Review Article

Appropriate Use of F18-FDG PET/CT in Oncology, Cardiology, and Neurology in Thailand: Report and Recommendations from the Health Intervention and Technology Assessment Program

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Objective: Positron emission tomography/computed tomography (PET/CT) is currently one of the most important emerging imaging modalities. Due to its high cost, appropriate guidance for use of the modality should be tailored to the context of each country. The present review aimed to provide guidance for appropriate use of PET/CT in Thailand.

Materials and Methods: Studies of PET/CT use in the top ten most prevalent cancers in Thailand and in Cardiology and Neurology between January 1, 2005 and March 31, 2015 were searched. Four nuclear medicine physicians summarized and synthesized the evidence regarding use of PET/CT in target conditions. Summarized evidence was presented to a multidisciplinary panel of experts, and recommendations for PET/CT use were made.

Results: Recommendations regarding F18-FDG PET/CT use are presented in the present review. This information should help policy makers in deciding the indications that F18-FDG PET/CT should made reimbursable in the key health insurance schemes.

Conclusion: The present study is the first published recommendation, from reviewed of the literatures, on the appropriate use of PET/CT in Thailand. This should help clinicians and healthcare policy makers in their decision regarding the use and benefit of PET/CT.

Keywords: Positron emission tomography, PET/CT, Appropriate use, Cancer, Diagnostic imaging

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During the past few decades, positron emission tomography/computed tomography (PET/CT) particularly with the radiopharmaceutical 2-deoxy-2-(18F)fluoro-D-glucose (F18-FDG) has played a crucial role in the management of cancer patients. Applications in cardiology and neurology of F18-FDG PET/CT are also steadily increasing. Newer non-fluorine-based radiopharmaceuticals using radioisotopes such as carbon-11 (C11) and gallium-68 (Ga68) have also been gaining momentum and interest. Imaging with PET/CT and other functional nuclear medicine imaging techniques offer the advantage of providing insights into tumor and organ biology that conventional anatomical imaging modalities cannot provide. Thus, PET/CT has been used as an adjunct, and in some cases, a replacement for conventional imaging for various applications in Oncology, Cardiology, and Neurology. Despite the many advantages of PET/CT, the main caveat of this imaging modality lies within its high cost, which is mainly due to the price of the PET/CT scanner and that most PET radiopharmaceuticals require a cyclotron for production. In Thailand, there are currently six centers that provide PET/CT service. The cost of PET/CT in Thailand ranges from 40,000 to 45,000 Baht (1,140 to 1,285 USD) for government hospitals and 60,000

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to 80,000 Baht (1,715 to 2,285 USD) for private hospitals. This price can be prohibitively expensive in relation to the average income of the Thai population. To further impede patient access to PET/CT services, the only indications that are reimbursable under the Social Security Scheme (Social Security Office), Universal Coverage Scheme (National Health Security Office), and Civil Servant Medical Benefit Scheme (Comptroller General's Department) are staging of potentially resectable non-small cell lung cancer (NSCLC), and diagnosis of recurrent colorectal cancer in patients with rising carcinoembryonic antigen (CEA) level. Despite these limitations, use of PET/CT should be made more accessible to maximize patient benefit while maintaining cost-effectiveness. The aim of the present study was to provide, through review of clinical evidence, guidance of the appropriate use criteria for PET/CT in Thailand. This could help guide policy makers to determine the indications that PET/CT should be reimbursable.

Materials and Methods

Target conditions

This literature review focused on summarizing the available evidence for the use of PET/CT in oncological, cardiological, and neurological diseases. The target diseases for oncological conditions for evaluation of the utility of PET/CT included the ten most prevalent cancers in Thailand, which are breast cancer, colorectal cancer, lung cancer, uterine cervical cancer, primary liver and bile duct cancer, oral cancer, lymphoma, esophageal cancer, nasopharyngeal carcinoma, and ovarian cancer[1] in terms of diagnosis, staging, evaluation of therapeutic response, detection of recurrence, and disease prognosis. Diagnosis of Alzheimer disease and other dementias were the target of review of the utility of PET/CT in Neurology, while diagnosis of coronary artery disease was the target of the utility of PET/CT in Cardiology. Only clinical studies and economic evaluation studies were evaluated.

Literature search and selection

A systematic electronic search restricted to studies in humans published in English language between January 1, 2005 and March 31, 2015 was performed to identify potentially relevant studies. For clinical studies, two indexing databases were searched including PubMed/PubMed Central/Medline, and Scopus. Types of studies included were 1) studies that examine the diagnostic accuracy of PET/CT compared with a reference standard, with or without comparison with a comparator test e.g., computed tomography (CT), or magnetic resonance imaging (MRI) where the study reported diagnostic statistics including sensitivity and specificity or presents adequate details to permit derivation of true positive, true negative, false positive, and false negative results for construction of a 2×2 table, and 2) comparative clinical studies that examine effect of PET/CT use in patient outcome and impact on clinical decision making. For economic evaluation studies, the EBSCOhost database was searched. Inclusion criteria included studies involving cost-minimization analysis, cost-effectiveness analysis, cost-benefit analysis, and cost-utility analysis of PET/CT of the target diseases. Studies where full-text articles could not be found were excluded.

Literature review

For diagnostic studies, data extraction from each included study were 1) first author, 2) journal and year of publication, 3) location of study, 4) number of patients, 5) allocation of patients, 6) indication for performing PET/CT, 7) reference standard used, 8) comparator test(s) if any, and 9) duration of study. For economic evaluation studies, data extraction from each included study were 1) type of economic evaluation, 2) target population characteristics, 3) setting and location, 4) comparators, 5) health outcome evaluated, 6) currency and conversion rate, and 7) analytical methods used. Data extraction was performed by the four authors who are experienced Nuclear medicine physicians.

Expert panel consensus

After literature review for each clinical indication was completed, results were presented to a panel of experts that consisted of medical oncologists, radiation oncologists, gynecological oncologists, cardiologists, neurologists, surgeons, and health economic specialists for consensus on whether or not a particular indication for PET/CT was appropriate when taking into account diagnostic accuracy, local disease variation, and economic burden. The final recommendation was then concluded for each clinical indication.

Report of findings

Recommendations for the use of PET/CT for each clinical indication of each target disease were reported. Recommendations were categorized as 'beneficial' i.e., when there was strong evidence of PET/CT benefit in terms of survival or guiding

therapeutic decision from randomized controlled trials or multiple high quality comparative studies; 'possibly beneficial' i.e., PET/CT benefits shown in some studies, but overall weaker strength of evidence due to a small number of studies or studies with lower methodological quality; or 'no proven benefit' when there is a paucity of primary studies that evaluate the usefulness of PET/CT for a particular indication or when there is evidence that PET/CT is not beneficial for that particular indication.

Results

Review of literature was done and data regarding diagnostic accuracy of F18-FDG PET/CT was extracted and summarized and compared with conventional imaging, if applicable. Results of the review were presented to the expert panel and recommendations were made. A summary of recommendations for each cancer are listed in Table 1, Table 2, and Table 3.

Breast cancer

Review of evidence: Various aspects of F18-FDG PET/CT in the management of breast cancer have been studied. For preoperative lymph node staging, F18-FDG PET/CT had overall sensitivity and specificity of 56% and 97%, on a lesion-based analysis while patient-based analysis yielded values of 58% and 98%, respectively[2-15]. For detection of bone metastasis F18-FDG PET/CT had sensitivity, and specificity of 100% and 95%, respectively[6,16-21], but compared with bone scintigraphy, which had corresponding values of 81% and 96%, respectively[22], the added cost and radiation dose of F18-FDG PET/CT outweighed the small incremental increase of sensitivity. Studies regarding diagnostic accuracy of detection distant metastasis found that F18-FDG PET/CT had overall sensitivities and specificities of 98% and 96%, respectively[6,16,17,19,20,23,24], which indicates superior accuracy compared with conventional imaging work-up including chest radiograph, CT, and liver ultrasonography, which had sensitivity of 56% and 91%[25], respectively. F18-FDG PET/CT had sensitivity and specificity of 89% and 74% for prediction of response to preoperative neoadjuvant chemotherapy[26-34]. For detection of disease recurrence, F18-FDG PET/CT had sensitivity and specificity of 90% and 89%, respectively[35-40].

Expert consensus: For preoperative staging, F18-FDG PET/CT as well as ultrasound and sentinel lymph node biopsy are not routinely recommended. Regarding screening for bone metastasis, bone scintigraphy is likely more cost effective than F18-FDG PET/CT. F18-FDG PET/CT may be of use when occult distant metastasis is suspected, which may escape detection by other conventional imaging modalities.

Colorectal cancer

Review of evidence: Review of evidence found that for initial staging, F18-FDG PET/CT had sensitivity and specificity of 54% and 80% for lymph node staging, with slightly increased sensitivity for detection of lymph node metastasis in anal cancer where F18-FDG PET/CT had sensitivity and specificity of 79% and 76%, respectively[41-49]. For diagnosis of liver metastasis, F18-FDG PET/CT had sensitivity and specificity of 77% and 98%, respectively, and changed clinical management in 10% to 30% of cases[50-53]. F18-FDG PET/CT was found to have clear benefit in detection of disease recurrence since it has superior accuracy compared with CT. F18-FDG PET/CT had sensitivities and specificities of 95% and 91% for detection of overall recurrence; 98% and 95% for detection of local recurrence; 86% and 99% for detection of hepatic recurrence; 85% and 95% for detection of extrahepatic recurrence; and 94% and 77% for detection of recurrence when CEA is elevated[54-70]. Regarding evaluation of response to chemotherapy or radiation therapy, both F18-FDG PET/CT and MRI had suboptimal sensitivity of approximately 60% to 64% for this indication and patients still need radical surgery even with negative imaging[71-79].

Expert consensus: F18-FDG PET/CT cannot replace CT or MRI for initial staging but would be useful when CT or MRI yields equivocal findings that could potentially impact clinical decision making. F18-FDG PET/CT is useful for preoperative evaluation when distant metastasis has been found by other imaging modalities but is potentially resectable with curative aim. F18-FDG PET/CT is useful for detection of disease recurrence when there is elevated CEA level and CT, or MRI is negative or equivocal.

Lung cancer

Review of evidence: From the literature review, the sensitivity and specificity of F18-FDG PET/CT for diagnosis of solitary pulmonary nodules is 96% to 97% and 78% to 86%, respectively. This indicates superiority to CT imaging, which has reported sensitivity of 93% and specificity of 76%[80-85]. For initial disease staging, F18-FDG PET/CT has been found to detect unexpected distant metastasis in

Table 1. Summary of recommendations from review of evidence and expert consensus for the use of F18-FDG PET/CT in the ten most prevalent cancers in Thailand

Clinical indication	Review of evidence	Expert consensus
Breast cancer		
Preoperative lymph node staging	No proven benefit	Not routinely recommended
Detection of lymph node metastasis	Possibly beneficial	Not routinely recommended
Evaluation of response to preoperative neoadjuvant chemotherapy	Possibly beneficial	Not routinely recommended
Detection of recurrence	Possibly beneficial	Not routinely recommended
Colorectal cancer		
Disease staging	Possibly beneficial	Recommended only in cases with equivocal findings on conventional imaging
Detection of recurrence	Beneficial	Recommended
Preoperative evaluation of recurrent disease	Beneficial	Recommended
Evaluation of response to preoperative neoadjuvant chemotherapy or chemoradiation	No proven benefit	Not routinely recommended
Lung cancer		
Diagnosis of solitary pulmonary nodule	Beneficial	Recommended only in cases with equivocal findings on conventional imaging
Initial staging	Beneficial	Recommended in NSCLC patients planned for curative treatment
Diagnosis of recurrence	Possibly beneficial	Recommended only in cases with equivocal findings on conventional imaging
Radiation therapy planning	Beneficial	Recommended when FDG PET/CT findings may change of treatment volume
Uterine cervical cancer		
Initial staging	Possibly beneficial	Recommended for locally advanced stage IB uterine cervical cancer
Diagnosis of recurrence	Possibly beneficial	Recommended only in cases with equivocal findings on conventional imaging
Evaluation of response to chemotherapy or chemoradiation	No proven benefit	Selective use for restaging of disease before proceeding to pelvic exenteration.
Hepatobiliary cancers		
Initial extrahepatic staging of HCC	Possibly beneficial	Not routinely recommended
Diagnosis of recurrence of HCC	Possibly beneficial	Not routinely recommended
Initial staging of gall bladder and bile duct cancers	No proven benefit	Not routinely recommended
Oral cavity cancer		
Initial staging	Possibly beneficial	Recommended in stage III and IV disease
Evaluation of response to therapy and detection of recurrence	Possibly beneficial	Recommended for evaluation of suspected recurrence
Radiation therapy planning	Possibly beneficial	Recommended in locally advanced disease or when CT cannot provide accurate delineation of tumor volume, and when reirradiation of residual tumor is considered
Lymphoma		
Initial staging of Hodgkin lymphoma	Beneficial	Recommended
Interim evaluation of response to chemotherapy in Hodgkin lymphoma	Beneficial	Recommended

NSCLC=non-small cell lung cancer; FDG=fluoro-D-glucose; PET=positron emission tomography; CT=computed tomography; DLBCL=diffuse large B-cell lymphoma; HCC=hepatocellular carcinoma

Table 1. (continued)

Clinical indication	Review of evidence	Expert consensus
Evaluation of response after completion of chemotherapy or radiation therapy in Hodgkin lymphoma and DLBCL	Beneficial	Recommended
Esophageal cancer		
Preoperative staging	No proven benefit	Not routinely recommended
Evaluation of response to preoperative chemotherapy or chemoradiation	Possibly beneficial	Not routinely recommended
Radiation therapy planning	Beneficial	Recommended
Evaluation of response to definitive radiation therapy or chemoradiation	Possibly beneficial	Recommended, especially when residual disease which may need salvage surgery is suspected
Diagnosis of recurrence	Possibly beneficial	Not routinely recommended
Initial staging	Possibly beneficial	Recommended in advanced stage disease and poorly differentiated tumors
Evaluation of response to therapy and detection of residual disease	Possibly beneficial	Recommended, especially when residual disease which may need salvage surgery is suspected
Radiation therapy planning	Possibly beneficial	Recommended when FDG PET/CT findings may change of treatment volume
Ovarian cancer		
Diagnosis of pelvic masses	Possibly beneficial	Not routinely recommended
Intraabdominal staging	No proven benefit	Not routinely recommended
Diagnosis of recurrence	Possibly beneficial	Recommended only in cases with equivocal findings on conventional imaging

NSCLC=non-small cell lung cancer; FDG=fluoro-D-glucose; PET=positron emission tomography; CT=computed tomography; DLBCL=diffuse large B-cell lymphoma; HCC=hepatocellular carcinoma

Table 2. Summary of recommendations for the use of F18-FDG PET/CT in neurological disease from review of evidence and expert consensus

Clinical indication	Review of evidence	Expert consensus
Diagnostic evaluation of atypical Alzheimer disease	Beneficial	Recommended especially when the differential diagnoses are between Alzheimer disease and frontotemporal dementia
Diagnostic evaluation of idiopathic Parkinson disease	Possibly beneficial	Recommended for differentiating between idiopathic Parkinson disease and drug-induced parkinsonism
Differentiating between idiopathic Parkinson disease and atypical parkinsonism	Possibly beneficial	Not routinely recommended
Preoperative localization of epileptogenic zone	Beneficial	Recommended in patients with intractable epilepsy with negative intracranial EEG and undermined epileptogenic zone

EEG=electroencephalogram

Table 3. Summary of recommendations for the use of F18-FDG PET/CT in cardiology from review of evidence and expert consensus.

Clinical indication	Review of evidence	Expert consensus
Diagnosis of coronary artery disease	Beneficial	Not routinely recommended
Determination of myocardial viability	Beneficial	Recommended only in cases with equivocal cardiac MRI findings

24% of cases and changing management in 20% of cases[86-92]. For T-staging, traditional F18-FDG PET/CT using non-contrast CT is inferior to conventional CT or MRI, but this limitation can be overcomed by using contrast in the CT portion of the study. For detection of lymph node metastasis, F18-FDG PET/CT has been found to have overall sensitivity of 67% to 90% and specificity of 83% to 95%, which is greater than conventional CT, which was found to have sensitivity of 55% and specificity of 81%[93-105]. F18-FDG PET/CT is particularly useful in excluding lymph node metastasis. In patients with NSCLC of less than 3 cm in diameter, located at the peripheral third of the lung, and no enlarged lymph node on the CT image, a negative F18-FDG PET/CT has a negative predictive value of 94%. No further mediastinal staging is recommended for these patients[106]. F18-FDG PET/CT is particularly useful in detection of distant metastasis with sensitivity and specificity of 91% to 93% and 95% to 98%, respectively. Corresponding values for bone scintigraphy for diagnosis of bone metastasis are 87% and 82%, respectively[107-109]. Studies comparing F18-FDG PET/CT with conventional CT also found that F18-FDG PET/CT was more sensitive and specific for diagnosis of distant metastasis[86,110,111]. For detection of distant metastasis to specific sites, F18-FDG PET/CT had poor sensitivity of 24% to 27% for detection of brain metastasis but 97% sensitive for detection of adrenal gland metastasis, with an overall specificity of 91%[112-114]. For detection of pleural metastasis F18-FDG PET/CT was 86% sensitive and 80% specific[115]. Studies regarding the application of F18-FDG PET/CT in small cell lung cancer (SCLC) are not as abundant compared with NSCLC. Some studies have found that F18-FDG PET/CT changed disease staging from limited disease to extensive disease in about 6% to 33% of cases and down-staged disease in 3% to 14%. Overall, F18-FDG PET/CT changes management in 16% to 38% of SCLC cases[116,117]. For diagnosis and localization of disease recurrence in lung cancer, F18-FDG PET/CT had sensitivity and specificity of approximately 90%, while conventional CT has been found to have corresponding values of 78% and 80%, respectively[118,119]. F18-FDG PET/CT has been proposed to be beneficial in radiation therapy planning. Results from well-designed randomized controlled trials are needed, but results from preliminary reports have suggested that F18-FDG PET/CT provides a more accurate target than CT since F18-FDG PET/CT can differentiate between the primary tumor and adjacent atelectasis. Planning with F18-FDG PET/CT has also been suggested to reduce recurrence and prolong survival.

Expert consensus: F18-FDG PET/CT should be used for initial staging of patients with NSCLC, especially those who are candidates for curative treatment. Current reimbursement criteria should be amended in that bone scintigraphy and conventional CT should not be prerequisites before performing F18-FDG PET/CT, since F18-FDG PET/CT is superior to both of these conventional imaging modalities. Therefore, mandating that patients need to undergo CT and bone scintigraphy before proceeding to F18-FDG PET/CT would only increase cost. The panel also recommends removing the criterion that only patients with Karnofsky performance score (KPS) of more than 70 are eligible for F18-FDG PET/CT, since patients with KPS of less than 70 may also be fit enough for curative surgical treatment. For patients with T1 disease detected by conventional imaging, obtaining tissue diagnosis before performing F18-FDG PET/CT may be difficult and not practical, therefore, removal of this criterion for reimbursement should be considered. F18-FDG PET/CT is useful in radiation therapy planning, especially in patients with CT findings that cannot differentiate between atelectasis and the primary tumor. F18-FDG PET/CT may be useful and should be considered in patients with suspected disease recurrence and non-diagnostic CT findings. F18-FDG PET/CT is not useful and should not be done in patients with advances stage disease with distant metastasis readily found on conventional imaging, those with bulky disease, extensive lymph node metastasis i.e., conditions that clearly preclude curative surgical resection.

Uterine cervical cancer

Review of evidence: From review of literature, the overall sensitivity and specificity of F18-FDG PET/CT for staging of uterine cervical cancer is 75% and 96%, respectively. For N-staging, F18-FDG PET/CT has been found to have sensitivity and specificity of 82% and 95%, respectively, which is superior to CT and MRI, which have corresponding values of 50% to 56% and 91% to 92%, respectively[120-127]. For diagnosis of disease recurrence, F18-FDG PET/CT has overall sensitivity of 94% and specificity of 84%, while CT and MRI have corresponding values of 89% and 87%, and 82% and 78%, respectively[128-136]. A negative F18-FDG PET/CT at the end of treatment was also found to be predictive of lower rates of recurrence[137].

However, economic studies by Meads et al[138] and

Auguste et al[139] suggested that F18-FDG PET/CT was not cost-effective when compared with CT and MRI, since F18-FDG PET/CT had an incremental cost-effectiveness ratio (ICER) of more than £1 million per quality-adjusted life-year (QALY), compared with the incremental cost increase of £600,000 for each recurrence. For evaluation of response to either chemotherapy and radiation therapy, both F18-FDG PET/CT and MRI did not have sufficient sensitivity for exclusion of residual disease after completion of treatment[140,141].

Expert consensus: F18-FDG PET/CT is likely beneficial for staging of locally advanced stage IB uterine cervical cancer, especially for detection of regional lymph node and extrapelvic metastasis that would impact therapeutic decisions. F18-FDG PET/CT is also likely beneficial for restaging of disease before proceeding to pelvic exenteration.

Hepatobiliary cancers

Review of evidence: There are no clear guidelines for use of F18-FDG PET/CT in cholangiocarcinoma and gall bladder cancer, but some retrospective studies have determined that F18-FDG PET/CT may be helpful in patients who are candidates for surgical treatment as the modality may help identify disease spreads to regional lymph nodes[142-144]. From review of literature, for hepatocellular carcinoma (HCC), F18-FDG PET/CT has sensitivity and specificity of approximately 79% and 92%, respectively[145-147] for diagnosis of extrahepatic metastasis. For diagnosis of disease recurrence, F18-FDG PET/CT has sensitivity and specificity of 76% and 93%, respectively, and is useful in patients with negative anatomical imaging but elevated serum tumor markers[148-151]. Only two studies regarding F18-FDG PET/CT in gall bladder cancer and cholangiocarcinoma were available. These studies determined for disease staging, F18-FDG PET/CT had sensitivity and specificity of 62% to 84% and 75%to 94%, respectively[144,152].

Expert consensus: For HCC, F18-FDG PET/CT is likely not beneficial for disease staging since diagnostic accuracy of F18-FDG PET/CT is not significantly superior to CT or MRI. For detection of recurrence, F18-FDG PET/CT is also not likely beneficial since most recurrences are intrahepatic in nature. Even in patients with elevated alpha-fetoprotein (AFP) and negative CT or MRI, F18-FDG PET/CT would likely play little role because in this scenario, it is more likely that AFP is elevated due to other causes such has liver cirrhosis or hepatitis rather than due to tumor recurrence. F18-FDG PET/CT has limited value in the staging of cholangiocarcinoma, because CT and MRI already have good diagnostic accuracy. F18-FDG PET/CT is disadvantageous in diagnosis of regional lymph node metastasis, because concomitant cholangitis can occur in patients with cholangiocarcinoma may result in falsely positive lymph nodes on F18-FDG PET/CT. For detection of distant metastasis, F18-FDG PET/CT does not have clear benefits since the prevalence of distant metastasis from cholangiocarcinoma is low.

Cancer of the oral cavity

Review of literature: From review of literature, in the initial staging of oral cavity cancer, F18-FDG PET/CT has lower sensitivity and specificity than MRI for T-staging, comparable sensitivity and specificity to CT and MRI for N-staging, and is superior to CT and MRI for M-staging with sensitivity and specificity for diagnosis of distant metastasis of 89% and 95%, respectively[153-162]. For evaluation of response to therapy and detection of disease recurrence, F18-FDG PET/CT has sensitivity and specificity of 92% and 91%, respectively, if done more than 12 weeks after completion of treatment[162-166]. For planning of radiation therapy, F18-FDG PET/CT has been found to be superior to CT for delineation of tumor volume as well as superior to CT and MRI for N-staging.

Expert consensus: F18-FDG PET/CT could be beneficial for initial staging of tumors located in areas difficult to assess by CT and MRI. The modality should be considered in patients with locally advanced stage III and IV disease before initiation of radiation or chemoradiation therapy with curative intent. For radiation therapy planning, F18-FDG PET/CT should be considered for routine planning of patients with locally advanced stage disease, in patients that CT cannot provide accurate delineation of tumor volume, and in cases where reirradiation of residual tumor is considered. F18-FDG PET/CT is also recommended for diagnosis of recurrent disease because anatomical imaging is generally limited in this scenario due to anatomical distortions from treatment.

Lymphoma

Review of literature: From review of literature, F18-FDG PET/CT has been found to have 90% sensitivity and 86% specificity for diagnosis of bone marrow involvement from lymphoma[167-174]. Bone marrow biopsy may be omitted in patients with negative bone marrow uptake as demonstrated by F18-FDG PET/CT. For interim assessment of response to chemotherapy in Hodgkin lymphoma,

F18-FDG PET/CT is 73% sensitive and 84% specific for predicting eventual treatment failure[175-181]. For restaging after completion of therapy, F18-FDG PET/CT has sensitivity of 74% to 100% and specificity of 92% to 99%, respectively[182-184].

Expert consensus: For Hodgkin lymphoma and diffuse large B-cell lymphoma (DLBCL), F18-FDG PET/CT is recommended for initial staging, interim evaluation of response to treatment, and evaluation of response after of treatment completion. F18-FDG PET/CT should also be considered for planning before initiation of radiation therapy and after completion of neoadjuvant chemotherapy since F18-FDG PET/CT provides more accurate tumor volume delineation.

Esophageal cancer

Review of literature: From review of literature of use of F18-FDG PET/CT in esophageal cancer, for preoperative lesion localization, on a lesion-based analysis, F18-FDG PET/CT had sensitivity and specificity of 43%, and 99%[185-191], respectively, whereas the sensitivity was 56% and 72% on a patient-based analysis[188,192-196]. For evaluation of response to preoperative chemotherapy or chemoradiation, using delta-SUV between baseline and post-therapeutic scans, a reduction of SUV by 42% to 70% resulted in prediction of therapeutic response with 81% sensitivity and 80% specificity, when using histopathological diagnosis as the gold standard[197-204]. For radiation therapy planning, F18-FDG PET/CT was found to be superior to conventional CT for delineation of gross tumor volume (GTV). GTV from CT was found to be discrepant from that obtained from F18-FDG PET/CT[205,206], which could result in inappropriate planning tumor volume (PTV) or geographic miss of tumor lesions while unnecessarily irradiating normal tissue[207,208]. One study found that 84% of patients had altered GTV when imaged with F18-FDG PET/CT in addition to conventional CT[209]. For diagnosis of recurrence, on a lesion-based analysis, F18-FDG PET/CT was found to have sensitivity and specificity of 96% and 60%, respectively, whereas on a patient-based analysis, the sensitivity and specificity was 96% and 67%, respectively. Conventional CT, on the other hand, had comparably high sensitivity of 97% on both lesion-based and patient-based readings, but markedly lower specificity of 36% and 21% for lesion-based and patient-based readings, respectively[210].

Expert consensus: The expert panel agreed that F18-FDG PET/CT is very useful for radiation therapy planning since most Thai patients have squamous cell carcinoma that requires treatment with radiation therapy as compared with Caucasian patients that typically have adenocarcinoma requiring surgical treatment. F18-FDG PET/CT provides more accurate GTV and PTV delineation than conventional CT especially for lymph node metastasis localization. F18-FDG PET/CT is also useful and should be done to assess residual disease after radiation therapy, which would require further salvage surgery.

Nasopharyngeal carcinoma

Review of literature: The sensitivity and specificity of F18-FDG PET/CT has been found to be 96%, 94%, respectively, which were significantly better than those of CT, which had corresponding values of 71% and 76%, respectively[211]. For lymph node staging FDG PET/CT was found to have sensitivity of 97% to 100% and specificity of 73% to 97%, respectively whereas MRI had corresponding values of 84% to 92%, of 73% to 97%, respectively[212-214]. For detection of distant metastasis at initial staging, a meta-analysis found that F18-FDG PET/CT had pooled sensitivity and specificity of 83% and 97%, respectively[215].

Expert consensus: For nasopharyngeal carcinoma, F18-FDG PET/CT is particularly useful in radiation therapy planning. Moreover, Thai patients commonly have undifferentiated, poorly differentiated, or non-keratinizing tumors that are more aggressive than those typically found in Caucasian patients. Thus, extensive staging imaging including head and neck CT, chest CT, upper abdominal CT, and bone scintigraphy are generally performed in Thai patients. For this reason, it is conceivable that F18-FDG PET/CT could potentially serve as a one-stop imaging in these patients. F18-FDG PET/CT is also useful for evaluation of patients whose CT or MRI finding are non-diagnostic. Additionally, F18-FDG PET/CT is beneficial for evaluation of response to radiation or chemoradiation to identify patients with residual disease that requires salvage surgery. In this setting F18-FDG PET/CT is advantageous compared with anatomical imaging since patients with head and neck cancers often have distortion of anatomical structures that would complicate structural imaging interpretation.

Ovarian cancer

Review of literature: From review of literature, F18-FDG PET/CT was found to have sensitivity and specificity of 89% and 92% for diagnosis of malignant pelvic masses[216-222]. For diagnostic staging of intraabdominal disease extent, F18-FDG PET/CT was 51% to 83% sensitive and 68% to 98% specific[223-225],

whereas CT had sensitivity of 41% and specificity of 92%[223]. However, F18-FDG PET/CT had increased probability of being falsely negative in lesions less than 0.5 cm in diameter and in patients with peritoneal carcinomatosis. For detection disease recurrence, F18-FDG PET/CT was found to have sensitivity and specificity of 94% and 92%, respectively[226-243] and is particularly useful in those patients with elevated tumor markers.

Expert consensus: F18-FDG PET/CT has no primary role in diagnosis of malignant pelvic masses since there are already robust diagnostic guidelines. For example, germ cell tumors are evaluated by tumor markers and epithelial cell tumors need surgical exploration. Similarly, surgical staging is the mainstay of diagnostic staging of ovarian cancers, thus F18-FDG PET/CT also has no primary role. However, F18-FDG PET/CT may be considered when recurrence is suspected due to elevated tumor markers and evaluation with CT or MRI yields equivocal results.

F18-FDG PET/CT in neurological diseases

Review of literature: For evaluation of dementias, F18-FDG PET/CT was found to have overall sensitivity and specificity of 90% and 87%[244-247], respectively. For differentiating Alzheimer disease from other dementias, whereas amyloid PET radiopharmaceuticals have corresponding values ranging between 88% to 97% and 85% to 95%, respectively[242,245-247]. PET/CT imaging has also been used for evaluation of patients with movement disorders. L-3,4-dihydroxy-6-(18F)fluorophenylalanine (F18-FDOPA) PET/CT has been found to have sensitivity and specificity of 83% to 97% and 100%, respectively for diagnosis of idiopathic Parkinson disease[251,252]. F18-FDG PET/CT has been used to differentiate between idiopathic Parkinson disease and other movement disorders with sensitivity and specificity ranging from 81% to 95% and 91% to 100%, respectively[253-256]. Several imaging modalities including electroencephalogram (EEG), MRI, ictal single photo emission computed tomography (ictal SPECT), and interictal F18-FDG PET/CT have been used for preoperative localization of epileptogenic zone of in patients with refractory focal epilepsy[257-261]. One study determined that in patients with focal abnormality seen on MRI, F18-FDG PET/CT successfully detected 87% of epileptogenic zone with histopathological diagnosis as the gold standard and 85% in patients with no abnormality seen on MRI[257]. The same study reported outcome after F18-FDG PET/CT guided surgery. Response rate as determined by Engel class I/II outcome was 88% and 80% in patients with positive and negative MRI, respectively.

Expert consensus: For evaluation of dementias, F18-FDG PET/CT is recommended for evaluation of patients with suspected atypical Alzheimer's dementia, and for differentiating between Alzheimer's dementia and frontotemporal lobe dementia. For evaluation of patients with mild cognitive impairment, there is not strong enough evidence of benefit of F18-FDG PET/CT. For patients with movement disorder, F18-FDOPA PET/CT is recommended for differentiating between idiopathic Parkinson disease and drug-induced parkinsonism. For interictal brain, F18-FDG PET/CT is recommended in patients with intractable epilepsy with negative intracranial EEG and undermined epileptogenic zone.

F18-FDG PET/CT in Cardiology

Review of evidence: In Cardiology, F18-FDG PET/CT has been used for diagnosis of coronary artery disease (CAD) and determination of myocardial viability. From review of literature, PET/CT was found to have sensitivity of 93% and specificity of 81%, respectively. Whereas the sensitivity of cardiac MRI and SPECT myocardial perfusion imaging (SPECT MPI) was 91% and 88%, respectively, and specificity was 79% and 76%, respectively[262-274]. For determination of myocardial viability, one large meta-analysis of studies with moderate quality determined that F18-FDG PET/CT had a pooled sensitivity of 90%, pooled specificity of 73%, and a likelihood ratio negative of 0.16[275]. Economic studies regarding utility of F18-FDG PET/CT suggested that using F18-FDG PET/CT would result in lower cost and positively impact patient survival compared with SPECT[275-277].

Expert consensus: For diagnosis of CAD, since there are many imaging modalities with high accuracy such as stress echocardiography, coronary CTA, cardiac MRI, and SPECT MPI, the added cost of PET/CT is unjustified. For determination of myocardial viability, currently the diagnostic performance of cardiac MRI is similar to that of F18-FDG PET/CT, so MRI should be done first and F18-FDG PET/CT be utilized on case of equivocal MRI findings.

Discussion

The present study was endorsed and funded by the Health Intervention and Technology Assessment Program (HITAP), a health technology assessment research unit under Thailand's Ministry of Public Health. The authors aimed to examine available evidence regarding the usefulness of F18-FDG PET/

CT in the top ten most prevalent cancers in Thailand as well as the modality's usefulness in Neurology and Cardiology. Available literature regarding the diagnostic performance and impact on patient management of F18-FDG PET/CT in each target condition was reviewed, summarized, and assessed while in light of the context regarding the country's disease burden, difference of disease characteristics from western countries, and socioeconomic factors in Thailand. The recommendations presented in this article were reached by results from the reviewed evidence and consensus of a panel of multidisciplinary experts. From the review, in addition to the two current reimbursable indications for F18-FDG PET/CT i.e., staging of NSCLC aimed to be treated with curative intent, and diagnosis of suspected colorectal cancer recurrence based on rising CEA levels, the authors and expert panel recommend many additional indications that F18-FDG PET/CT should be covered by current health insurance schemes to make this powerful imaging modality more accessible to the general public of the country. The authors did not specifically state the indications that should be made reimbursable, but instead, presented the available evidence and expert consensus as a guide for policy makers in future decisions of which indications to be made reimbursable.

This review has several limitations. Due to time constraints and the shear scope of the target conditions being reviewed, full systematic reviews and meta-analyses of the role of F18-FDG PET/CT in each indication for each target condition could not be done. Instead, the authors chose to summarize key evidence for each indication of each target condition along with input of the expert to reach the recommendations presented herein. From review of evidence, a limited number of economic research studies regarding F18-FDG PET/CT has been done and none that would likely fit the local context of Thailand. Therefore, further studies in this regard may need to be conducted with the national context as the focus.

In conclusion, the authors and expert panel posit recommendations regarding indications where F18-FDG PET/CT would be of benefit. This information should help policy makers in deciding the indications where F18-FDG PET/CT should made reimbursable in the key health insurance schemes of Thailand to make the modality most benefit the people of the country.

Conclusion

The present work, the authors reviewed the available evidence and provided recommendations regarding appropriate use of PET/CT in the ten most common malignancies in Thailand, as well as application in Cardiology and Neurology, taking into account the context and disease burden of the country. The authors believe that this work will provide guidance for clinicians and policy makers to make decisions regarding the appropriate utilization of PET/CT.

What is already known on this topic?

PET/CT, especially using the radiophatmacuetical F18-FDG, is a well-established imaging modality in Oncology, with increasing use in Cardiology and Neurology. International guidelines have outlined the appropriate use of PET/CT in most cancers. However, in Thailand, there are no appropriate use guidelines for utilizing this imaging modality.

What this study adds?

This review is the first to review and recommend appropriate use of PET/CT with regards to the disease burden and context of Thailand. The authors graded the appropriateness of use of PET/CT in the ten most prevalent cancers in Thailand, as well as indications in Cardiology and Neurology which should help clinicians and policy makers in their decision of utilizing PET/CT.

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Conflicts of interest

The authors declare no conflict of interest.

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