Production of Lu-177 Radionuclide using Deuteron Beams: Comparison between (d,n) and (d,p) Nuclear Reactions

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Abstract. Lutetium-177 (177Lu) radioisotope has been suggested for radioimmunotherapy application in nuclear medicine. Presently 177Lu has been mostly produced using neutron activation in nuclear reactors, whereas cyclotron-based production has not been well explored. In this paper, we theoretically propose cyclotron-based deuteron beams for 177Lu production. By Employing the TALYS 2017 codes, we calculated nuclear cross-sections and the End-of-Bombardment (EOB) yields of 176Yb(d,n)177Lu reaction for direct production of 177Lu as well as 176Yb(d,p)177Yb → 177Lu reaction for indirect production of 177Lu. The TALYS calculated cross-sections indicated that the threshold energy of both investigated nuclear reactions is 0 MeV; thus 177Lu could be produced at low deuteron energy bombardment, though significant amount of 177Lu radioactivity could only be generated for deuteron beams with energy greater than 6 MeV. The calculated EOB yields for 176Yb(d,n)177Lu reaction and 176Yb(d,p)177Yb reaction were 0.519 and 181.1 MBq/µAh respectively, which well agreed with previous experimental results published elsewhere. In conclusion, both nuclear reactions are possible for 177Lu production though the indirect method via 176Yb(d,p)177Yb → 177Lu reaction would give much better EOB yield than that of direct method.

Keywords: 177Lu, deuteron beam, nuclear cross-section, radioactivity yield, TALYS

1. Introduction

In nuclear medicine, cancer therapy requires alpha, beta or gamma emitting radioisotopes since the particles could destroy cancer cells, though direct proton beam irradiation could also be employed in solid cancer therapy [1-2]. One of the emerging radioisotopes suggested for targeted therapy is lutetium-177 (177Lu), which emits beta particle at a half life of 6.65 days. When 177Lu is labeled to a certain chemical compound or antibody, it can be employed as a therapeutic agent, which is often coined as radioimmunotherapy. Recent studies suggest that 177Lu could deliver positive therapeutic effects to a wide range of solid cancers such as prostate cancer [3-7], neuroendocrine tumor [8-10], breast cancer [11-14] and some other tumors.

Lutetium-177 production has been mostly conducted by irradiating enriched 176Yb target with high flux neutrons in nuclear reactors [15-18], though 177Lu separation from the impurities could be very difficult. New methods of 177Lu production have also been suggested for new reactor-based neutron source [19] as well as for targets other than enriched 176Yb [20-23]. Alternative 177Lu production pathways have also been suggested, particularly using accelerators or cyclotrons where particle such
as proton, deuteron, $^3$He and $^4$He are accelerated to gain high energy applicable for radioisotope production [24-25] as well as for material studies [26-28].

There has been very limited number of literatures on production of $^{177}$Lu using deuteron beam which indicates that such a new method needs more studies. Previous investigations by Hermanne et al [29] and Manenti et al [30-31] reported that excitation functions for $^{176}$Yb(d,p)$^{177}$Yb $\rightarrow$$^{177}$Lu and $^{176}$Yb(d,n)$^{177}$Lu nuclear reactions could be sufficiently high for indirect and direct production of $^{177}$Lu using deuteron beams. Similar experimental investigation on the nuclear cross-section for $^{177}$Lu production was also highlighted by Tárkányi et al [32-33]. Another nuclear cross-section research by Siiskonen et al [34] suggested that proton beam could be employed to produce $^{177}$Lu by bombarding $^{180}$Hf target through $^{180}$Hf(p,x)$^{177}$Lu nuclear reaction. Moreover, a theoretical investigation was conducted to study (d,x) nuclear reactions on natural ytterbium up to 24 MeV relevant for deuteron-based $^{177}$Lu production [35].

To the best of our knowledge, there has been no specific report on $^{177}$Lu production at various deuteron doses; therefore this work will explore the dependence of deuteron dose on the end-of-bombardment (EOB) yield of $^{177}$Lu radionuclide for (d,n) and (d,p) nuclear reactions.

2. Materials and Methods

In this study, deuteron was the main particle used in the calculations and simulations while the target of interest would be enriched $^{176}$Yb. The range and stopping power (energy loss) of deuteron in $^{176}$Yb target was simulated using the Stopping and Range of Ion in Matter (SRIM) code version 2013 which had been widely used elsewhere [36].

The excitation functions of two nuclear reactions, namely $^{176}$Yb(d,p)$^{177}$Yb $\rightarrow$$^{177}$Lu and $^{176}$Yb(d,n)$^{177}$Lu were calculated using the TALYS code [37]. The TALYS-calculated nuclear cross-sections were then employed to calculate the end-of-bombardment (EOB) yield using available mathematical expression published earlier [38-39]; and in this work, a Matlab code was developed for the EOB yield calculation.

To study the dependence of deuteron beam dose on the EOB yield, the bombardment was simulated with a fixed 50-µA deuteron beam current (referred to the IBA’s cyclone 70 specifications [40]) while the deuteron energy was varied from 15 to 35 MeV and the irradiation time was varied from 1 to 6 hours.

3. Results and Discussion

3.1 SRIM-calculated Range and Stopping Power

When deuteron passes through a target, it is expected to lose some or all of its energy. According to the SRIM calculation, a 10-MeV deuteron is able to penetrate as deep as 314.93 µm in a $^{176}$Yb target, whereas the range of a 40-MeV deuteron in the same target is approximately 2930 µm as shown in Figure 1. In addition, the energy losses (stopping powers) of the deuteron particles are relatively large, i.e. $2.90\times10^{-2}$ and $1.16\times10^{-2}$ mg/cm$^2$ for 10-MeV and 40-MeV deuterons respectively.
For the purpose of $^{177}$Lu radionuclide production, the recommended thickness of $^{176}$Yb target is listed in Table 1 for deuteron energy ranging from 10 to 40 MeV. The target thickness prepared for the irradiation should be made thicker with increasing deuteron energy. Increasing deuteron energy from 15 MeV to 30 MeV would consequently require increasing the $^{176}$Yb target thickness from nearly 0.6 mm to nearly 2 mm. Note that one could add up to 10% of the recommended thickness to account for the deviation of the deuteron range.

Table 1. Recommended target thickness for $^{176}$Yb target for $^{177}$Lu production

| Deuteron energy (MeV) | $^{176}$Yb target thickness (µm) |
|-----------------------|---------------------------------|
| 10                    | 315                             |
| 15                    | 594                             |
| 20                    | 941                             |
| 25                    | 1350                            |
| 30                    | 1820                            |
| 35                    | 2350                            |
| 40                    | 2930                            |

3.2 Nuclear Cross-sections and EOB yields

The TALYS-calculated nuclear excitation functions for $^{176}$Yb(d,p)$^{177}$Yb $\rightarrow^{177}$Lu and $^{176}$Yb(d,n)$^{177}$Lu nuclear reactions are shown in Figure 2, which indicates that the threshold energy for both reactions is 0 MeV. While the shape of the excitation function for both reactions is very similar, there is a notable difference in the cross-sections between the two reactions, particularly the maximum cross-section for the (d,p) reaction, which is nearly 9 times that of the (d,n) reaction. As well, the maximum cross-section for both reactions occurs at deuteron incident energy of 10 MeV.
As can be seen in Figure 3, based on the calculated EOB yields, the radioactivity yield for $^{176}$Yb(d,n)$^{177}$Lu nuclear reaction is relatively negligible compared to the $^{176}$Yb(d,p)$^{177}$Yb$\rightarrow^{177}$Lu nuclear reaction. In the inset of Figure 3, it is clear that the maximum $^{177}$Lu EOB yield is only 0.519 MBq/µAh, which occurs when the incoming deuteron energy is 40 MeV. In contrast, the maximum $^{177}$Lu EOB yield for the $^{176}$Yb(d,p)$^{177}$Yb$\rightarrow^{177}$Lu reaction is 181.1 MBq/µAh at deuteron energy of 22 MeV. Thus, when deuteron beam is used for $^{177}$Lu production, (d,n) nuclear reaction would give insignificant contribution to the radioactivity yield as compared to the (d,p) reaction. Furthermore, these calculated results are in good agreement with earlier published work [29-33].

3.3 Deuteron Dose Dependence of $^{177}$Lu Radioactivity Yield

The $^{177}$Lu production yield is strongly dependence on the deuteron dose as can be seen in Figure 4 and Figure 5 for $^{176}$Yb(d,n)$^{177}$Lu and $^{176}$Yb(d,p)$^{177}$Yb$\rightarrow^{177}$Lu nuclear reactions respectively. In general, the yield increases with increasing deuteron dose. The yield calculations for different deuteron energies ranging from 10 to 35 MeV and various deuteron doses between 50 and 300 µAh indicate that the $^{177}$Lu yield obtained from $^{176}$Yb(d,n)$^{177}$Lu nuclear reaction remains low (maximum of 151.82 MBq for incident deuteron energy of 35 MeV and deuteron dose of 300 µAh). Such a low yield would not be sufficient for radioimmunotherapy purpose even just for 1 patient (assuming 1 patient requires at least over 300 MBq). Therefore $^{177}$Lu production through $^{176}$Yb(d,n)$^{177}$Lu reaction would not be economically viable.
Figure 4. Calculated $^{177}$Lu yields at selected deuteron doses for $^{176}$Yb(d,n)$^{177}$Lu nuclear reaction

In contrast to the previous $^{177}$Lu production route, the latter pathway through $^{176}$Yb(d,p) $^{177}$Yb $\rightarrow$ $^{177}$Lu nuclear reaction seems very promising as shown in Figure 5. Even for low deuteron energy (10 MeV, for instance) the $^{177}$Lu radioactivity yield at the end of irradiation would be as high as 25231.8 MBq for deuteron dose of 300 µAh. Such a value would be sufficient for over 80 patients to get radioimmunotherapy procedures. Even one can use 20-MeV deuterons to produce much higher $^{177}$Lu of up to 50139 MBq (enough to support as many as 167 patients). Therefore this typical route of $^{177}$Lu production is highly recommended. Further examples of the produced radioactivity yield corresponding to the number of patients could benefit from is shown in Table 2.

Table 2. Estimated number of patients could benefit from $^{177}$Lu production

| Deuteron dose (MeV) | $^{177}$Lu radioactivity yield (MBq) | number of patients |
|---------------------|---------------------------------|-------------------|
| 100                 | 16713                           | 55                |
| 150                 | 25069                           | 83                |
| 200                 | 33426                           | 111               |
| 250                 | 41782                           | 139               |
| 300                 | 50139                           | 167               |
| 350                 | 58495                           | 194               |
| 400                 | 66852                           | 222               |

4. Conclusion

Production of $^{177}$Lu radioisotope using deuteron beams have been discussed in this paper, particularly for two different nuclear reactions, namely through $^{176}$Yb(d,n)$^{177}$Lu and $^{176}$Yb(d,p) $^{177}$Yb $\rightarrow$ $^{177}$Lu. Theoretical calculations show that as thick as 1 mm $^{176}$Yb target should be prepared when bombarding the target with 20-MeV deuterons to produce $^{177}$Lu. The TALYS-calculated excitation functions indicate that the deuteron threshold energy for $^{177}$Lu production is 0 MeV, though significant radioactivity yield would not be generated for deuteron energy lower than 6 MeV. In general, the calculated the nuclear cross-section for $^{176}$Yb(d,p) $^{177}$Yb $\rightarrow$ $^{177}$Lu is much higher than that of $^{176}$Yb(d,n)$^{177}$Lu reaction. In conclusion, $^{177}$Lu radioisotope production is very promising using deuteron beam irradiation through $^{176}$Yb(d,p) $^{177}$Yb $\rightarrow$ $^{177}$Lu nuclear reaction, in which up to 50139 MBq could be produced at a 300-µAh deuteron dose.

5. Acknowledgements

The author would like to acknowledge funding from The Indonesian National Nuclear Energy Agency (BATAN). Discussion with the staff and technicians of the Center for Radioisotope and Radiopharmaceutical Technology, BATAN is also gratefully acknowledged.

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