Proton-produced radionuclides for radiodiagnostic modalities in cancer studies

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Abstract. With increasing rates of cancer cases globally, scientists and technologists have proposed cancer diagnosis using radioisotope-labelled chemical compounds. In this paper, using the TALYS 2017 codes we calculated excitation functions of several (p,n), (p,α), (p, 2n) and (p,3n) nuclear reactions. The TALYS-calculated results indicated that a few radionuclides such as 18F, 11C, 64Cu, 124I could be produced at relatively low threshold energies ranging from as low as 2.7 MeV to 4 MeV, whereas other radionuclides such as 123I, 201Tl, 111In and 67Ga could only be generated with protons of over 10 MeV. While 18F, 15O, 64Cu and 124I radionuclides could be produced via (p,n) nuclear reactions, other radionuclides including 99mTc, 123I, 111In and 67Ga could be produced through (p,2n) nuclear reactions. In addition, (p,α) nuclear reaction was found to suit 11C and 13N radionuclide production, whereas (p,3n) fit 201Tl production. In general, most radionuclides used for Single Photon Computed Tomography (SPECT) modality requires higher proton incident energies compared to those for Positron Emission Tomography (PET) modality in nuclear medicine.

1. Introduction

One of the issues facing urban communities is health problems which require thorough studies and proper policies to overcome the issues. Health problems include different types of communicable and non communicable diseases. As a non communicable disease, cancer has been one of the highest causes of death worldwide. The Indonesian Ministry of Health (Kemenkes) reported that cancer prevalence in Indonesia was at 1.4% in 2013, whereas according to the World Health Organization (WHO) report, the number of cancer cases in Indonesia could increase to 7 times by 2030. Of the reported cancer cases, 56% of the cases and 64% of the deaths occurred in developing countries [1-4]. The spiraling cancer cases require specific actions for prevention, diagnosis and therapy.

Over the past decades, nuclear technology has been offering methods to diagnose cancers and other metabolic disorders. Two nuclear or radiodiagnostic modalities currently available in several hospitals in Indonesia are Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT). Both PET and SPECT modalities require radioactive sources (radionuclides) for the analysis. Radionuclides emitting positrons are employed in PET based diagnosis [5,6] whereas radionuclides emitting gamma rays are used in SPECT based diagnosis [6-8].

Production of PET and SPECT radionuclides could be done using a cyclotron – a machine that accelerates particles such as proton, deuteron, He-3 and He-4 (alpha) circularly to a high energy suitable for nuclear reactions in radionuclide production [9-10], though such a machine could also be employed for material studies [11-13]. At high energy (usually greater than 5 MeV), protons are able to penetrate through target atoms’ nuclei resulting in nuclear reactions which generate new radionuclides. Most of the produced radionuclides are short-lived, which are suitable for medical uses.
Cyclotron-based radionuclide production requires thorough understanding of nuclear cross-section or excitation function, nuclear reaction, threshold energy, irradiation parameters and other requirements, theoretically and experimentally. This paper discusses the TALYS 2017-calculated excitation functions of proton-activated nuclear reactions, namely \((p, n)\), \((p, \alpha)\), \((p, 2n)\) and \((p, 3n)\) corresponding to several ongoing and emerging radionuclides applicable for nuclear medicine imaging.

2. Materials and Methods

In this research, theoretical calculations using the TALYS codes\(^{14}\), which has been used elsewhere\(^{15-16}\) were also performed for several nuclear cross-sections related to PET and SPECT radionuclide production. Available data on cyclotron produced radionuclides were collected from various references, while experimental data of F\(^{18}\) production was mainly derived from cyclotron irradiation data at Dharmais cancer hospital in Jakarta by employing a 30-µA proton beam at irradiation time of 50 minutes.

3. Results and Discussion

3.1 TALYS-Calculated Nuclear Cross-sections of PET Radionuclides

In general, PET radionuclides could be immediately generated through \((p, n)\), \((p, \alpha)\) and other nuclear reactions. The TALYS 2017-calculated nuclear cross-sections of several PET radionuclides can be seen in Fig. 1, which indicates that the highest excitation function (735 mBarn) occurs for \(^{64}\text{Ni}(p,n)^{64}\text{Cu}\) nuclear reaction. Moreover, \(^{64}\text{Cu}\) radioactivity starts to be realized at low threshold energy of 2.7 MeV. The second highest excitation function (nearly 700 mBarn) is \(^{124}\text{Te}(p,n)^{124}\text{I}\) nuclear reaction and its threshold energy is 4 MeV.

![Figure 1. TALYS 2017-calculated nuclear cross sections of some PET radionuclides](image)

For \(^{18}\text{F}\) production, one requires at least 3.7 MeV-proton beams so that \(^{18}\text{O}(p,n)^{18}\text{F}\) nuclear reaction could occur, whereas for \(^{11}\text{C}\), \(^{13}\text{N}\) and \(^{15}\text{O}\) production the threshold energies are 3.1, 5.6 and 9.3 MeV respectively. The relatively low threshold energies of the investigated nuclear reactions indicate that production such radionuclides are possible using low energy cyclotrons. In Indonesia, there are three medical cyclotrons installed and being operated for radionuclide production, particularly for F-18 production\(^{9-10}\). The three cyclotrons are based in Jakarta at Gading Pluit hospital, Dharmais cancer hospital and Siloam hospital. The MINITrace-type cyclotron at Gading Pluit hospital is capable of accelerating protons of up to 9.6 MeV with a maximum beam current of 50 µA. In Dharmais cancer hospital, an Eclipse RDS 111 cyclotron can accelerate protons of up to 11 MeV with a maximum beam current of 60 µA. The biggest medical cyclotron in Indonesia is Cyclone 18/9 cyclotron owned by Siloam hospital, which is able to accelerate protons and deuterons of up to 18 MeV at a maximum beam current of 100 µA.
3.2 TALYS-Calculated Nuclear Cross-sections of SPECT Radionuclides

Production of SPECT radionuclides using cyclotrons generally requires high energy proton beam since most of them could be generated through \((p,2n)\), \((p,3n)\) and some other nuclear reaction modes. Current news on shortage of \(^{99m}\)Tc supplyavorable for Indonesian researchers and practitioners to think about new ways of producing \(^{99m}\)Tc. Cyclotron offers a promising method of producing \(^{99m}\)Tc from enriched molybdenum \((^{100}\text{Mo})\) target for the purpose of SPECT modality. As shown in Fig. 2, the TALYS-2017 calculated nuclear cross-section for \(^{100}\text{Mo}(p,2n)^{99m}\)Tc nuclear reaction is quite high (over 969 mbarn at 17-MeV protons). The threshold energy for \(^{100}\text{Mo}(p,2n)^{99m}\)Tc nuclear reaction is relatively low (7.8 MeV). While theoretical studies on \(^{99m}\)Tc production has been discussed elsewhere [23], experimental production of the gamma emitting radionuclide has not been properly explored due to funding and regulatory issues. Nevertheless, the Cyclone 18/9 cyclotron at Siloam hospital would be the best medical cyclotron in Indonesia to produce \(^{99m}\)Tc.

![Figure 2. TALYS-2017 calculated nuclear cross-sections of some SPECT radionuclides](image-url)

The TALYS-2017 calculated nuclear cross-sections also indicate that \(^{124}\text{Te}(p,2n)^{123}\)I and \(^{112}\text{Cd}(p,2n)^{111}\)In nuclear reactions have similar cross-section behavior in which the threshold energy is around 11 MeV while the maximum cross-section is around 1000 mBarn. While \(^{203}\text{Tl}(p,3n)^{201}\)Tl has the highest excitation function (1200 mBarn) among the investigated SPECT radionuclides, \(^{201}\)Tl production requires high energy proton since its threshold energy is 17.5 MeV. In contrast, \(^{67}\)Ga radionuclide is possibly produced with relatively lower energy protons (over 12.2 MeV) through \(^{68}\text{Zn}(p,2n)^{67}\)Ga nuclear reaction.

3.3 Radionuclide Production Aspects

Several production aspects should be considered when producing PET and SPECT radionuclides using cyclotrons including:

1. Target preparation and geometry
   The target for radionuclide production can be in the form of solid, liquid and gas. For \(^{18}\)F production the target is usually enriched water \((\text{H}_2^{18}\text{O})\) [9-10] whereas for \(^{64}\)Cu production the target is an electroplated enriched \(^{64}\)Ni [17-20]. Target volume and thickness are also important particularly for optimized yields. For example, using 11-MeV proton beams one will need 300-\(\mu\)m thick \(^{64}\)Ni target to produce \(^{64}\)Cu, whereas producing \(^{124}\)I using the same proton beam will require 650-\(\mu\)m thick \(^{124}\)Te target [10].

2. Types and energy of irradiating particles
   Types and energy of irradiating particles are of paramount importance since they influence the target preparation and geometry as well as the yields of radionuclides produced. For example, F-18 radionuclide can be produced from enriched water \((\text{H}_2^{18}\text{O})\) target using proton beams,
whereas the same radionuclide can be produced from ordinary water (H$_2$O) target using He-3 beams.

(3) Irradiation dose (irradiation time and beam current)

Radionuclide yield is also dependent on the irradiation time and beam current employed during the target bombardment. The multiplication of the irradiation time and beam current is physically called irradiation dose. In general, the higher the irradiation dose, the higher the radionuclide yield.

One of the most common radionuclides produced for PET scan is fluorine-18 ($^{18}$F), which emits positron at a half life of 110 minutes. In Indonesia, $^{18}$F has been routinely produced using the cyclotrons at Gading Pluit hospital, Dharmais Cancer hospital and Siloam hospital. An example of $^{18}$F production using the 11-MeV proton accelerating cyclotron at Dharmais cancer hospital is shown in Fig. 3, which indicates an annihilation peak at 0.511 MeV. The gamma ray peak at 0.511 MeV is due to the annihilation process which occurs when positrons interact with free electrons.

![Gamma ray spectrum emitted by F-18 detected 1 hour and 2 hours after the end of bombardment (EOB)](image)

### Table 1 Cyclotron produced radionuclides

| Radionuclide | Nuclear reaction | Half life (minutes) | Threshold energy (MeV) | Type of radiodiagnostic modality | Type of disease diagnosed |
|--------------|------------------|---------------------|------------------------|---------------------------------|--------------------------|
| $^{18}$F     | $^{18}$O(p,n)$^{19}$F | 110                 | 3.7                    | PET                             | Prostate cancer           |
| $^{11}$C     | $^{14}$N(p,n)$^{11}$C | 20.4                | 3.1                    | PET                             | Alzheimer’s disease       |
| $^{15}$O     | $^{15}$N(p,n)$^{15}$O | 2                   | 9.3                    | PET                             | Stroke imaging            |
| $^{13}$N     | $^{16}$O(p,n)$^{13}$N | 10                  | 5.6                    | PET                             | Cardiac disease           |
| $^{64}$Cu    | $^{64}$Ni(p,n)$^{64}$Cu | 762                 | 2.7                    | PET                             | Prostate cancer           |
| $^{124}$I    | $^{124}$Te(p,n)$^{124}$I | 6019.2              | 4.0                    | PET                             | Thyroid disease           |
| $^{99m}$Tc   | $^{100}$Mo(p,2n)$^{99}$mTc | 360                 | 7.8                    | SPECT                           | Kidney disease            |
| $^{123}$I    | $^{124}$Te(p,2n)$^{123}$I | 793.2               | 11.5                   | SPECT                           | Thyroid imaging           |
| $^{201}$Tl   | $^{203}$Tl(p,3n)$^{201}$Tl | 4386                | 17.5                   | SPECT                           | Thyroid imaging           |
| $^{111}$In   | $^{112}$Cd(p,2n)$^{111}$In | 4039.2              | 11.1                   | SPECT                           | Neuroendocrine tumor      |
| $^{67}$Ga    | $^{68}$Zn(p,2n)$^{67}$Ga | 4680                | 12.2                   | SPECT                           | Blood studies             |

Apart from $^{18}$F radionuclide, there are several other potential PET and SPECT radionuclides which can be produced using cyclotrons as shown in Table 1. Usually relatively low energy cyclotrons are required to produce PET radionuclides such as $^{18}$F, $^{11}$C, $^{13}$N, $^{64}$Cu and $^{123}$I since their nuclear threshold energies are relatively low (between 2.7 and 5.6 MeV). However, medium cyclotrons capable of accelerating protons of greater than 10 MeV are needed for SPECT radionuclide production. Again, based on the threshold energy given in Table 1, Siloam hospital’s 18-MeV cyclotron is capable of...
producing all of the listed radionuclides, whereas Dharmais hospital’s and Gading Pluit hospital’s cyclotrons can be used to generate most radionuclides except $^{124}$I, $^{205}$Tl, $^{111}$In and $^{67}$Ga.

4. Conclusion
Different types of nuclear reactions responsible for proton-produced radionuclides have been discussed and their respective nuclear cross-sections have been calculated using the TALYS codes. According to the calculated results, PET radionuclides such as $^{18}$F, $^{11}$C, $^{64}$Cu, $^{124}$I could be produced at relatively low threshold energies ranging from as low as 2.7 MeV to 4 MeV as a result of $(p,n)$ and $(p,\alpha)$ nuclear reactions. In contrast, SPECT radionuclides such as $^{123}$I, $^{201}$Tl, $^{111}$In and $^{67}$Ga could only be generated with protons of over 10 MeV through $(p,2n)$ and $(p,3n)$ nuclear reactions. While $^{18}$F radionuclide has been routinely produced in Indonesian hospitals, other PET radionuclides such as $^{11}$C, $^{13}$N, $^{15}$O, $^{64}$Cu, $^{124}$I and SPECT radionuclides such as $^{99m}$Tc, $^{123}$I, $^{201}$Tl, $^{111}$In and $^{67}$Ga could also potentially be produced using the three available cyclotrons. Continuous supply of such radionuclides is of paramount importance since they are useful for cancer diagnosis and other studies.

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6. References

[1] Jemal A, Bray F, Center M, Ferlay J, Ward E, Forman D 2011 CA Cancer J. Clin. 61 69
[2] Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM 2010 Int J Cancer 127 2893
[3] Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, Law SC, Ahn YO, Xiang YB, Yeole BB, Shin HR, Shanta V, Woo ZH, Martin N, Sumitsawan Y, Sriplung H, Barboza AO, Eser S, Nene BM, Suwanrungruang K, Jayalekshmi P, Dikshit R, Wabinga H, Esteban DB, Laudico A, Bhurgi Y, Bai H, Al-Hamdan N 2010 Lancet Oncol. 11 165
[4] Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia R, Baili P, Rachet B, Gatta G, Hakulinen T, Micheli A, Sant M, Weir HK, Elwood JM, Tsukuma H, Koifman S, E Silva GA, Francisci S, Santauliani M, Verdecchia A, Storm HH, Young JL; CONCORD Working Group 2008 Lancet Oncol. 9 730
[5] Chua S 2014 Biomedical Imaging 2014 3-40
[6] Mattos DMM, Gomes ML, Freitas RS, Moreno S, Lima-Filho GL, Paula EF, Jales RLC, Bernardo-Filho M. 2001 J. Labelled Cpd Radiopharm 44 S841
[7] Khalil MM, Tremoleda JL, Bayomy TB, Willy Gsell W 2011 International Journal of Molecular Imaging 2011 1
[8] D’Asseler Y 2009 Q. J. Nucl. Med. Mol. Imaging 53 343
[9] Kambali I, Parwanto, Suryanto H, Huda N, Listiawadi FD, Astarina H, Ismuha RR, Kardinah 2017 Physics Research International 2017 1
[10] Kambali I, Suryanto H, Parwanto 2016 Australas. Phys. Eng. Sci. Med. 39 403
[11] Kambali I, Suryanto H 2016 Journal of Engineering and Technological Sciences 48 482
[12] Gladys M J, Kambali I, Karolewski MA, Soon A, Stampfl C, O’Connor DJ 2010 J. Chem. Phys. 132 024714
[13] Kambali I, O’Connor DJ, Gladys MJ, Karolewski MA 2008 Appl. Surf. Sci. 254 4245
[14] Koning A, Rochman D 2012 Nuclear Data Sheets 113 2841
[15] Goriely S, Hilaire S, Koning AJ 2008 Astronomy and Astrophysics 487 767
[16] Hilaire S, Goriely S, Koning AJ, Bauge E 2008 AIP Conference Proceedings 1012 123
[17] Kim JY, Park H, Lee JC, Kim KM, Lee KC, Ha HJ, Choi TH, An GI, Cheon GJ 2009 Appl Radiat Isot 67 1190
[18] Xie Q, Hua Zhu H, Wang F, Meng X, Ren Q, Xia C, Yang Z 2017 Molecules 22 641
[19] Al Rayyes AH, Ailouti Y 2013 World Journal of Nuclear Science and Technology 3 72
[20] Engelbrecht H, Byrne J, Packard A, Pandey M, Gruetzmacher J, De Grado T 2013 *J. Nucl. Med.* **54** 1175

[21] Ballinger JR 2010 *J. Label Compd. Radiopharm.* **53** 167

[22] Ruth TJ 2014 *J. Nucl. Med. Technol.* **42** 245

[23] Kambali I 2017 *Makara Journal of Science* **21** 100