Radiopharmaceuticals for Positron Emission Tomography Imaging of Amyloid: Research and Clinical Applications in Thailand

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ABSTRACT

In the past two decades, the research community has focused on defining reliable molecular biomarkers for the early diagnosis of Alzheimer's disease (AD). Several positron emission tomography (PET) radiopharmaceuticals have been developed and gained regulatory approval for the non-invasive detection of amyloid-β (Aβ) amyloid deposits in the brain. Nowadays, there are several PET imaging radiopharmaceuticals available in Thailand for amyloid imaging including [^{11}C]-labeled Pittsburgh compound B ([^{11}C]PiB), [^{18}F]Florbetapir, and [^{18}F]Florbetaben. This review provides a summary of commonly used amyloid PET radiopharmaceuticals, focusing on the available radiopharmaceuticals in Thailand and the experiences of using amyloid PET radiopharmaceuticals and imaging for clinical and research applications at Siriraj Hospital.

Keywords: Positron emission tomography; radiopharmaceuticals; Alzheimer's disease; amyloid-β; plaque; molecular imaging; dementia; amyloid; brain (Siriraj Med J 2023; 75: 688-698)

INTRODUCTION

Alzheimer's disease (AD) is a significant cause of dementia in persons older than 65 years.[1] Cognitive deficiencies in those with AD manifest as a progressive neurodegenerative disorder that is clinically characterized to lead to loss of memory, cognitive decline[2], difficulty finding the right words or difficulty in interpreting what people say, difficulty performing previously routine tasks, and mood swings.[3] Progressive cognitive decline negatively impacts daily life activities, resulting in the person needing assistance to undertake even simple activities such as shopping or managing finances[4], leading eventually to death, normally about seven to ten years after diagnosis.[5] Therefore, an early and accurate diagnosis is very important in patients with AD.

Approximately 48% of the world's population with dementia lives in Asia and this percentage is evaluated to grow to 59% within 2050.[6] The prevalence of dementia in the elderly in Thailand ranges from 18% to 33%.[7,8] Several biomarker screening tests have been used in clinical studies for the early detection of AD, including apolipoprotein E gene status[9,10], total Tau, phosphorylated Tau levels in cerebrospinal fluid[11], Aβ 1-42, and reduced platelet amyloid precursor protein ratio.[12]

In the past two decades, several PET radiopharmaceuticals have been developed for the non-invasive detection of specific molecular biomarkers involved in the pathophysiology and pathomorphology of AD, such as amyloid- plaques including [^{11}C]-labeled Pittsburgh compound B [^{11}C]PiB, [^{18}F]Flobetapir (Amyvid®, Avid radiopharmaceuticals &

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Eli Lilly and Company), [18F]Florbetaben (Neuraceq®, Bayer Healthcare), [18F]Flutemetamol (Vizamyl®, GE Healthcare), [18F]Flutafuranol (Astra-Zeneca and Navidea) and [18F]FIBT.

To date, [18F]Flobetapir, [18F]Flutemetamol and [18F]Florbetaben have been approved for clinical applications by the Food and Drug Administration (FDA: April 2012) and the European Medicines Agency (EMA: January 2013).

A brief history of radiopharmaceuticals for Aβ imaging

The development of PET radiopharmaceuticals for Aβ imaging started in 1984 with the radiolabeling of derivatives of dyes used for histopathological staining of amyloid plaques and neurofibrillary tangles (NFTs), such as thioflavin-S, thioflavin-T[26], Congo red[27], and chrysamine-G[28] (Fig. 1).

The first Aβ radiopharmaceutical for imaging cerebral Aβ deposits, [18F]FDDNP, was developed in 1999 by Barrio et al.[29] at the University of California Los Angeles. The [18F]FDDNP was able to bind with non-selectively extracellular Aβ plaques and intracellular NFTs.[30]

After the [18F]FDDNP was developed, the [11C]PIB was the first generation of radiopharmaceuticals for selective in vivo imaging of Aβ plaques in AD patients. [11C]PIB has been developed from thioflavin-T[31] which binds with high affinity and selectivity to fibrillar Aβ plaques. Currently, [11C]PIB is a widely used PET radiopharmaceutical and remains the gold standard for imaging Aβ plaques in the brain. Despite this, the short half-life of [11C] nuclide (about 20 mins) limits the centralized commercial production and distribution of [11C]PIB for routine clinical use. These limitations can be overcome by [18F] labeled Aβ radiopharmaceuticals because the half-life of [18F] is 109.77 mins. Furthermore, the longer half-life of radioactive decay [18F] allows a longer time for washout of the non-bound radiopharmaceutical from the brain and lower non-specific brain tissue background activity, and more precise quantitation of cerebral Aβ accumulation sites during the initial phases AD. In general, the [18F] labeled radiopharmaceuticals generate more specific images of the location and magnitude of Aβ plaques and allow for better visual interpretation and quantitative analysis of the results.[32]

The improvement of [18F]-labeled radiopharmaceuticals for PET imaging Aβ plaques in the brain was a notable step. The next generation of radiopharmaceuticals with Aβ-specific binding included [18F]Florbetaben[33], [18F]Flutemetamol[34], and [18F]Florbetapir.[35] Presently, all three radiopharmaceuticals in this generation have been approved for clinical diagnosis by the EMA and the FDA.

The [18F]Florbetapir is a [18F] labeled PET radiopharmaceutical that specifically binds to Aβ peptide in amyloid plaques. The detection of Aβ is one of the diagnostic hallmarks of AD and accumulation of the Aβ in the brain is the most significant factor associated with the development of AD.[13] In clinical applications, it helps to assess the efficacy of disease-modifying therapies and future treatments to slow down the progression of AD if administered during the early stages of the disease. However, the mere presence of amyloid plaques alone does not correlate with the magnitude of neurodegeneration, disease severity, and cognitive decline.[14,15] Moreover, it should be noted that cerebral Aβ deposits could be found in other categories of dementia, including dementia with Lewy bodies, in patients with cerebrovascular disease,

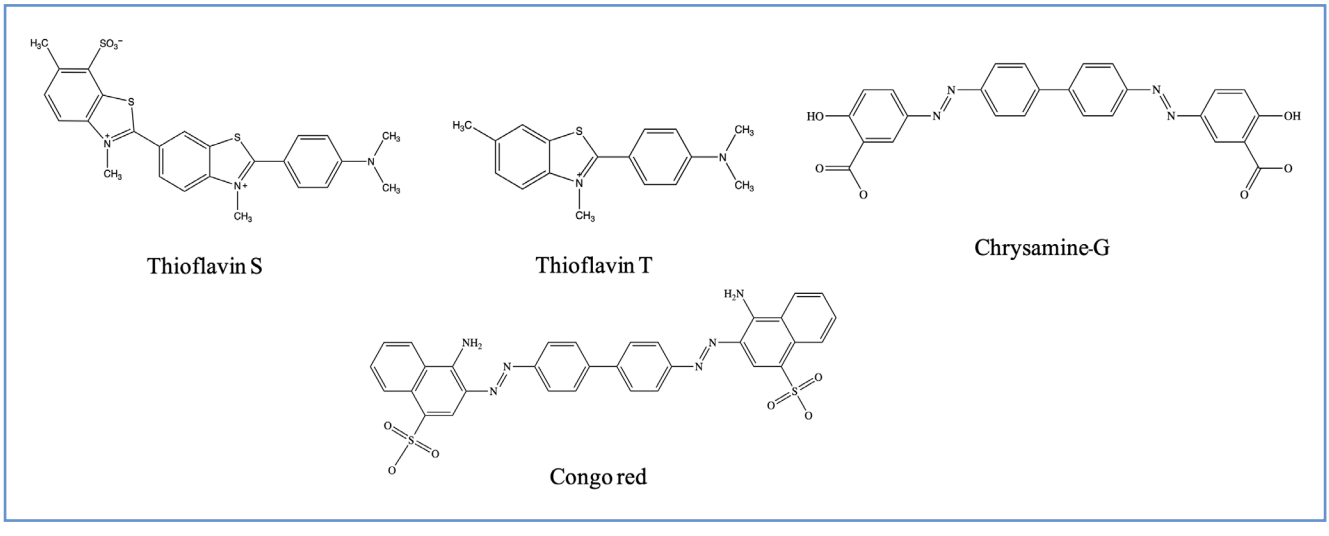


Fig 1. The chemical structure of derivatives of dyes used for histopathological staining of amyloid plaques and NFTs.

corticobasal degeneration, frontotemporal dementia, cortical amyloid angiopathy[16], and Parkinson's disease (PD) with dementia.[17] The absence of Aβ deposits can be anticipated in frontotemporal lobe dementia[18], Creutzfeldt–Jakob disease[19], and cognitively intact PD.[20]

The spatial distribution of accumulation of [^{18}F] Florbetapir is highly correlated with that of the [^{11}C]PiB[21] and is useful for primary and differential diagnosis of AD.[22] A recent Phase III trial has demonstrated that [^{18}F] Florbetapir has 92% sensitivity and 100% specificity for Aβ pathology.[23] Meanwhile, in anpther phase III multicenter trial, [^{18}F]Florbetaben PET detected cortical fibrillar Aβ plaques with 98% sensitivity and 89% specificity as compared to histopathology.[24] Additionally, the retention of [^{18}F]Florbetaben at global and regional levels is highly correlated with the retention of [^{11}C]PiB.[25] The results of the standard centiloid analysis showed a little higher Aβ binding and slightly lower variance than [^{11}C]PIB, significant properties for detecting the early stages of Aβ deposition.[36] However, the second generation of radiopharmaceuticals do not bind well to NFTs, and the true extent of cortical retention of [^{18}F]Florbetapir and [^{18}F]Florbetaben is below [^{11}C]PIB.[25]

For this reason, [^{18}F]NAV4694 (AKA [^{18}F]AZD4694) was recently developed and is now used in phase III clinical trials[37] as [^{18}F]Flutafuranol (Navidea Biopharmaceuticals). [18F]Flutafuranol exhibits rapid pharmacokinetics, strong binding to Aβ plaques, and slightly lower non-specific binding in the cerebral white matter.

Table 1 provides a summary of PET radiopharmaceuticals for imaging Aβ amyloid plaques, including their current chemical abbreviation, chemical structure, trade name, parent molecule, mechanism of binding to amyloid plaque, limitations, and the approval status.

Radiopharmaceuticals employed for imaging Alzheimer's patients in Thailand

At present, three cyclotron centers in Bangkok, Thailand, are producing PET radiopharmaceuticals for the detection of Aβ plaques in the brains of AD patients. The Wattanosoth Hospital in Bangkok was the first center in Thailand to start developing [^{11}C]PIB in November, 2012.[45] The National Cyclotron and PET Centre at the Chulabhorn Hospital, Chulabhorn Royal Academy, Bangkok, started producing [^{11}C]PIB in 2017[46] and [^{18}F] Florbetaben in 2019. The Siriraj Hospital in Bangkok started producing [^{18}F]Florbetapir in 2015.

Clinical and research applications at the Wattanosoth Hospital.

The [^{11}C]PiB at Wattanosoth Hospital was produced by TR-19 PET cyclotron using iPHASE [^{11}C] PRO-2 automated radiosynthesizer module (iPHASE technologies). The [^{11}C]CO_2 was produced via ^{14}N(p,α)^{11}C nuclear reaction. The radiosynthesis of [^{11}C]PiB was started with [^{11}C]CO_2 delivered from the cyclotron to the [^{11}C] PRO-2 automated synthesis module. It was synthesized via the Grignard reaction using 6-OH-BTA-0 precursor (2-(4'-aminophenyl)-6-hydroxybenzothiazole). The specific activity of [^{11}C]PiB was 2.5 Ci/μmol. The radiochemical purity was about 18%-20% (delay corrected) with a total synthesis time of 30 minutes.[45]

The current [^{11}C]PiB production at Wattanosoth Hospital can service 2-3 dementia patients a day requiring amyloid PET scan for an early diagnosis to allow a better chance of benefiting from treatment, participating in clinical drug trials, and allowing more time to plan for the future. Nevertheless, to our knowledge, there has been no available published data on clinical performance of [^{11}C]PiB PET scan.

Clinical and research applications at the National Cyclotron and PET centre.

In 2017, The National Cyclotron and PET Centre at Chulabhorn Hospital developed [^{11}C]PIB and studied the determination of the preliminary optimal cutoff points for SUVRs in amyloid using [^{11}C]PIB. The results showed that the [^{11}C]PIB accumulation pattern in healthy control subjects was used to confirm the early onset AD of a limited or no accumulation in cortical brain regions. This indicates that 10%–30% of normal elderly participants could show significant [^{11}C]PIB retention.[50] [^{11}C]PIB was uptake in the gray matter of neocortical regions, including the frontal lobes, parietal lobes, temporal lobes, and posterior cingulate cortex. The study of clinical performance of [^{11}C]PiB in AD patients and normal controls in the Thai population found significantly higher mean SUVR in AD patients than that of normal controls ($P < 0.05$), with distinctly elevated [^{11}C]PiB deposition in the anterior and posterior cingulate in AD. The proposed [^{11}C]PiB cut-off for regional SUVR was approximately 1.46-1.81 in their study yielded sensitivity ranging from 81.25% to 93.75%, and specificity of 100% (CI 0.82-1.00).[64] Another study on the additional diagnostic value of molecular imaging using [^{11}C]PiB amyloid PET together with [^{18}F] FDG metabolic PET and [^{18}F]THK5351 Tau PET on the diagnosis of dementia subtypes found primary diagnosis change in 60% of patients and the combined PET scan information was able to solve 95.2% pre-PET diagnostic dilemmas.[65] To the best of our knowledge, the clinical performance of [^{18}F]Florbetaben PET scan at The National Cyclotron and PET Centre has not been published yet.

TABLE 1. Examples of commonly used [^{18}F]-labeled radiopharmaceuticals for Aβ imaging.

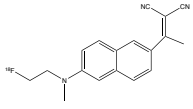
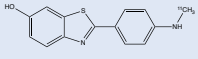
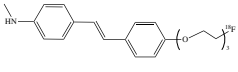
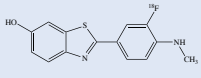
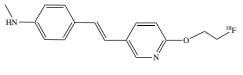
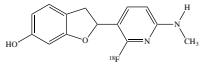
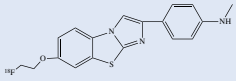
Radiopharmaceuticals	Chemical structure	Trade name / company	Parent molecule	Mechanism of binding to amyloid plaque	Limitation	Approval status and approval organization
[^{18}F]FDDNP[30,38]		-	Amyloid dyes such as thioflavin-S, thioflavin-T, Congo red and	Bind non-selectivity to both of extracellular Aβ plaques and intracellular chrysamine-G	Limited binding to both Aβ plaques and NFTs NFTs	-
[^{11}C]PIB[31,39]		- (Research use)	Benzothiazole	High affinity and selectivity for fibrillar Aβ plaques and in another Aβ containing lesion	Short radioactive half-life	- (Research use)
[^{18}F]Florbetaben [33,40] ([^{18}F]AV-1, [^{18}F]BAY-94-9172)		Neuraceq®/ Piramal Imaging, Berlin, Germany	Stilbene	High level of non-specific white matter retention	May not be useful for correct mapping of Aβ plaque load in low-density regions and in prodromal phases of AD.	The FDA and the EMA in 2014
[^{18}F]Flutemetamol[34] ([^{18}F]GE-067)		Vizamyl®/ GE Healthcare, Milwaukee, Wisconsin, USA	Benzothiazole	High specificity and sensitivity for the in vivo detection of brain Aβ density	-	The FDA in 2013 and the EMA in 2014
[^{18}F]Flobetapir[35] ([^{18}F]AV45)		(Amyvid; Avid Radiopharma-ceuticals, Eli Lilly and Company, USA)	Styrylpyridine	Higher non-specific white matter uptake	-	The FDA in 2012 and the EMA in 2013

TABLE 1. Examples of commonly used [^{18}F]-labeled radiopharmaceuticals for Aβ imaging. (Continue)

Radiopharmaceuticals	Chemical structure	Trade name / company	Parent molecule	Mechanism of binding to amyloid plaque	Limitation	Approval status and approval organization
[^{18}F]Flutafuranol[41-42] ([^{18}F]NAV4694 or ([^{18}F]AZD4694)		- (Phase 3 clinical trial) / AstraZeneca; Cambridge, England)	Benzothiazole	Fast kinetics reaching apparent steady state and very low non-specific white matter binding.	May not be useful for correct mapping of Aβ plaque load in low-density regions and in prodromal phases of AD.	- (Under clinical trials)
[^{18}F]FIBT[43-44]		- (Clinical trial)	Imidazobenzo-thiazole	High contrast Aβ imaging agent, excellent pharmacokinetics and high binding affinity to Aβ fibrils in vitro and in vivo	-	- (Under clinical trial)

Clinical and research applications of brain PET scans using [^{18}F]Florbetapir at the Siriraj Hospital

Since 2015, the research team from the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Siriraj Hospital, started a research project entitled [^{18}F]Florbetapir PET to evaluate brain amyloid deposition in patients with AD, mild cognitive impairment, and regular aging. The project was initially funded by the National Research Council of Thailand via the Health System Research Institute. In 2016, another research project entitled "Evaluation of multimodal imaging in the assessment and diagnosis of early-stage AD with and without comorbidities" was initiated; it was funded by the International Atomic Energy Agency as a part of an international multi-center coordinated research project. These clinical research projects were ethically permitted by the institutional review board and co-funded by the Faculty of Medicine, Siriraj Hospital, Mahidol University in 2018 under the departmental project entitled "Research and technology development of PET scans for the assessment of brain amyloid deposition in patients with Alzheimer's dementia".

The routine production of [^{18}F]Florbetapir has been established at the Siriraj Cyclotron Centre following the Good Manufacturing Practice standards, as described in detail in previous publications[31,48] using the cyclotron model HM20S (Sumitomo Heavy Industries Ltd., Japan) and two CFN-MPS200 automated radiosynthesis modules (Fig 2) (Sumitomo Heavy Industries Ltd., Japan).[47] Briedly, the [^{18}F] radionuclide was produced using ^{18}O(p,n)^{18}F nuclear reaction using [^{18}O]H_2O. Then, [^{18}F-] was combined with the AV-105 precursor via substitution of the tosylate leaving group in the fluorination process. Then, the boxylic protecting group was hydrolytically removed by adding 1M of hydrochloric acid, and neutralized with 1M sodium hydroxide. Purification of [^{18}F]Florbetapir was accomplished using semi-preparative HPLC; the [^{18}F]Florbetapir product was diluted with 20 ml of 0.5% sodium ascorbate/ultra-pure water and purified with a tC18 cartridge. The purified [^{18}F] Florbetapir was transferred

into the reactor vial, then dried up to remove the residual solvent, diluted with normal saline, and then the final product was sterilized by passing through the 0.22 µm GV filter (Merck Millex™). [^{18}F]Florbetapir quality control was in accordance with US Pharmacopeia Standards Chapter 823. The total synthesis time was about 60 minutes; the radiochemical yield was about 14% and the radiochemical purity was more than 98%. The quality control results of the produced [^{18}F]Florbetapir were similar to those reported previously.[33,49] The amount of produced [^{18}F]Florbetapir radioactivity could support PET imaging of about 5 patients per production run.

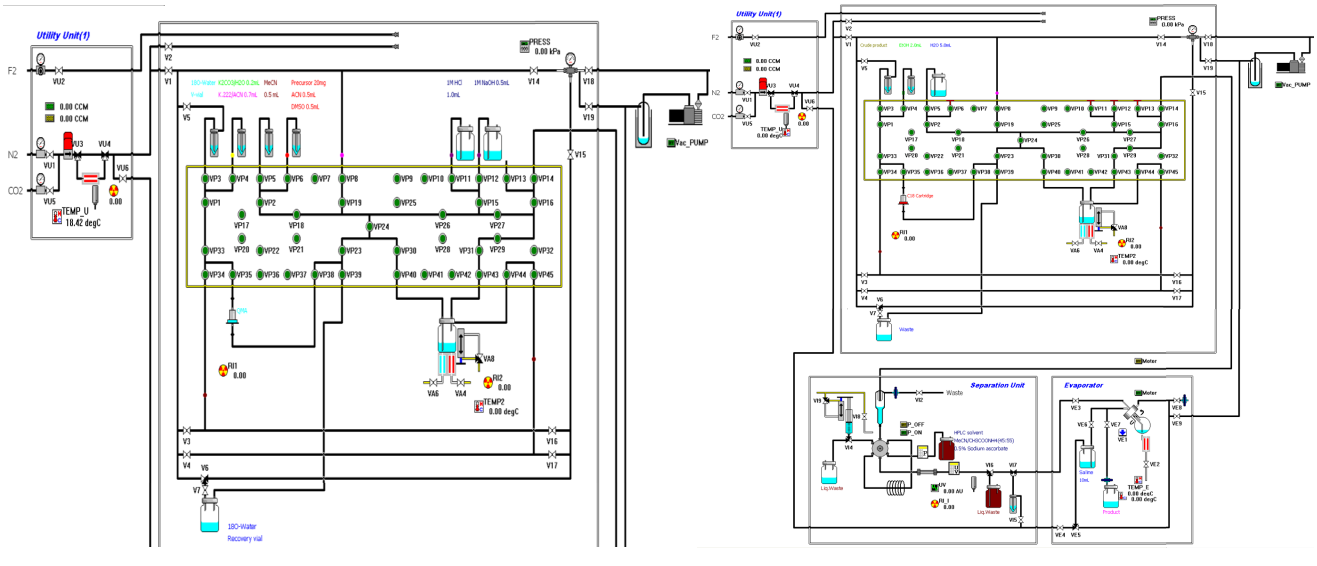
After gaining experience from these research projects, PET imaging with [^{18}F]Florbetapir has been utilized to support the clinical management of patients with neurocognitive impairment and suspected AD. The current clinical applications are following the appropriate use criteria which were recommended in previous publications.[62,63] The application of amyloid PET scans is considered most likely helpful for improving diagnostic certainty or for adjusting the clinical management plan of patients with confirmed cognitive impairment of an uncertain cause after a comprehensive evaluation by a dementia expert, where AD is considered in the differential diagnosis. In order to conduct an amyloid PET scan, the following acceptance criteria are used: 1) patients who have persistent or progressive unexplained MCI; 2) the core clinical criteria for possible AD are complacent but there is an ambiguous clinical presentation (atypical clinical course or mixed presentation); 3) patients who have progressive dementia with an unusually early onset age (< 65 years). The update of the appropriate use criteria to include the potential role of amyloid PET, for example, in selecting candidates for amyloid-targeting therapy, is still ongoing.

[^{18}F]Florbetapir PET imaging protocols

The quality of images obtained with PET/CT scanners (Discovery STE and Discovery MI; GE Healthcare) were qualified using a Hoffman brain phantom. All research volunteers underwent PET/CT imaging 50-70 min after IV injection of 10 mCi (370 MBq) of [^{18}F] Florbetapir using a 20 min acquisition (acquired in 4 x 5 min-frames), following the protocols in ADNIGO[51] and ADNI2.[52] The full description of amyloid PET image acquisition and reconstruction protocols and the image quality obtained from the Hoffman brain phantom were described in our previous publications.[47,53-55] In some clinical cases when patients had significantly poor cooperation, we reduced the acquisition time to the standard 10 minutes acquisition (acquired in 2 x 5 min-frames), in line with the manufacturer's recommendations.[53]

PET image analysis and interpretation

All PET images underwent quality control before further visual interpretation and analysis. The visual interpretation was carried out by nuclear medicine specialists and was categorized as either 'positive' or 'negative' following the standard guidelines.[56] The semi-quantitative analysis to determine the localization and dimensions of Aβ depositions in the brain was also



Schematic diagram of [^{18}F]Florbetapir synthesis

Schematic diagram of [^{18}F]Florbetapir purification

Fig 2. Schematic diagram of the [^{18}F]Florbetapir synthesis and purification process

accomplished using software packages. The DICOM image files of each PET scan were further processed using specialized software packages: either the Neurological Statistical Image Analysis Program (NEUROSTAT / 3D-SSP software, University of Utah, SLC, USA), Pneuro PMOD image analysis software (PMOD Technologies; Zurich, Switzerland)[57], FreeSurfer[58], or Statistical Parametric Mapping (SPM) version 12 (The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK).[57] The results from our research using these software packages have been reported in previous publications.[47,53,54,59] The NEUROSTAT software was used to spatially normalize the amyloid PET scans obtained in cognitively-normal volunteers (age 60-82 years), whose original scans were interpreted as negative for both glucose hypometabolism and Aβ deposition, and who provided a normal database for the calculation of z-scores and generation of images of z-score maps. The Pneuro, FreeSurfer, and SPM software packages were used to analyze the T1-weighted MRI images from individual patients for segmentation and volumetric analyses of brain structures, co-registration with corresponding PET images, and measurements of the regional brain uptake values [standardized uptake value (SUVs)] and standardized SUV ratios, as well as the volume of the corresponding brain regions. Figs 3 & 4 provide examples of [^{18}F]Florbetapir brain PET images in the evaluated patients for both visual and quantitative analyses.

Clinical studies conducted at the Siriraj Hospital using [^{18}F]florbetapir PET and visual assessment of images demonstrated a sensitivity of 86.7% and specificity of 95.0% for differentiating patients with AD from normal control subjects. When using the global SUVR cut-off of 1.15 obtained from 3D-SSP NEUROSTAT Software, we found a sensitivity of 83.3% and a specificity of 90%.[54] Moreover, we found that high amyloid uptake in occipital region is associated with clinically advanced AD and may be useful for evaluating AD severity.[53] Therefore, [^{18}F] Florbetapir amyloid PET scan may be feasible for both diagnostic and prognostic applications. Furthermore, our results from combining imaging information from amyloid PET, FDG PET, and MRI volumetry to create the specific AV45/FDG/NVol index found significant correlation with clinical neurocognitive status and higher than using amyloid PET, FDG PET, or MRI alone. We expected this combined molecular imaging index may facilitate more accurate diagnosis, staging, and prognosis of AD.[47]

Future directions of brain PET radiopharmaceuticals and imaging development in Siriraj Hospital

The cyclotron-radiochemistry core facility team at Siriraj Hospital is currently working on setting up the production of the latest generation of radiopharmaceuticals for PET imaging of amyloid beta deposits in the brain, such as [^{18}F]Flutafuranol. Another radiopharmaceutical in development is [^{18}F]MK-6240, which binds to tau protein fibrils and provides an advantage in terms of detecting early tau pathologies. The evaluation of amyloid beta and tau proteinopathies, along with A-T-(N) criteria[60,61], and the potential roles of PET imaging biomarkers in selecting suitable candidates for clinical

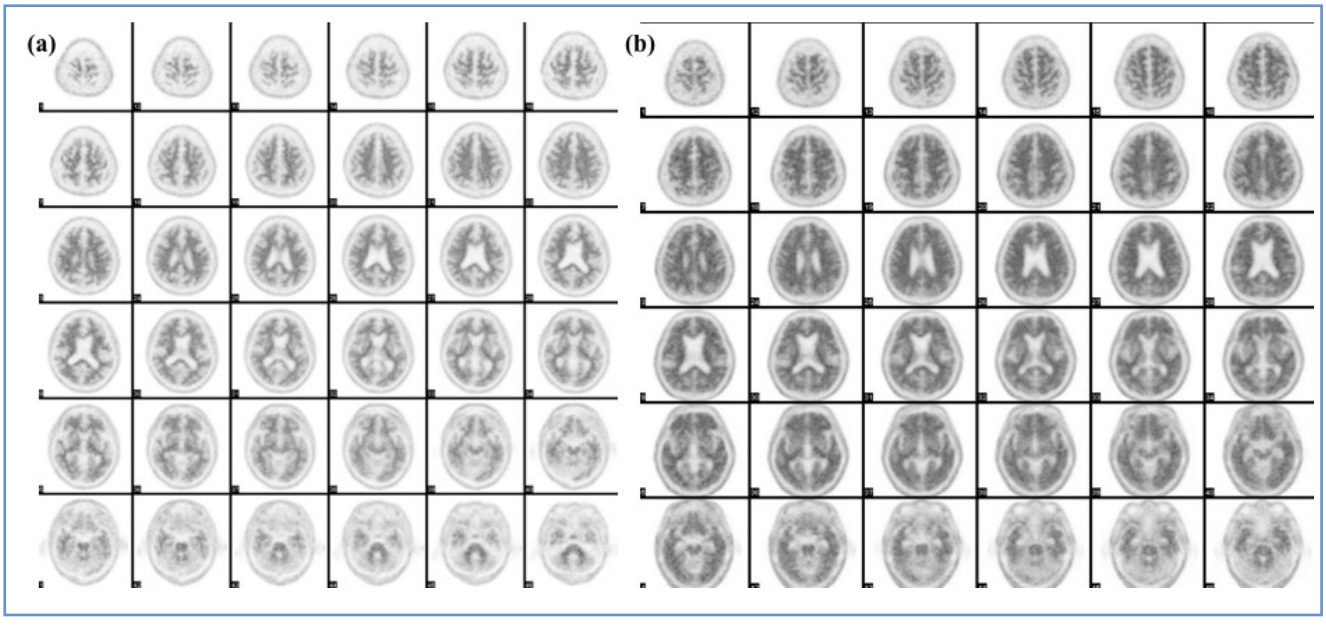


Fig 3. Examples of [^{18}F]Florbetapir brain PET images: (a) amyloid-negative in an elderly individual with normal cognition, and (b) amyloid-positive in a patient with AD.

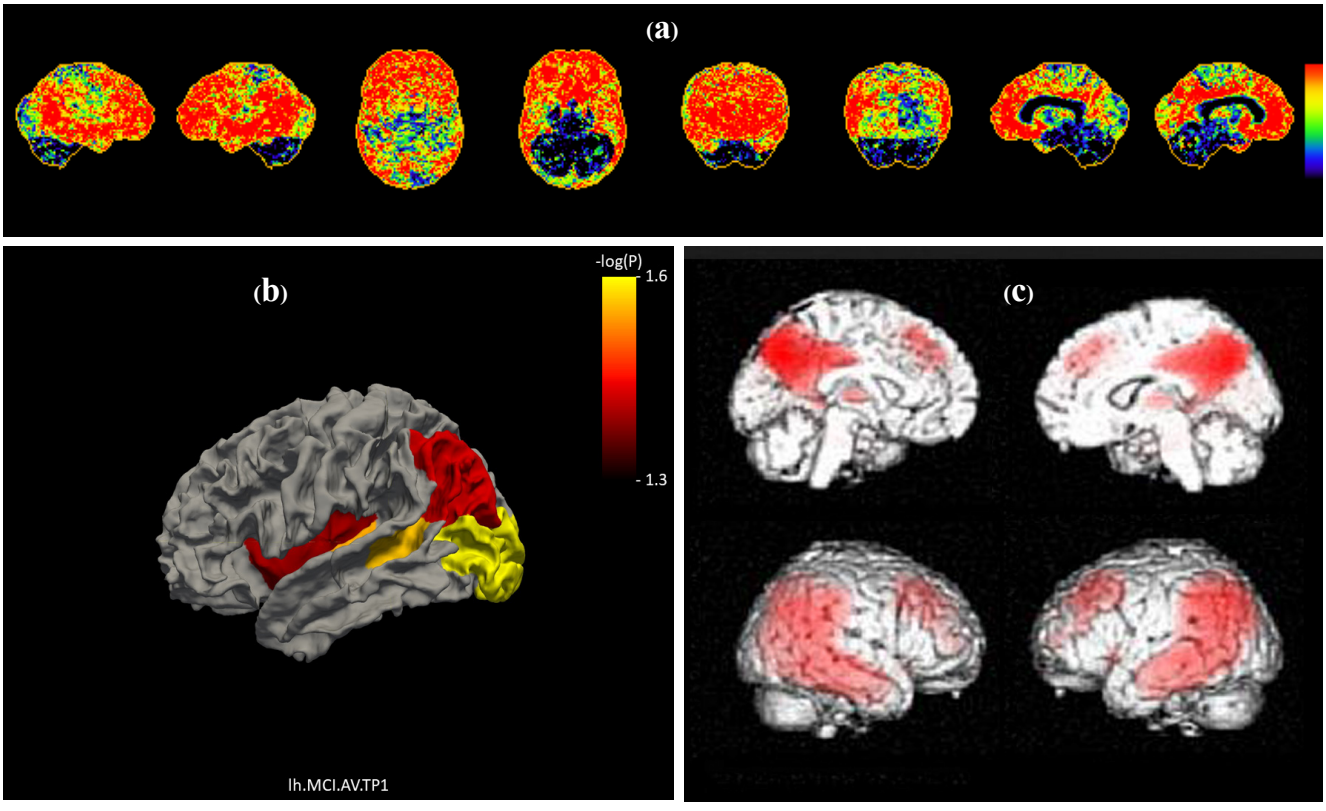


Fig 4. Examples of quantitative and semi-quantitative analyses using software packages with NEUROSTAT (a), FreeSurfer (b), and SPM (c).

trials or monoclonal antibody therapy have been recently discussed. Moreover, the ongoing longitudinal clinical studies are aimed to elucidate the dynamic changes in brain amyloid deposition, glucose metabolism, and morphological changes (neurodegeneration) in relation with neurocognitive performance tests and other biomarkers of AD. The focus of these ongoing studies is to develop and translate these PET imaging biomarkers into routine clinical practice.

CONCLUSION

In Thailand, amyloid PET neuroimaging has been confirmed as a helpful technique for the detection of the Aβ plaques in the primary and differential diagnosis of AD and possibly for the evaluation disease progression. So far, the use of amyloid PET radiopharmaceuticals in Thailand including at Siriraj Hospital has been successfully implemented without any complications or side effects. The available reported clinical performance and impact of amyloid PET in Thailand are similar to those reported from other countries. Larger scale clinical research involving patients with different types of dementia-associated neurodegenerative diseases should be conducted to provide more information on the diagnostic, prognostic, and therapeutic values of PET imaging of amyloid in the brain.

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Conflict of interest

All authors declare there is no competing interest.

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