Original Article

Benefit of Contrast-Enhanced PET/CT versus Non-Contrast-Enhanced PET/CT Relative to Lesion Detection, Lesion Characterization, and Diagnostic Accuracy in Patients with Cancer

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Objective: To investigate the benefit of contrast-enhanced PET/CT (PET/CECT) versus non-contrast-enhanced PET/CT (PET/NCCT) relative to lesion detection, characterization, and diagnostic accuracy in cancer patients.

Materials and Methods: The present study was a prospective study that included patients older than 18 years with histopathologically proven cancer who underwent [F-18] fluorodeoxyglucose ([F-18]FDG) PET/CT at the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine, Siriraj Hospital between December 2014 and November 2017. PET/NCCT was performed followed by PET/CECT scan in all patients. The results of PET/NCCT, PET/CECT, and pre- and post-contrast enhanced PET/CT (PET/NCCT-CECT) for each patient were interpreted by one nuclear medicine physician and one radiologist. The sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV) were calculated from ROC curve analysis.

Results: One hundred ten patients were included. The mean age was 52.45±17.14 years, and 52.7% were female. Lymphoma was the most common cancer diagnosis (47.3%). No significant difference was observed between PET/CT techniques for detection rate at the primary tumor site, lymph node, or distant organ. High agreement was observed between PET/CT techniques for lesion characterization. Lesion characterizations were not significantly correlated with age, gender, BMI, or FBS; however, lesion characterization was found to be significantly associated with primary tumor site, indication for PET/CT and lesion size. The following ranges were observed from all PET/CT techniques: sensitivity 81.5% to 85.3%, specificity 94.4% to 95.5%, accuracy 89.4% to 91.4%, PPV 90.4% to 92.1%, and NPV 88.9% to 91.3%.

Conclusion: [F-18]FDG PET/CECT demonstrated no significant advantage over PET/NCCT for lesion detection, lesion characterization, or diagnostic accuracy in patients with cancer. The use of intravenous contrast material should be limited to select cases to reduce the risk of renal toxicity or anaphylactic reaction, and to minimize unnecessary costs.

Keywords: Contrast-enhanced PET/CT, Non-contrast-enhanced PET/CT, Lesion detection, Lesion characterization, Diagnostic accuracy, Cancer, [F-18]FDG

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Integrated positron emission tomography and computed tomography or PET/CT scan using [F-18] fluorodeoxyglucose ([F-18]FDG) is a well-accepted imaging technique that is used for diagnosis, staging, response assessment, recurrence detection, and follow-up among patients with suspected or definitively diagnosed cancer. PET/CT was shown to have greater diagnostic accuracy than PET or CT alone relative to primary tumor detection, lymph node metastasis, and distant metastasis[1]. To obtain a CT scan that can be diagnosed efficiently when combined with PET, the administration of intravenous contrast material may be required. The use of intravenous contrast material

facilitates precise identification and differentiation of vascular and parenchymatous organ tissue from surrounding tissues. Moreover, the evaluation of lesion enhancement improves lesion detection and lesion characterization. Additionally, assessment of a lesion's relationship with adjacent vascular structures is important for surgical planning[2,3]. Previous studies suggested that contrast-enhanced PET/CT improves the detection and characterization of liver lesions in patients with colorectal cancer[2], recurrent rectal cancer[4], ovarian cancer[5], and lung cancer[6]. In contrast, other studies found no significant difference between non-contrast-enhanced CT (NCCT) and contrast-enhanced CT (CECT) integrated with PET in patients with malignant lymphoma[7], and in patients with head and neck cancer[8,9]. Importantly, intravenous contrast material should be used only when the potential benefits outweigh the potential risks since contrast material can cause renal toxicity or anaphylactic reaction in some patients. Some authors recommend against routine intravenous contrast administration for PET/CT, but they agree that it may be selectively used in patients with early-stage head and neck cancer that requires meticulous anatomic and topographic data to plan the operation, and in patients with advanced-stage cancer for assessing vascular invasion[9]. No consensus has yet been reached regarding if, how, and when intravenous contrast material should be used in PET/CT study.

The aim of the present study was to investigate the benefit of contrast-enhanced PET/CT versus non-contrast-enhanced PET/CT in relation to lesion detection, characterization, and diagnostic accuracy in patients with cancer.

Materials and Methods

The present study was approved by the Siriraj Institutional Review Board (SIRB) (COA no. Si413/2014), and all patients provided written consent before enrollment into the study. A flow diagram describing patient enrollment and the study protocol is shown in Figure 1.

Patients

The present study was a prospective study conducted in patients older than 18 years with histopathologically proven cancers who underwent [F18]FDG whole body PET/CT scan at the Division of Nuclear Medicine, Department of Radiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand between December 1, 2014 and November 30, 2017. Patients with severe renal dysfunction (glomerular filtration rate [GFR] of less than 20 mL/minute; n=3), contraindications for contrast material (n=2), and marked hyperglycemia (fasting blood sugar [FBS] of more than 200 mg/dL, n=2) were excluded.

All PET/CT studies were performed at least four weeks after biopsy or surgery, six weeks after chemotherapy, twelve weeks after radiotherapy, and two weeks after granulocyte-colony stimulating factor (GCSF) treatment to prevent false-positive results due to inflammatory changes. Clinical, histopathological, radiological follow-up, and other correlative investigation were used as reference standards to evaluate the diagnostic accuracy of PET/CT.

PET/CT protocol

All data were acquired using an integrated PET/CT system (Discovery®; GE Healthcare, Milwaukee, WI, USA) that integrates a 16-detector row CT scanner with a lutetium oxyorthosilicate (LSO)-based PET scanner. Patients fasted at least six hours prior to [F-18]FDG administration, and blood glucose level was checked using a glucose meter (Stat Strip®; Nova Biomedical, Waltham, MA, USA) just before [F-18]FDG administration. Tracer injection was performed only in patients whose blood glucose level was less than 150 mg/dL. Whole-body emission images were obtained 60 minutes after intravenous administration of [F-18]FDG (0.14 to 0.2 mCi/kg), with an average injected dose of 381.19±76.4 MBq (10.3±2.0 mCi).

In all patients, 2 mL/kg of non-ionic contrast material using either Iopamidol (Iopamiro®; Bracco Imaging, Milano, Italy) or Iohexol (Omnipaque®; GE Healthcare, Milwaukee, WI, USA) or Ioversol (Optiray®; Guerbet, Cedex, France) or Iodixanol (Visipaque®, GE Healthcare, Milwaukee, WI, USA) was intravenously injected. Whole body CT (30 to 300 mAs using automatic exposure control (AEC) and smart mA, 14.0 noise index, 120 kVp, and helical thickness of 2.5 mm collimation) was performed immediately before and after contrast injection. Contrast-enhanced CT scan was performed after contrast injection using the appropriate delay time (40 seconds for lesion at head, neck, or chest, and 70 seconds for lesion at abdomen). PET data was acquired in 3-D mode, three minutes per bed position, and reconstruction was performed using a standard 3D iterative reconstruction algorithm (VUE Point HD).

Image interpretation

The reconstructed, attenuation-corrected images of all PET/CT datasets were reviewed in consensus

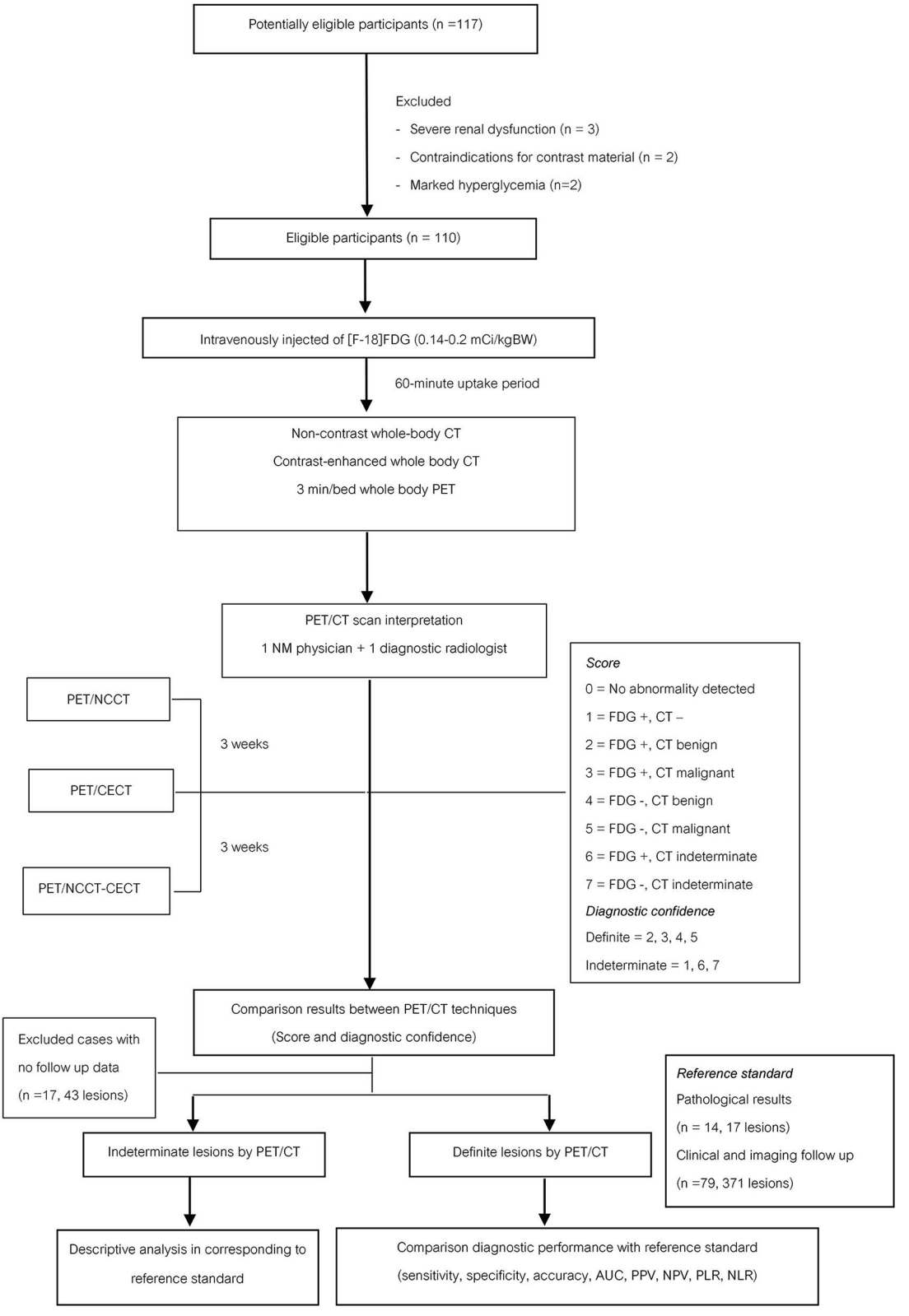

Figure 1. Flow diagram of patient enrollment and the study protocol.

by one board-certified nuclear medicine physician (14-years' experience) and one diagnostic radiologist (11-years' experience). Both were blinded to the patient clinical information, using an AW Workstation (GE Healthcare, Milwaukee, WI, USA). Images without attenuation correction were available for evaluation in cases with suspicious artifacts. For non-contrast PET/CT, a lesion was defined as either a focus of increased [F-18]FDG uptake compared with background, or as morphologic change with features that increase suspicion of the presence of a tumor. For contrast-enhanced PET/CT, abnormal enhancement was added to the criteria adopted for non-contrast PET/CT (e.g., enhancement greater than 15 HU in pulmonary nodule sized greater than 8 mm)[10-13]. Lymph node metastasis was considered in lymph nodes with FDG avidity and when their shortest axial diameter was greater than 11 mm in the jugulodigastric region and greater than 10 mm in the cervical, abdominal, or pelvic region (greater than 5 mm in rectal cancer), or if irregular border or central necrosis was evident, or if there was a cluster of three or more lymph nodes of borderline size[14-16]. Distant metastasis was defined as a focally increased [F-18]FDG activity compared with background, with associated soft tissue mass outside of the primary lesion or bony destruction. Equivocal lesion detected by PET or CT that failed to satisfy any of the aforementioned diagnostic criteria was designated as an indeterminate lesion.

Outcome assessment

All whole body PET/CT studies were assessed using an 8-point scale, as follows: 0=no abnormality detected, 1=focal FDG uptake without CT abnormality, 2=focal FDG uptake with CT abnormality, favoring benign, 3=focal FDG uptake with CT abnormality, favoring malignant, 4=CT abnormality without FDG avidity, favoring benign, 5=CT abnormality without FDG avidity, favoring malignant, 6=focal FDG uptake with CT abnormality, indeterminate, and 7=CT abnormality without FDG avidity, indeterminate. These lesions were then classified as indeterminate (scores 1, 6, or 7), definite benign lesion (scores 2 or 4), or, definite malignant lesion (scores 3 or 5). Both observers reviewed PET/NCCT first, followed by PET/CECT and PET/NCCT-CECT, with at least a 3-week interval between each of the three sets to prevent recall bias.

Study outcome was assessed by comparing total number, characterization scores (0 to 7), and diagnostic confidence (determinate versus indeterminate) for all lesions detected by the three PET/CT techniques. Both patient-based and lesion-based data were collected and analyzed. To compare diagnostic performance, the authors compared the interpretation obtained from PET/CT studies with the corresponding results from intra-operative findings, pathologic study, or change in imaging findings during a minimum follow-up period of six months. Among patients with no intraoperative findings, lesions that decreased in size or that remain unchanged without receiving any further treatment were considered benign, while progressive lesions were considered malignant.

Statistical analysis and sample size calculation

All data were analyzed using the statistical software package PASW Statistics for Windows, version 18.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 18.2.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2018). Categorical variables were analyzed using chi-square test, and continuous variables were tested using one-way analysis of variance (ANOVA) with post hoc analysis. McNemar's test was used to determine the statistical significance of differences in lesion detection accuracy by PET/NCCT, PET/CECT, and PET/NCCT-CECT. Kappa statistic was used to analyze agreement of interpretation between PET/CT techniques. For all tests, a p-value of less than 0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was performed to assess diagnostic performance relative to the results obtained from intra-operative finding, pathological study, or change in imaging findings from each technique. The sensitivity, specificity, accuracy, likelihood ratio, positive predictive value (PPV), and negative predictive value (NPV) of all techniques were determined. Net reclassification improvement (NRI) of PET/CECT as compared to PET/NCCT was also calculated, with malignancy from final diagnosis being considered an event.

The sample size for the present study was calculated using data from a study by Cantwell et al[2]. Using a detection rate of liver lesion by non-contrast enhanced PET/CT in patients with colorectal cancer of 70%, a significance level of 0.05, and a power of 80%, the calculated sample size was 33. To cover the three most common types of cancer for which PET/CT study was requested and to compensate for a 10% loss of data for any reason, the calculated minimum sample size was 110 patients.

Results

Demographic data

One hundred ten cancer patients were included. The types of cancer presented were lymphoma, lung cancer, gastrointestinal and hepatobiliary tract cancer, genitourinary cancer, and other cancers (five breast cancer, three sarcoma, two melanoma, two metastatic cancer of unknown primary, and one thyroid cancer). The mean age of the patients was 52.45±17.14 years, and 52.7% were female. Approximately one-third of the patients were indicated for PET/CT to monitor response during treatment, with or without baseline study. Detailed demographic and clinical data of the study population is shown in Table 1.

Table 1. Demographic and clinical data of the 110 included cancer patients

Characteristics	n (%)
Age (year); mean±SD	52.45±17.14
Sex	
Female	58 (52.7)
Male	52 (47.3)
Primary cancer type	
Lymphoma	52 (47.3)
Lung	19 (17.3)
GI & HB tract	19 (17.3)
Genitourinary	8 (7.3)
Other	12 (10.8)
Indication for PET/CT	
Monitoring treatment response	42 (38.2)
Suspected recurrence	26 (23.6)
Re-staging	20 (18.2)
Initial staging	13 (11.8)
Diagnosis for suspicious lesion	5 (4.5)
Unknown primary tumor	4 (3.6)
BMI (kg/m^2); mean±SD	23.3±3.55
Fasting blood glucose level (mg/dL) on the day of PET/CT; mean±SD	94.25±14.71
Contrast material	
Iohexol	66 (60.0)
Ioversol	22 (20.0)
Iopamidol	11 (10.0)
Iodixanol	11 (10.0)
Follow-up period (month); mean±SD	30±10.75

GI=gastrointestinal tract; HB=hepatobiliary tract; PET/CT=positron emission tomography and computed tomography; BMI=body mass index

Lesion detection and characterization

Indeterminate lesions (scores 1, 6, and 7) were found at the primary site in 7/53 (13.2%), 6/55 (10.9%), and 6/56 (10.7%) of cases; at lymph node in 8/82 (9.8%), 6/84 (7.1%), and 6/84 (7.1%) of cases; and at distant metastatic site in 33/93 (35.5%), 33/95 (34.7%), and 31/95 (32.6%) of cases with PET/NCCT, PET/CECT, and PET/NCCT-CECT, respectively. No significant difference in indeterminate lesions was found among PET/CT techniques. There was very high agreement for diagnostic characterization of these lesions among PET/CT techniques ($p>0.05$) relative to both score and diagnostic confidence (determinate versus indeterminate) (Table 2).

The authors also compared the differences between potential factors and the possibility of indeterminate lesions detected by each PET/CT technique, as shown in Table 3.

Overall, there was no statistically significant difference in diagnostic confidence between any PET/CT technique and gender, primary tumor type, or indication for PET/CT at primary tumor site, lymph node, or distant metastatic site. However, statistically significant differences in diagnostic confidence were observed at distant metastatic sites relative to primary tumor type (mostly in GU and GI systems with p-values of 0.026, 0.017, and 0.003 in PET/NCCT, PET/CECT, and PET/NCCT-CECT, respectively), and indication for PET/CT (mostly in CUP with p-values of 0.07 and 0.025 in PET/CECT and PET/NCCT-CECT, respectively).

From the 371 detectable lesions, the most common location was thoracic lymph node (n=76),

Table 2. Lesion characterization agreement among different combinations of PET/CT techniques

Characterization	PET/NCCT vs. PET/CECT		PET/CECT vs. PET/NCCT-CECT		PET/NCCT vs. PET/NCCT-CECT	
	Kappa (SD)	95% CI	Kappa (SD)	95% CI	Kappa (SD)	95% CI
Score	0.941 (0.01)	0.913 to 0.969	0.808 (0.02)	0.763 to 0.853	0.762 (0.02)	0.713 to 0.810
Definite vs. indeterminate	0.864 (0.03)	0.799 to 0.929	1.000 (0.00)	1.000 to 1.000	0.864 (0.03)	0.799 to 0.929

PET=positron emission tomography; NCCT=non-contrast computed tomography; CECT=contrast-enhanced computed tomography; SD=standard deviation; CI=confidence interval

Table 3. Comparison between potential factors and the possibility of indeterminate lesions detected by each PET/CT technique

Factors	Site	Interpreted results	PET/NCCT Mean±SD	PET/CECT Mean±SD	PET/NCCT-CECT Mean±SD
Age (year)	Primary	Definite	50.43±19.07	49.94±18.81	49.86±18.62
		Indeterminate	53.43±15.49	54.67±16.58	54.67±16.58
		p-value	0.709	0.553	0.543
	Node	Definite	53.57±17.27	53.79±17.03	53.79±17.03
		Indeterminate	50.50±18.64	50.00±20.68	50.00±20.68
		p-value	0.802	0.794	0.794
	Metastasis	Definite	52.20±17.65	52.52±17.18	52.22±17.32
		Indeterminate	55.79±15.70	55.52±16.18	56.32±15.63
		p-value	0.394	0.453	0.329
Sex; % female	Primary	Definite	60.87%	61.22%	60.00%
		Indeterminate	57.14%	66.67%	66.67%
		p-value	0.208	0.117	0.117
	Node	Definite	44.59%	46.15%	46.15%
		Indeterminate	50.00%	50.00%	50.00%
		p-value	0.549	0.556	0.556
	Metastasis	Definite	55.00%	56.45%	57.81%
		Indeterminate	45.45%	45.45%	41.93%
		p-value	0.573	0.379	0.379
BMI (kg/m^2)	Primary	Definite	23.28±-3.61	23.32±-3.51	23.36±3.48
		Indeterminate	23.83±5.09	23.75±5.57	23.75±5.57
		p-value	0.949	0.844	0.806
	Node	Definite	23.32±3.56	23.24±3.50	23.24±3.50
		Indeterminate	23.08±2.88	23.54±3.00	23.54±3.00
		p-value	0.988	0.627	0.627
	Metastasis	Definite	22.88±3.58	22.77±3.34	22.89±3.50
		Indeterminate	23.86±3.93	24.17±4.16	23.36±3.48
		p-value	0.137	0.070	0.102
FBS (mg/dL)	Primary	Definite	94.93±16.118	94.35±15.79	94.74±15.88
		Indeterminate	86.00±11.79	86.17±12.91	86.17±12.91
		p-value	0.294	0.451	0.414
	Node	Definite	95.69±17.12	95.41±16.77	95.41±16.77
		Indeterminate	87.38±4.50	88.00±4.89	88.00±4.89
		p-value	0.211	0.348	0.348
	Metastasis	Definite	94.63±15.07	94.40±15.07	93.91±15.09
		Indeterminate	94.79±15.10	94.97±14.88	96.03±14.71
		p-value	0.994	0.903	0.480
Size (cm)	Primary	Definite	2.32±2.26	2.30±2.25	2.30±2.25
		Indeterminate	1.59±1.52	1.68±1.54	1.68±1.54
		p-value	0.141	0.341	0.341
	Node	Definite	1.29±1.05	1.32±1.05	1.32±1.05
		Indeterminate	1.21±0.79	1.09±0.75	1.09±0.75
		p-value	0.754	0.403	0.403
	Metastasis	Definite	1.39±1.16	1.43±1.15	1.43±1.15
		Indeterminate	2.05±1.81	2.26±2.10	2.26±2.10
		p-value	0.098	0.226	0.226

PET=positron emission tomography; NCCT=non-contrast computed tomography; CECT=contrast-enhanced computed tomography; BMI=body mass index; FBS=fasting blood sugar; SD=standard deviation

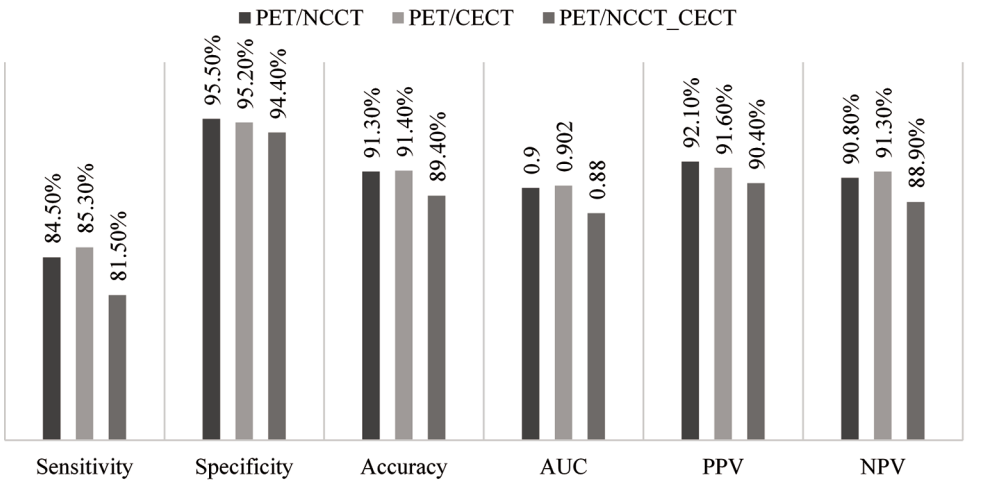

Figure 2. Diagnostic performance among PET/NCCT, PET/CECT, and PET/NCCT-CECT*.

PET=positron emission tomography; NCCT=non-contrast computed tomography; CECT=contrast-enhanced CT; AUC=area under the curve; PLR=positive likelihood ratio; NLR=negative likelihood ratio; PPV=positive predictive value; NPV=negative predictive value

* Indeterminate results by each PET/CT technique were excluded

followed by lung (n=59), bone (n=47), liver (n=44), and abdominal lymph node (n=31). The average size of all 291 measurable lesions was 1.73±1.68 cm. From ROC curve analysis, the best cut-off for detectable lesion size was 1.25 cm, with a sensitivity and specificity of 71.1% and 71.2%, respectively. Interestingly, there were significant differences in lesion size between definite and indeterminate lesions in some techniques, but in the opposite ways. Specifically, inderminate lesions tended to be found more often in larger lesions at the primary site, but in smaller lesions at distant metastatic sites.

Diagnostic performance

Seventeen patients (15.5%, 48 lesions) did not follow-up at the authors' center, so their outcomes were not available. The sensitivity, specificity, accuracy, PPV, and NPV of PET/CT techniques in the remaining 93 patients were evaluated against the corresponding results of intra-operative finding in 14 patients (17 lesions: 16 malignant, 1 benign). In the other 79 patients, 97 lesions were considered to be malignant based on observed disease progression, and 209 lesions were considered to be benign due to no change or decrease in lesion size during the mean follow-up of 30 months. The following ranges were observed from all PET/CT techniques: sensitivity 81.5% to 85.3%, specificity 94.4% to 95.5%, accuracy 89.4% to 91.4%, positive likelihood ratio 14.572 to 18.719, negative likelihood ratio 0.155 to 0.196, PPV 90.4% to 92.1%, and NPV 88.9% to 91.3% (Figure 2).

The AUC obtained from ROC curve analysis was 0.9, 0.902, and 0.88 for PET/NCCT, PET/CECT, and PET/NCCT-CECT, respectively. The indeterminate lesions (81 lesions in PET/NCCT, 65 lesions in PET/CECT and PET/NCCT-CECT) were excluded from diagnostic performance evaluation, but they were discussed further in the Discussion section. Based on the likelihood of malignancy per each lesion score (Table 4), lesion with positive FDG uptake and characteristics indicative of malignancy from CT findings (score 3) showed the highest likelihood of malignancy in all techniques, followed by lesion with evidence of malignancy by CT without FDG uptake (score 5). Other lesions without suggestive evidence of malignancy either by PET together with CT or CT alone showed relatively low likelihood of malignancy.

Of the other 252 lesions with definite impression by both PET/NCCT and PET/CECT, there was no lesion identified as benign in PET/NCCT that was changed to malignant by PET/CECT (or vice versa), regardless of final diagnosis group. Therefore, the calculated NRIe, NRIne, and sum NRI were all 0. For more detail, please see the Supplement data.

Adverse reaction from contrast material

Two patients developed skin rash within 24 hours after intravenous contrast injection made prevalence of adverse reaction of 1.8%. Both events were mild, and no active treatment was required. No serious adverse events were observed during the present study.

Table 4. Positive likelihood ratio for malignancy by score of lesions obtained from each PET/CT technique

Score	PET/NCCT (95% CI)	PET/CECT (95% CI)	PET/NCCT-CECT (95% CI)
1	N/A	N/A	0.586 (0.186 to 1.842)
2	0.219 (0.079 to 0.601)	0.219 (0.079 to 0.601)	2.928 (1.711 to 5.0120
3	24.469 (11.018 to 54.341)	22.301 (10.679 to 46.572)	8.458 (2.105 to 33.981)
4	0.179 (0.101 to 0.319)	0.165 (0.093 to 0.292)	0.431 (0.239 to 0.777)
5	5.575 (0.587 to 52.983)	5.575 (0.587 to 52.983)	10.150 (0.943 to 109.279)
6	0.786 (0.404 to 1.532)	0.446 (0.189 to 1.055)	0.846 (0.310 to 2.306)
7	0.32 (0.128 to 0.805)	0.489 (0.188 to 1.275)	0.597 (0.144 to 2.484)

PET=positron emission tomography; NCCT=non-contrast computed tomography; CECT=contrast-enhanced; CI=confidence interval; N/A=not available

Score 1=focal FDG uptake without CT abnormality; 2=focal FDG uptake with CT abnormality, favoring benign; 3=focal FDG uptake with CT abnormality, favoring malignant; 4=CT abnormality without FDG avidity, favoring benign; 5=CT abnormality without FDG avidity, favoring malignant; 6=focal FDG uptake with CT abnormality, indeterminate; and 7=CT abnormality without FDG avidity, indeterminate

Discussion

In contrast to the added beneficial effect of intravenous contrast material found and reported in some studies[2-6], the authors found no significant added value from the use of intravenous contrast material relative to diagnostic confidence or diagnostic performance of [F-18]FDG PET/CT study using CECT alone or combined NCCT/CECT. The detection rate, diagnostic confidence as defined by percentage of indeterminate lesions, and diagnostic performance of PET/CECT and PET/NCCT-CECT were almost identical. This can be explained by the fact that the main component of results interpretation on PET/NCCT-CECT is mainly based on CECT image. Thus, dual CT scans provide no additional benefit; however, they expose the patient to added and unnecessary radiation, even though only minimal exposure from the low-dose CT used in PET/CT is claimed. Similar results were also observed in previous studies in patients with lymphoma[7], and head and neck cancer[8,9]. Despite the reported added value of contrast material in PET/CT study that has been reported in cancers of the head and neck, abdominal and pelvic regions, and possibly in tumors with mild or no [F-18] FDG avidity[2,4-6,8], the present study results failed to show statistically significant added value of CECT regardless of the region of the detectable lesions. However, there were 16 indeterminate lesions from PET/NCCT that were definitely classified by PET/CECT, and 5 of those were found to be malignant in the final diagnosis. Most of those lesions were small intra-abdominal lesions with faint FDG activity that were easier to identify and diagnose via the use of contrast enhancement.

There was no significant correlation between incidence of indeterminate lesion at the primary site or lymph node and gender, primary cancer type, or indication for PET/CT. However, significant correlation was found between indeterminate metastatic lesions with primary cancer type and indication for PET/CT, particularly the PET/CECT and PET/NCCT-CECT techniques. The highest incidence of indeterminate metastatic lesions was found in approximately half of genitourinary cancer, gastrointestinal tract cancer, and hepatobiliary tract cancer, and in approximately two-thirds of patients indicated for PET/CT due to cancer of unknown primary (CUP) and for diagnosis of suspicious lesion(s). Most indeterminate lesions (71 in PET/NCCT and 55 in PET/CECT) demonstrated mild FDG uptake. As a result, the findings from CT did not fulfil the criteria for malignancy. Even though the use of contrast material seemed to lower the number of indeterminate lesions, the difference between PET/CT techniques was not statistically significant. Considering the highest likelihood of malignancy that can be obtained from lesions with positive findings from both FDG PET and CT, while the lowest likelihood in lesions detected by CT only without FDG uptake, unless strong evidence of malignancy from CT, the significance of these additional non-FDG avid lesions might be relatively low. In additional lesions detected by CT without FDG avidity, a final diagnosis of malignancy was found in 11/135 (8.1%) versus 11/125 (8.8%), 3/4 (75%) versus 3/4 (75.0%), and 5/24 (20.8%) versus 5/34 (14.7%) of lesions classified as benign, malignant, and indeterminate by NCCT and CECT, respectively. All of these results show no significant incremental advantage of intravenous material in PET/CT study. In addition,

the unnecessary use of contrast material should be avoided due to its potentially serious side effects. The incidence rate of side effects in the present study was a low 1.8% due to the authors' strict adherence to setting-specific guidelines. Moreover, the cost of contrast material is approximately 100 USD per patient, which makes unnecessary high expense in cases of no benefit from contrast enhancement. Taken together, the present study data do not support the routine use of contrast material in the whole body PET/CT study.

The present study has some limitations. First, this was a single-center study with a relatively small sample size compared to the previous publications. The [F-18]FDG PET/CT study in Thailand has limited indications for reimbursement (at the time when the study was conducted only in colorectal cancer and non-small cell lung cancer), so this technique is still underutilized. This explains why the sample size is so small and the study period is so long. Second, most of the enrolled PET/CT studies were performed post-treatment, which may affect the detection rate of malignant diseases. The prevalence of malignancy was only 35% among all detectable lesions. Third, only a small number of case (n=14, 12.7%) had pathologically proven lesions detected by PET/CT, particularly among lesions identified as benign or indeterminate. However, with the mean follow-up of approximately two years, lesions that decreased in size or that remain unchanged without receiving any further treatment were considered benign, while progressive lesions were considered malignant. Fourth and last, the contrast-enhanced PET/CT in the present study was performed in single-phase manner, so the results may not be generalizable to multi-phase contrast-enhanced PET/CT, which was previously suggested by some authors[17].

In contrast to other reports studied in specific types of cancer, the strengths of the present study are its prospective design and the fact that the authors studied different types of cancer, which increases the generalizability of the findings. However, further investigation in those cancers with a small number of cases, as well as in other indications, is needed to confirm the results of the present study.

Conclusion

The results of the present prospective study revealed no significant advantage of [F-18]FDG PET/CT over PET/NCCT for lesion detection, lesion characterization, or diagnostic accuracy in patients with cancer. Although the rate of adverse events was extremely low, the use of intravenous contrast material should be limited to selected cases to reduce the risk of renal toxicity or anaphylactic reaction, and to minimize unnecessary costs.

What is already known on this topic?

[F-18]FDG PET/CT scan is a well-accepted imaging technique for diagnosis, staging, response assessment, recurrence detection, and follow-up among patients with suspected or definitively diagnosed cancer. There is no consensus regarding if, how, and when intravenous contrast material should be used in PET/CT study.

What this study adds?

This study results found no significant difference between PET/CT techniques for detection rate at the primary tumor site, lymph node, or distant organ as interpreted by experienced radiologists. High agreement was observed between PET/CT techniques for lesion characterization. Lesion characterizations were not significantly correlated with age, gender, BMI, or FBS; however, lesion characterization was found to be significantly associated with primary tumor size, indication for PET/CT, and lesion size. In summary, [F-18]FDG PET/CT showed no significant advantage over PET/NCCT for lesion detection, lesion characterization, or diagnostic accuracy in patients with cancer. The use of intravenous contrast material should be limited to select cases to reduce the risk of renal toxicity or anaphylactic reaction, and to minimize unnecessary costs.

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Conflicts of interest

The authors declare no conflict of interest.

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