be obtained [73-74].

#### (7) $^{99\text{m}}\text{Mo}/^{99\text{m}}\text{Tc}$

$^{99\text{m}}\text{Tc}$  ( $T_{1/2}=6.02$  h) can emit a single  $\gamma$ -ray with 0.141 MeV and it is most used in SPECT, for diagnosis of stroke, bone, myocardium, kidney, thyroid, salivary glands and other organs [42-43].

$^{99m}\text{Tc}$  is generally produced by a  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator. Currently,  $^{99m}\text{Tc}$  can be produced by cyclotrons:

(1)  $^{100}\text{Mo}$  (p,2n) $^{99m}\text{Tc}$  [75-76] - The main production method, optimal with a proton energy range of 19- 24MeV and a highly enriched  $^{100}\text{Mo}$  target, so that  $^{98}\text{Tc}$ ,  $^{97}\text{Tc}$  and other impurities are mitigated. However the shipped distance should be considered due to the direct product and its half-life [77];

(2)  $^{96}\text{Zr}$  ( $\alpha$ , n)  $^{99}\text{Mo} \rightarrow ^{99m}\text{Tc}$  [78-79] - This production channel will produce  $^{99m}\text{Tc}$  with high specific activity, but low yield, and high current  $\alpha$  beam is difficult to obtain.

#### (8) $^{123}\text{I}$

$^{123}\text{I}$  ( $T_{1/2} = 13.2$  h) is a  $\gamma$ -ray emitter which can be utilized for SPECT diagnosis. Currently,  $^{123}\text{I}$  can be used for diagnosis of Parkinson's disease, and can detect primary and metastatic pheochromocytoma and neuroblastoma. It also can be used for diagnosis of thyroid, brain and myocardium.

There are 4 production methods to produce  $^{123}\text{I}$ :

(1-2)  $^{124}\text{Xe}$  (p, 2n)  $^{123}\text{Cs} \rightarrow ^{123}\text{Xe} \rightarrow ^{123}\text{I}$  and  $^{124}\text{Xe}$  (p,pn) $^{123}\text{Xe} \rightarrow ^{123}\text{I}$  -These nuclear reactions require a medium-energy cyclotron but can obtain a high radionuclide purity. However, due to the use of enriched Xe targets, those methods are costly [80-81];

(3)  $^{123}\text{Te}$  (p, n)  $^{123}\text{I}$  - This production method can use a low-energy cyclotron and is less costly as well. When enriched targets are used, ultrapure nuclide can be obtained [82-84];

(4)  $^{127}\text{I}$  (p, 5n)  $^{123}\text{Xe} \rightarrow ^{123}\text{I}$  -This nuclear reaction needs a compact cyclotron but its main advantage is that its radioactive waste is lower and has a high output. On the other hand, it requires high-energy protons [85].

#### (9) $^{225}\text{Ac}$



$^{225}\text{Ac}$  ( $T_{1/2}=10$  d) has a unique decay chain that can emit four  $\alpha$  rays for  $\alpha$  therapy which can more effectively destroy tumor cells. Presently, it can be used for the treatment of prostate cancer, glioma and acute myeloid leukemia [86-88].

While  $^{225}\text{Ac}$  can be produced in proton irradiation facilities with medium-energy cyclotrons via  $^{226}\text{Ra}$  (p, 2n)  $^{225}\text{Ac}$ , the radioactive inventory is difficult to handle [89-91]. Production of  $^{225}\text{Ac}$  through spallation induced by high-energy protons bombarding a Th target can lead to high yields but it requires high intensity and energy [92].

#### (10) $^{211}\text{At}$

$^{211}\text{At}$  ( $T_{1/2}=7.2$  h) will emit  $\alpha$  particles upon which can be utilized in  $\alpha$  therapy [93]. Currently,  $^{211}\text{At}$  can be used to treat glioma, ovarian cancer, and recurrent brain tumors [94-96].

$^{211}\text{At}$  is generally produced by medium-energy cyclotron through the reaction  $^{209}\text{Bi}$  ( $\alpha$ , 2n)  $^{211}\text{At}$  [97-98]. However, careful monitoring of the energy of  $\alpha$  is often required as over 28.4 MeV the production of toxic impurities such as  $^{210}\text{Po}$  becomes relevant [99-100].

#### (11) $^{67}\text{Cu}$

$^{67}\text{Cu}$  ( $T_{1/2}=2.58$  d) emits  $\gamma$ -rays for SPECT diagnosis, and  $\beta$  particles that can be used for medical treatment. Thus, it can be used individually or with  $^{64}\text{Cu}$  as radiopharmaceuticals for theranostics. At present, it is used for the nuclear medicine diagnosis of neuroendocrine tumors and lymphomas [101-102] and for the medical treatment of lymphoma and colon cancer [103].

There are two production methods using cyclotron:

(1)  $^{68}\text{Zn}$  (p, 2p)  $^{67}\text{Cu}$  - a reaction with a high recovery which needs both a medium-energy cyclotron and a highly enriched target [104-106];

(2)  $^{67}\text{Zn}$  (n, p)  $^{67}\text{Cu}$ - this reaction is induced by neutrons but it can produce  $^{67}\text{Cu}$  with only traces of radioactive impurities [107-108].

In addition to the medical isotopes mentioned above,  $^{11}\text{C}$  [109]、 $^{13}\text{N}$  [110]、 $^{15}\text{O}$  [111]、 $^{86}\text{Y}$  [112]、 $^{44}\text{Sc}$  [113-114]、 $^{201}\text{Tl}$  [115]、 $^{47}\text{Sc}$  [116-117]、 $^{32}\text{P}$  [118]、 $^{67}\text{Ga}$  [119] and other medical isotopes produced by cyclotron have also been reported.

Cyclotrons are the main accelerator-based driver of medical isotopes production. Their output is constantly improving due to advancements in targets [120-121], research on new nuclear reactions [122-124], and accelerator technology developments [125-127], leading not only to increased yields but also a reduction of radioactive impurities. In fact, currently most medical isotopes produced by reactors can also alternatively be produced by cyclotrons. The constant improvements of cyclotrons to produce medical isotopes have had great significance to the stable supply of medical isotopes.

## 2.2. Medical isotopes produced by Linacs

The charged particles accelerated by a linear accelerator only pass through the focusing magnetic field and the linear acceleration field once without deflection [39] and, once ejected, they will irradiate the target to produce medical isotopes. The linear accelerator beam is characterized by high beam intensity and a lower energy [40].

In terms of linacs currently used to produce medical isotopes, proton linacs can be relatively easily employed in the current production of medical isotopes. For example, proton linacs that produce PET nuclides can reduce the weight of cyclotron magnets and some high-energy and high-fluxes proton linacs can produce therapeutic nuclides [128-130]. While the feasibility of electron linacs to produce medical isotopes has reported so much, its pulsed beam and the cross section may bring the challenges [37,131-133]. There are other linacs which accelerate other charged particles that will not be described here.

### (1) $^{18}\text{F}$

PET radioisotopes can be produced with proton linacs. In fact, the first compact proton linear accelerator in the United States for the generation of medical isotopes has been producing  $^{18}\text{F}$  for a local hospital [134].  $^{18}\text{F}$  ( $T_{1/2}=109.8$  min) can also be produced by electron linacs through the photonuclear reaction  $^{19}\text{F}(\gamma, n)^{18}\text{F}$ , which means other standard PET radioisotopes such as  $^{11}\text{C}$  ( $T_{1/2}=20.38$  min),  $^{13}\text{N}$  ( $T_{1/2}=9.96$  min) and  $^{15}\text{O}$  ( $T_{1/2}=122$  s) can be produced as well. Although when using photonuclear reactions to produce these standard PET radioisotopes, it is found that the cross section of the photonuclear reaction is 1-2 orders of magnitude lower than that of the proton reaction. However, in the case of producing  $^{18}\text{F}$  by photonuclear reaction, it just needs  $^{19}\text{F}$  target of natural (100%) abundance. Compared with proton reaction, it costs lower [128].

### (2) $^{99}\text{Mo}$

$^{99}\text{Mo}$  ( $T_{1/2}=66$  h) decays to  $^{99\text{m}}\text{Tc}$  ( $T_{1/2}=6.02$  h), hence  $^{99}\text{Mo}$  production is also important. An electron linac can be utilized to produce  $^{99}\text{Mo}$  via the photonuclear reaction  $^{100}\text{Mo}(\gamma, n)^{99}\text{Mo} \rightarrow ^{99\text{m}}\text{Tc}$  [135-137]. This production method can use a natural target. Though it will produce the isotopes of Mo, the isotopes of Tc will not be produced which means it is easy to separate by chemical or evaporation temperature difference [138]. This production method can also use an enriched target, which is both more efficient and expensive [36]. Presently, NorthStar, Canadian Light Source and TRIUMF have conducted feasibility research and are planning to produce  $^{99}\text{Mo}$  [139-140].

In addition to the medical isotopes mentioned above, the production of  $^{67}\text{Cu}$ [141-143]、 $^{64}\text{Cu}$ [144]、 $^{225}\text{Ac}$ [145-146]、 $^{68}\text{Ga}$ [147]、 $^{111}\text{In}$ [132]、 $^{177}\text{Lu}$ [148]、 $^{47}\text{Sc}$ [149] and other medical isotopes through linacs have also been reported.

Overall, linacs have some disadvantages, in terms of design and yields [37,133,150-151]. As a backup method for production of medical isotopes, it still needs further exploration and research.

## 2.3. Medical isotopes produced by neutron generator

A neutron generator is an accelerator-based neutron source device capable of delivering neutrons through nuclear fusion reactions, which will in turn irradiate target to produce medical isotopes. The nuclear fusion reactions used commonly to produce neutrons are shown in the table 3:

**Table 3.** Fusion reactions that produce neutrons [152-156].

| Reaction                  | Energy [MeV] | Suitable reaction of isotopes production |
|---------------------------|--------------|------------------------------------------|
| D-D reaction              | 2-3          | (n, $\gamma$ )                           |
| D-T reaction              | 14-15        | (n, 2n) (n, p)                           |
| D- $^7\text{Li}$ reaction | 10&13        | (n, 2n) (n, p)                           |

#### (1) $^{99\text{m}}\text{Mo}/^{99\text{m}}\text{Tc}$

$^{99\text{m}}\text{Tc}$  ( $T_{1/2}=6.02\text{h}$ ) can be produced by neutron generator [157-159]. After neutron moderation, neutrons of specific energy can be obtained which will be used to produce  $^{99\text{m}}\text{Tc}$  via nuclear reaction  $^{235}\text{U}(\text{n}, \text{f})^{99}\text{Mo} \rightarrow ^{99\text{m}}\text{Tc}$ . The advantages of this production method are easy to supervise and safer but the yield of  $^{99}\text{Mo}$  will be 1-2 orders of magnitude lower than the reactor [160]. Plus, this production method requires a long-term, stable and high intensity beam which is difficult to achieve [161].

In addition,  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  can be produced via nuclear reaction  $^{98}\text{Mo}(\text{n}, \gamma)^{99}\text{Mo}$  and  $^{100}\text{Mo}(\text{n}, 2\text{n})^{99}\text{Mo}$ , both of which use Mo target instead of U target. And sufficient activity and sufficient amount of  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  can be produced in principle [157,159,162]. The yields of these two nuclear reactions can be improved by improving the fluxes of neutrons and the irradiated time, using highly enriched target and other ways [163].

#### (2) $^{89}\text{Sr}$

$^{89}\text{Sr}$  ( $T_{1/2}=50.5\text{d}$ ) is a pure  $\beta^-$  emitter which can be used to relieve the pain caused by bone metastases from advanced cancers such as prostate cancer and breast cancer[164].

$^{89}\text{Sr}$  is commonly produced by the (n, p) reaction in a reactor framework but the advent of neutron generators provided a new way to produce  $^{89}\text{Sr}$  via the D-T reaction in yttria as  $^{89}\text{Y}(\text{n}, \text{p})^{89}\text{Sr}$  [165-166].

#### (3) $^{67}\text{Cu}$

$^{67}\text{Cu}$  ( $T_{1/2}=61\text{h}$ ) is generally produced by cyclotrons but it can also be produced by neutron generators via the D-T reaction in the form of  $^{67}\text{Zn}(\text{n}, \text{p})^{67}\text{Cu}$ . This production method will not produce a large amount of impurities, and the activity can reach hundreds to thousands of MBq [162].

In addition to the medical isotopes mentioned above,  $^{64}\text{Cu}$ [167],  $^{47}\text{Sc}$ [168],  $^{132}\text{Xe}$ [169],  $^{225}\text{Ac}$  [162] and other medical isotopes produced by neutron generator have also been reported.

As a neutron source, the neutron generator is essential to produce neutron-rich medical isotopes. Although it has the advantages of low cost and target reusability [162,170], providing continuously high fluxes of neutrons and to the separation-extraction of the medical isotopes remain challenging topics [170]. Despite these challenges it is presently regarded as a viable alternative to the reactor-production method.

### 3. The status of medical isotopes production by accelerator in China

#### 3.1. Available Accelerators for medical isotopes production in China

Medical isotopes manufacturers and large- and medium-sized hospitals are equipped with more than 110 small medical accelerators as of December 2017 for routine production of  $^{11}\text{C}$ ,  $^{18}\text{F}$  and other medical isotopes to meet clinical demands in China [171]. In addition, there are several high-energy accelerators in China introduced below that can be used for the medical isotopes production.

The Chinese Institute of Atomic Energy and Shanghai Ansheng Kexing Company each have a C-30 proton cyclotron with an adjustable proton energy of 15.5-30 MeV and reaching beam intensity of up to 350  $\mu$ A. It can be used to produce  $^{11}\text{C}$ 、 $^{18}\text{F}$ 、 $^{64}\text{Cu}$ 、 $^{68}\text{Ge}$ 、 $^{89}\text{Zr}$ 、 $^{123}\text{I}$ 、 $^{124}\text{I}$ 、 $^{201}\text{Tl}$  and other medical isotopes.

The Chinese Institute of Atomic Energy has a 100 MeV proton cyclotron with a beam intensity up to 200  $\mu$ A capable of producing  $^{67}\text{Cu}$ 、 $^{225}\text{Ac}$  among other medical isotopes of interest.

The Sichuan University owns a cyclotron capable of delivering beams of p,  $\alpha$  and d particles (p - 26 MeV and  $\alpha$  -30 MeV).

The Chinese Academy of Sciences Institute of Modern Physics built a 25 MeV superconducting proton linear accelerator with the intensity of the order of milliamps. At present, the linac can accelerate beams such as proton beam,  $^3\text{He}^{2+}$  beam, and  $^4\text{He}^{2+}$  beam. The energy of  $^3\text{He}^{2+}$  beams can reach 36 MeV at intensity of 200  $\mu$ A; the energy of  $^4\text{He}^{2+}$  beam can reach 32 MeV with a current of 100  $\mu$ A. The accelerator can meet the need of medical isotopes production and can produce various radioisotopes such as  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ 、 $^{117\text{m}}\text{Sn}$ 、 $^{211}\text{At}$ 、 $^{55}\text{Fe}$ 、 $^{73}\text{As}$ 、 $^{225}\text{Ac}$ 、 $^{109}\text{Cd}$ 、 $^{88}\text{Y}$ 、 $^{75}\text{Se}$ .

Lanzhou University has been instrumental in the development of advanced ion source selection, ion beam extraction and acceleration system design as well as target system design. Lanzhou University independently built a compact neutron generator which can produce neutrons with different energies and at present is the first compact neutron generator nationwide and one of the most advanced in the world.

### 3.2. The status of medical isotopes production via accelerators

There is a solid research foundation in terms of accelerator-based medical isotopes production in China. Since the 1960s, The CIAE has relied on cyclotron to try to produce medical isotopes such as  $^{22}\text{Na}$ 、 $^{54}\text{Mn}$ 、 $^{57}\text{Co}$ 、 $^{88}\text{Y}$ 、 $^{109}\text{Cd}$ . In the 1980s, Sichuan University and others have successively delivered medical isotopes such as  $^{211}\text{At}$ 、 $^{123}\text{I}$ 、 $^{111}\text{In}$  and  $^{201}\text{Tl}$  by relying on domestic cyclotrons and its CS-30 cyclotron[172].

In the last 20 years, with the popularization and rapid development of domestic nuclear medicine, PET equipment has increased significantly. For conventional PET nuclides such as  $^{18}\text{F}$ , The CIAE has been using CyClone-30 for routine production of  $^{18}\text{F}$  and  $^{18}\text{F}$ -FDG. At present, the hospitals equipped with small medical cyclotrons have mastered the production technology of  $^{18}\text{F}$  to meet clinical needs, with an annual consumption of more than 50,000 Ci. With the continuous entry of new diagnostic radiopharmaceuticals into the market, the production of new medical isotopes such as  $^{64}\text{Cu}$ 、 $^{89}\text{Zr}$ 、 $^{123}/^{124}\text{I}$  has been developed rapidly. Since 2007, The CIAE has cooperated with Atom Hitech to carry out research on the production of  $^{123}\text{I}$  by using Cyclone-30. In 2012, Atom Hitech produced carrier-free  $^{64}\text{Cu}$  based on the Cyclone-30. In 2016, Sichuan University bombarded  $^{89}\text{Y}$  target which had a purity of more than 99.99% with 13 MeV protons and obtained  $^{89}\text{Zr}$  with a radionuclide purity of more than 99% [12]. However, the production of therapeutic nuclides such as  $^{67}\text{Cu}$ 、 $^{225}\text{Ac}$  and  $^{223}\text{Ra}$  is limited by the availability of high-energy particle accelerators and lagging significantly behind the international advanced level. The CIAE for the first time obtained more than 22.2 MBq (0.6 mCi) of  $^{225}\text{Ac}$  with a radionuclide purity greater than 99% by using the CYCIAE100 in 2021.

## 4. Summary

Presently, cyclotron is the main way of accelerator-based medical isotopes production, while linacs and the neutron generator are rapidly becoming established as viable alternative methods of production.

Cyclotron can produce medical isotopes with different purposes through wide energy ranges and a medium-energy cyclotron can cover the most radiopharmaceuticals production in a region [40]. Yield and purity improvements of medical isotopes and the overall cost of cyclotron production led people to explore further possibilities including

proton linacs which have significant advantages in producing proton beams of tens to hundreds of megaelectron volt [130]. These can be developed in research institutes or laboratories conducting scientific experiments and physical research at the same time. As for electron linacs, the cross section of photonuclear interactions is relatively low which impacts its practical application. Other factors such as the impurity products, the economic costs also play a major role when evaluating production techniques and methods. Attempts to produce medical isotopes through neutron generator are promising and they can theoretically produce the medical isotopes that are produced by reactors. However, improving the neutron flux rate is still an urgent priority.

As the production of medical isotopes by reactors often faces supply crisis, the interest in the use of accelerator-based techniques to produce medical isotopes will definitely increase.

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