Review article

Radiopharmaceuticals production and background of the PET/CT & Cyclotron Center, Chiang Mai University

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Positron emission tomography combined with computed tomography (PET/CT) technology has become the gold standard for diagnosis in oncologic studies by imaging the distribution of radiopharmaceuticals which can reveal biological processes in the human body using radiopharmaceuticals produced by the cyclotron. In Thailand, although a cyclotron facility has existed in the capital city since 2005, it was not widely used by other regions of the country. The PET/CT & Cyclotron Center, Chiang Mai University became the first regional cyclotron center with high capacity for producing various PET radiopharmaceuticals including fluorine-18, carbon-11, nitrogen-13, oxygen-15 and iodine-124 in 2013. This study presents a background of the facility together with an overview of the radiopharmaceutical production processes for clinical and research studies in the field of oncology, cardiology and neurology. **Chiang Mai Medical Journal 2021;60(1):125-34. doi 10.12982/CMUMEDJ.2021.11**

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Introduction

Cancer is one of the leading causes of death around the world including many Southeast Asian countries. The World Health Organization 2018 report estimated 9.6 million deaths (16% of all deaths) worldwide in 2017 were a result of cancer (1). Over 10 million individuals are diagnosed with cancer each year, and more than two-thirds of all cancer deaths occur in low- or middle-income countries like Thailand (2). However, early detection and intervention can significantly improve both patient survival rates and their quality of life.

Since cancer became a leading cause of death all over the world, positron emission tomography and computed tomography (PET/CT) scanning has been developed as a novel multi-modality technique in nuclear medicine. Just as PET images provide information on biological functions, CT images provide accurate anatomical information on lesions for anatomical mapping (3,4). Not only does PET/CT technology provide exquisitely sensitive qualitative and quantitative imaging, the broad range of available positron-emitting radionuclides produced by a cyclotron, a type of particle accelerator, allows investigation of several clinical indications such as diagnosis, staging, restaging, detection of recurrent disease and monitoring response to cancer therapy. In addition, PET/CT plays a key role in research on tracers and drug development, in which the oncologic field has by far the highest number of new drugs in development (5-7).

The most widely used PET radiopharmaceutical is ^{18}F-fluorodeoxyglucose (^{18}F-FDG) which is

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a radiolabeled analog of glucose. Since ^{18}F-FDG is taken up selectively by hypermetabolic cancer cells, the use of ^{18}F-FDG PET/CT allows early detection and quantification of cancer. It is very useful in the diagnosis and treatment planning of many cancers, especially lung cancer, colorectal cancer, lymphoma, melanoma as well as in the fields of neurology, cardiology, and infection/inflammation (8,9). The National Cancer Institute (NCI) estimated that appropriate cancer screening could prevent 3-35% of cancer deaths since the earlier-stage cancers can often be treated with a less destructive approach (10).

As a result, the total number of domestic PET/CT studies in Thailand has increased steadily from 866 in 2006 to 2,316 in 2009 (11). One PET/CT scanner in a private hospital performed more than 6,000 case studies between 2005 and 2012, of which 97% were ^{18}F-FDG-PET/CT for oncological studies and the rest were neurological imaging (12). According to the United Nations, the population of Thailand in 2019 was 69.6 million of whom approximately 10 million lived in the northern region of the country (13). Thailand has a total of 9 PET and PET/CT scanner units, or approximately 0.1 units per million people while the Royal College of Radiologists in the United Kingdom and the World Health Organization recommend 1 to 2 units for every million people. The United States and Japan have the highest number, with 4 and 3 units per million inhabitants, respectively (14).

One reason PET/CT technology has not been more widely established throughout Thailand is the need for a cyclotron. Without a cyclotron facility as part of a PET radiopharmaceutical production unit, making use of the advanced technology of PET/CT imaging is not possible as PET radionuclides are very short-lived. However, despite the negative assessment report on the feasibility and appropriateness of using PET/CT in Thailand (15), the rising demand for high technology health care has been gradually overcoming the obstacles of human resource shortages and the high cost of cyclotron installation (16).

In 2005, Assoc. Prof. Sombut Boonyaprapa, M.D., Assoc. Prof. Nonglak Vilasdechanon, and Assoc. Prof. Molrudee Ekmahachai, M.D. from the Nuclear Medicine Unit, Department of Radiology, Faculty of Medicine, Chiang Mai University proposed the establishment of the first PET/CT and cyclotron center located outside the capital city of Bangkok and the first in a medical school in Thailand. For many years, the team worked hard until budget was obtained from the Thailand infrastructure development project and from hospital revenue, resulting in the construction of the facility in 2012. The PET/CT and Cyclotron Center Chiang Mai University (PCCCMU), which opened on 22 May 2013, is fully equipped with a medical cyclotron and synthesizers inside a standardized cleanroom facility (Figs. 1 and 2). A new imaging unit has also been installed, including a 128-slice PET/CT scanner (Fig. 3) and a 16-slice single photon emission computed tomography and computed tomography (SPECT/CT) scanner.

In 2020, Thailand had 4 cyclotron facilities for radiopharmaceutical production: Wattanosoth

Figure 1. The front of the PET/CT & Cyclotron Center Building, Chiang Mai University

Figure 2. HM-20S vertical plane, self-shielded cyclotron (Sumitomo Heavy Industries, Shinagawa City, Tokyo, Japan) in the negative-pressured cyclotron room

Figure 3. A 128-slice Biograph mCT PET/CT scanner (Siemens Healthineers, Erlangen, Germany)

Cancer Hospital (Bangkok), National Cyclotron and PET Centre, Chulabhorn Hospital (Bangkok), Siriraj Hospital (Bangkok), and PCCCMU (Chiang Mai). The establishment of the first regional PET/CT and cyclotron facility in Chiang Mai (North) has partly encouraged the birth of new centers in other parts of Thailand, for example, the under-construction 30 MeV cyclotron in Nakhon Nayok (East), the under-construction 19 MeV cyclotron in Songkhla (South) and the upcoming project in Khon Kaen (Northeast), as cyclotrons should be regionally located while scanners should be evenly distributed at a more local level. According to the International Atomic Energy Agency (IAEA) report on trends in nuclear medicine in developing countries (17), in order to achieve optimal performance in nuclear medicine, collaboration and training between each PET/CT and cyclotron center needs to be provided. Although the different manufacturing systems in each facilities have posed a challenge, gradually the network and knowledge-exchange through both IAEA-supported activities and national-level conferences and workshops has strengthened existing practices to help achieve the common goal of providing affordable and efficient radiopharmaceuticals in response to the needs of Thai patients (18).

Through extensive reviews and collaborations, the Chiang Mai facility aims to produce radiopharmaceuticals both for the direct benefit of patients and also in the form of medical diagnostics and advanced research. Since its opening, more than 781 case studies have been performed of which 97.8% were oncologic studies, 1.5% were in neurology and 0.7% in cardiology. The routine radiopharmaceutical products are ^{18}F-FDG and ^{18}F-PSMA-1007, while production for research and development includes ^{18}F-NaF, ^{13}N-ammonia, ^{11}C-methionine, ^{11}C-choline, ^{11}C-acetate, ^{15}O-water and ^{124}I-NaI. Moreover, PET imaging that can follow the metabolism inside a living organism is not only useful for medical purposes, but it also opens new windows for life science research. A joint project with the pharmaceutical sector is a promising prospect since *in vivo* molecular imaging has become a key technology for drug development, evaluation of drug efficacy, pharmacokinetics and drug delivery systems (19).

In addition, with the on-going severe shortage of nuclear medicine personnel worldwide (20,21), we also aim to be a training center for nuclear medicine technology, especially PET and SPECT/CT, as well as radiopharmacy and cyclotron technology. Since 2018, 31 nuclear medicine professionals from both the public and private sectors of the Philippines, Malaysia and Bangladesh have been trained at and are networked with PCCCMU. The transfer of knowledge and experience, including collaboration with personnel working both in Thailand and aboard, will strengthen best practices and result in high-quality studies.

A list of biomedical applications for radiopharmaceuticals produced at PCCCMU is shown in Table 1.

Production of radionuclides

As an isochronous cyclotron, the HM-20S cyclotron uses a magnetic field to guide negatively charged hydrogen ions in a circular trajectory and radiofrequency fields to accelerate them with a strong focusing effect (26). The protons (H^-) and deuterons (D^-), which can be accelerated to 20 MeV and 10 MeV and which have a beam current of 150 μA and 50 μA, respectively, bombard the target media inside the eight available target ports ($^{18}F^-$, ^{13}N, ^{11}C, ^{15}O, ^{124}I, $^{18}F_2$ and two dummy ports) which are equipped with a helium and water cooling system to produce radionuclides. The four most commonly used radionuclides are fluorine-18, nitrogen-13, carbon-11 and oxygen-15. A summary of the characteristics of radionuclides produced is shown in Table 2.

Production of PET radiopharmaceuticals

After a radionuclide is produced in the cyclotron, it is automatically sent to the adjacent hot laboratory cleanroom and into an automated synthesizer inside a hot cell, a shielded compartment which provides personnel with protection from exposure to high radiation. There are two double hot cells housing F300E no.1 (Fig. 4a), F300E no.2 plus a dispenser with an additional double hot cell for quality control for ^{18}F-FDG production. For ^{18}F-PSMA-1007, ^{18}F-NaF, ^{13}N-ammonia, ^{11}C-methionine, ^{11}C-choline and ^{11}C-acetate, synthesis occurs inside the CFN multipurpose synthesizer-MPS100 housed in one of the 2-unit hot cells (Fig. 4b). The ^{124}I-NaI production is done in the research and development hot cell housing an [^{124}I/^{123}I]-iodine transport unit. Only the ^{15}O-gas and water synthesizer is located in the cyclotron room as it requires no human intervention. All the equipment mentioned is from Sumitomo Heavy Industries. An overview of each radiopharmaceutical's production process is provided below.

^{18}F-FDG production. Fluorine-18 is produced by proton bombardment of O-18 enriched water via the ^{18}O(p,n) ^{18}F nuclear reaction. The fluorine-18 is transported in aqueous solution from the target and extracted by a SepPak Light QMA anion exchange cartridge. Ionic fluoride-18 is transferred into a reactor with an organic solvent for the stereospecific nucleophilic substitution reaction. The final product is passed through purifying cartridges and a sterile filter before dispensing (29).

^{18}F-PSMA-1007 production. The fluoride-18 trapped in the QMA cartridge is eluted by Tetrabutylammonium hydrogen carbonate (TBAHCO$_3$) into the reactor. After removing the solvent, dimethyl sulfoxide solution containing PSMA-1007 precursor is loaded for the fluorination reaction. The solid-phase extraction step is done with both PS-H and C18 cartridges using an ethanol solution (30,31).

Table 1. A list of radiopharmaceuticals produced at PCCCMU and examples of biomedical applications

Radiopharmaceuticals	Examples of biomedical applications
^{18}F-FDG	Glucose metabolism[a]
^{18}F-PSMA-1007	Prostate cancer[b]
^{18}F-NaF	Bone scintigraphy[a]
^{13}N-Ammonia	Myocardial perfusion imaging (MPI)[a]
^{11}C-Methionine	Amino acids metabolism[a]
^{11}C-Choline	Biosynthesis of phospholipid[a]
^{11}C-Acetate	Cell oxidative metabolism, prostate and liver tumors[a]
^{15}O-Water	Myocardial perfusion imaging (MPI)[c]
^{124}I-NaI	Thyroid diagnostics[d]

[a]data from (22), [b]data from (23), [c]data from (24), [d]data from (25)

Table 2. Characteristics of PET radionuclides produced at PCCCMU

Radio-nuclide	Half-life	Mode of decay	Nuclear re-action	Energy for cyclotron production (MeV)	Target media
^{18}F	110 min	β^+(97), EC (3)	$^{18}O(p,n)\ ^{18}F$	3-16[a]	^{18}O-H_2O
^{13}N	9.97 min	β^+ (100)	$^{16}O(p,\alpha)\ ^{13}N$	7-16[a]	H_2O+5mM ethanol
^{11}C	20.4 min	β^+ (100)	$^{14}N(p,\alpha)\ ^{11}C$	3-13[a]	N_2 + 0.5%O_2
^{15}O	122 sec	β^+ (100)	$^{14}N(d,n)\ ^{15}O$	0-8[a]	N_2 + 0.5%O_2
^{124}I	4.18 day	β^+(22), EC (78)	$^{124}Te(p,n)\ ^{124}I$	9-14[b]	$^{124}TeO_2$+ 5%Al_2O_3

[a] data from (27), [b] data from (28), EC; electron capture, β^+; positron emission

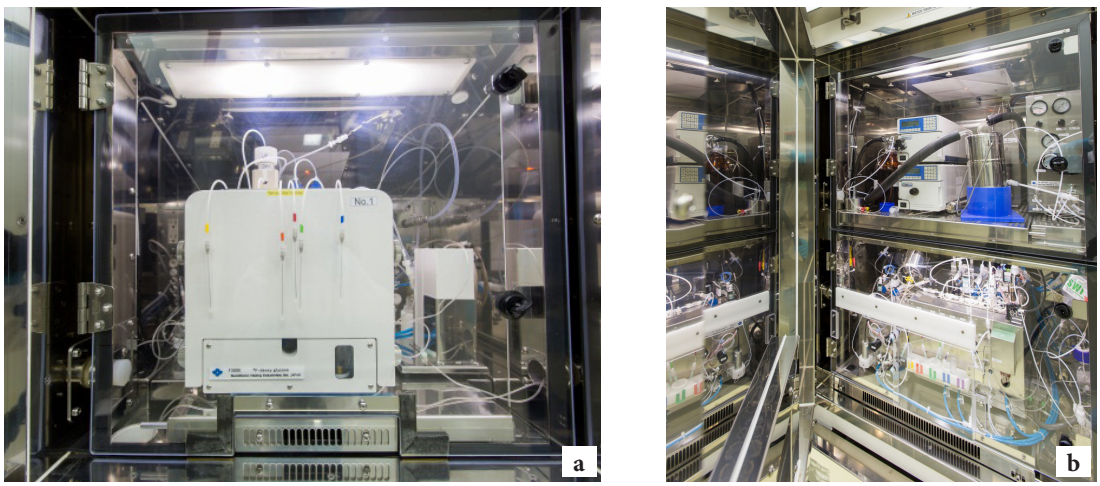

Figure 4. The F300E synthesizer for ^{18}F-FDG production (a): and the CFN multi-purpose synthesizer MPS-100 for production of other radiopharmaceuticals (b); inside the double-type and the unit-type class A hot cells in the ISO14644-1:1999(E) certified radiopharmaceutical cleanroom

^{18}F-NaF production. The fluoride-18 from the cyclotron is trapped in the QMA cartridge. The cartridge is washed with 5 ml of sterile water for injection to remove any residual O-18 enriched water. The fluoride-18 is then eluted with 5 mL of 0.9% sodium chloride and passed through a 0.22 µm sterile filter into a 10 ml sterile vial (32).

^{13}N-ammonia production. Proton bombardment of Type 1 Ultrapure water is used to produce Nitrogen-13. The 5mM ethanol, a scavenger for oxidizing radicals, is mixed into the target to minimize in-target oxidation. After the formulated product is trapped and washed with water in an ion exchange cartridge, a saline solution is applied to recover N-13-ammonia into a product vial (33).

^{11}C-methionine production. Radioactive carbon dioxide (^{11}C-CO_2) is produced via bombardment of natural nitrogen mixed with 0.5% oxygen. The ^{11}C-CO_2 is trapped and transported into the first reactor to produce ^{11}C-methyl iodide gas. After it is passed through a desiccant and an CO_2-adsorbent, the ^{11}C-methyl iodide is reacted with a precursor to produce ^{11}C-methionine in the second reactor. The last steps include evaporation of the organic solvent, neutralization with hydrochloric acid, and formulation with a normal saline solution (34).

^{11}C-choline production. The ^{11}C-CO_2 from the cyclotron is transferred into the reactor with lithium aluminum hydride and hydrolyzed with HI to produce gaseous ^{11}C-methyl iodide which is purified by passing it through a trap packed with Ascarite™ (Merck KGaA, Darmstadt, Germany) and phosphorus pentoxide. The ^{11}C-methyl iodide is passed through dimethylaminoethanol

(DMAE) applied on a cation exchange resin cartridge where the ^{11}C-choline is synthesized by ^{11}C methylation of DMAE. The product is eluted off the ion exchange cartridge with normal saline (35).

^{11}C-acetate production. Radioactive carbon dioxide (^{11}C-CO_2) from the cyclotron is trapped in line using liquid nitrogen. The carboxylation of Grignard reagent (CH_3MgBr) occurs after the release of ^{11}C-CO_2 into the reactor and is followed by hydrolysis and purification steps through cartridges and evaporation before the ^{11}C-acetate is prepared and purified by dissolution in normal saline and sterile filtration (36).

^{15}O-water production. Oxygen-15 is produced by deuteron bombardment of natural nitrogen gas via ^{14}N(d,n)^{15}O reaction. ^{15}O-water is produced by the reduction of ^{15}O-O_2 with H_2 gas (catalyzed by palladium at 150 °C). The ^{15}O-water vapor is then diffused into sterile saline solution before being transported to the injection unit near the PET/CT scanner (37).

^{124}I-NaI production. The manufacture of ^{124}I-NaI solution consists of 3 steps: platinum disk preparation, cyclotron irradiation, and ^{124}I recovery. 200 mg of $^{124}TeO_2$ and 10 mg of Al_2O_3 is mixed and pressed into the center (10 mm diameter) of a platinum disk with hydraulic press machine. The disk is sintered in an electric furnace at 450 °C (10 min), 650 °C (10 min) and 700 °C (5 sec). After irradiation, recovery is done by the dry distillation process where the quartz test tube containing the target disk is heated to 700 °C for 45 minutes to extract ^{124}I from the target material. The ^{124}I is bubbled in a sodium hydroxide solution and collected (38,39).

Quality control

Parenteral drugs like PET radiopharmaceuticals have to conform to quality control acceptance criteria before being used with a patient. For example, in our routine production of ^{18}F-FDG, the quality control tests followed are in accordance with the Japanese pharmacopeia and include the following: physical half-life (105-115 minutes), appearance (clear and colorless), endotoxin (≤ 17.5 EU/mL), sterility (no growth of microorganisms), pH (4.5-8.5), radionuclidic identity (511 keV peak observed), radionuclidic purity (only 511 and 1022 keV peaks observed), radiochemical purity (≥ 95%), ethanol (≤ 2,381 ppm), acetonitrile (≤ 400 ppm), aluminum ion (≤ 10 ppm), Kryptofix® 222 (Merck KGaA, Darmstadt, Germany) (≤ 40 ppm) and sterile filter integrity test (≥ 50 psi). The acceptance criteria are in compliance with both European and United States pharmacopoeias and the materials used are described in the guidelines of the Forum for Nuclear Cooperation in Asia (FNCA) (40) and the Council of Europe (41).

Importantly, due to the short half-life of PET radionuclides, the parenteral administration is done 14 days prior to the completion of the sterility test. Thus, the reliability of the radiopharmaceutical's quality is dependent on a properly validated and documented manufacturing process being strictly performed according to good manufacturing practices (GMP) as specified in the PIC/S Guide to Good Practices for the Preparation of Medicinal Products in Healthcare Establishments (42).

Conclusions

PET/CT is a well-established tool in clinical diagnosis with proven ability to provide images and quantification of selected abnormal biological process for disease management. As progress in nuclear medicine has always been inseparable from the availability and development of new radiopharmaceuticals, the role of PET/CT is expected to continue to expand as the production of new radionuclides becomes more efficient and new areas of radiopharmaceuticals are explored. The successful establishment of PCCCMU is the result of the extraordinary vision of our founders and of Clinical Prof. Niwes Nantachit, M.D., President of Chiang Mai University. After almost a decade of effort, the PCCCMU was successfully established, allowing routine radiopharmaceutical production of ^{18}F-FDG and ^{18}F-PSMA-1007 and the capacity to produce ^{18}F-NaF, ^{13}N-ammonia, ^{11}C-methionine, ^{11}C-choline, ^{11}C-acetate,

^{15}O-water, ^{124}I-NaI among others for research and development. As stated by the IAEA, the center has made international standard nuclear medicine diagnostics available in Northern Thailand and has opened several opportunities for resource-sharing in the region (43). With our facilities and collaboration between hospitals and research consortia, both national and international, we hope to provide outstanding service for patients, to create excellence in research and to be an accomplished training center through the production of radiopharmaceuticals for the fields of oncology, cardiology, neurology, cyclotron technology, radiation safety and more.

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Quality Management in Nuclear Medicine Practices Audited in December 2015 by the IAEA audit team.

The European Association of Nuclear Medicine (EANM) Research Ltd. (EARL) FDG PET/CT accreditation which was granted to a center which fulfilled the requirements indicated in EANM imaging guideline, completed (2015-2019).

Radiation safety certified of compliance by the Office of Atoms for Peace, Thailand, every year from 2013 to the present.

The radiopharmaceutical manufacturing facility consisting of cleanrooms grades A, B, C and D certified compliant with ISO14644-1:1999(E), every year from 2014 to the present.

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การผลิตสารเภสัชรังสีและที่มาของศูนย์เพทซีทีและไซโคลตรอน มหาวิทยาลัยเชียงใหม่

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เพทซีที (positron emission tomography - computed tomography หรือ PET/CT) เป็นเทคโนโลยีการตรวจที่เป็นมาตรฐาน ในการวินิจฉัยโรคมะเร็งชนิดต่าง ๆ โดยการถ่ายภาพการกระจายตัวของสารเภสัชรังสีซึ่งจะแสดงถึงขบวนการทางชีววิทยาต่าง ๆ ในร่างกายมนุษย์ โดยการใช้สารเภสัชรังสีที่ผลิตจากเครื่องไซโคลตรอน แม้ว่าในประเทศไทยจะมีเครื่องไซโคลตรอนที่กรุงเทพมหานครฯตั้งแต่ปี พ.ศ. 2548 แต่ยังไม่มีการใช้อย่างแพร่หลายโดยทั่วไป ศูนย์เพทซีทีและไซโคลตรอน มหาวิทยาลัยเชียงใหม่ เปิดบริการในปี พ.ศ. 2556 เป็นศูนย์ไซโคลตรอนศูนย์แรกในส่วนภูมิภาค ที่มีเครื่องไซโคลตรอนที่มีประสิทธิภาพสูง สามารถผลิตสารเภสัชรังสีชนิดต่าง ๆ สำหรับการตรวจเพทซีที เช่น ฟลูออรีน-18, คาร์บอน-11, ไนโตรเจน-13, ออกซิเจน-15, และ ไอโอดีน-124 ในบทความนี้จะกล่าวถึงที่มาและภาพรวมของขบวนการผลิตสารเภสัชรังสีทั้งหมด ที่ใช้ในทาง การแพทย์และการวิจัย ทั้งในโรคมะเร็ง โรคหัวใจ และโรคทางสมอง **เชียงใหม่เวชสาร 2564;60(1):125-34. doi 10.12982/CMUMEDJ.2021.11**

คำสำคัญ: การผลิตนิวไคลด์กัมมันตรังสีเพื่อการตรวจเพท การผลิตสารเภสัชรังสีเพื่อการตรวจเพท เครื่องไซโคลตรอนในส่วนภูมิภาค