Original Article

A pilot study of the correlation between lymph node metastasis in colorectal cancer patients found by pre-operative ^{18}FDG PET/CT scan and results of final histopathology

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OBJECTIVE. The purpose of this research is to compare the association between the diagnostic values of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}FDG PET/CT) scan (maximum standardized uptake value - SUV) for pre-operative lymph nodes status and the final histopathology report.

MATERIALS AND METHODS. This retrospective study gathered the information from patient medical records at Bangkok Hospital Medical Center. The patients were examined for colorectal cancer from May 2007 to November 2009 and received the pre-operative positron emission tomography/computed tomography (PET/CT) scan before having oncologic colorectal surgery during the time period mentioned above. The subjects in this study numbered 30 patients. Each ^{18}FDG PET/CT scan was reviewed and interpreted by one nuclear medicine professional who had no prior knowledge of patient details, including the diagnosis of any previous PET/CT scans.

RESULTS. Results demonstrated that the PET/CT scan correctly identified 24 out of 30 patients to have pre-operative lymphadenopathies. Moreover, 14 out of those 24 patients (58.3%) showed metastatic lymphadenopathies in the final histopathology. The remaining 2 out of 6 patients (33.3%) had metastatic lymphadenopathies according to final histopathology, but ^{18}FDG PET/CT did not detect them. There was a significant differentiation (p = 0.014) between the mean of the SUV in malignant lymphadenopathies (1.18 ± 0.69) and those of benign lymphadenopathies (0.59 ± 0.54) in primary colorectal cancer patients.

CONCLUSION. There was a clear association between pre-operative diagnosis of suspicious malignant lymphadenopathies by PET/CT scan and final histopathological lymphadenopathies. It will be beneficial to see further studies about the predictive role of using pre-operative ^{18}FDG PET/CT scanning in diagnosis of lymph node metastasis in colorectal cancer patients. The pre-operative PET scans of our colorectal cancer patients showed a higher uptake of ^{18}F-fluorodeoxyglucose (^{18}FDG) in malignant lymph nodes.

It is very common to use magnetic resonance imaging (MRI), computed tomography (CT) to evaluate the pre-operative lymph node status in colorectal cancer patients. However, the low sensitivity can lead to bias and incorrect evaluation.[1,2] The latest technology, which uses positron emission tomography/computed tomography. ^{18}FDG PET/CT is becoming more popular, especially with regard to using the surveillance and pre-operative staging to assess recurrence of disease and distant metastases.

Yoshiyuki's research[3] reported that the using of PET/CT scan for pre-operative diagnosis of lymph mode metastasis of colorectal cancer gives a sensitivity of around 51.2%, specificity of around 85.1% and accuracy of around 69.3% for the regional node group.The purpose of this research was to study the association between the diagnostic value of ^{18}FDG PET/CT scan (maximum standardized uptake value - SUV) for pre-operative lymph nodes status and the results shown by the final histopathology.

Materials and Methods

This was a retrospective study which gathered the information from patient medical records at Bangkok Hospital Medical Center. The patients were examined for colorectal cancer between May 2007 and November 2009; they received the pre-operative ^{18}FDG PET/CT scan before having oncologic colorectal surgery. The subjects in this study numbered 30 patients, 20 males and 10 females. The average age was 63, and 64.4 years old respectively for male and female patients. Table 1 shows the locations of primary tumors revealed in the colon of 20 patients and the rectum of 10 patients. However, in this sample, the primary tumor of one patient was not detected by ^{18}FDG PET/CT scan (post incomplete polypectomy) and the lymph node status of 6 patients was not revealed either.

Inclusion / Exclusion Criteria

The records of inpatients with carcinoma of rectum and/or colon (code ICD10), who were examined and operated on between May 2007 and November 2009, showed that every patient was examined by ^{18}FDG PET/CT scan in order to evaluate distant metastases within the 2 week period prior to their operations, and had tissue histopathology to confirm the diagnosis before surgery. Diabetic patients fasting blood sugar (FBS) should have been lower than 200 mg%, or have foregone insulin injection before having ^{18}FDG for PET/CT scan.

PET/CT scans Technique

The ^{18}FDG PET/CT, Gimini GXL was used for this study. The scintillator was gadolinium oxyorthosilicate (GSO) with a detector dimension of 4x6x30 mm. The axial field of view was 16.2 cm with sensitivity of 8.3 cps/kBq. Peak noise equivalent count rate (NECR) was 70 kcps. The transverse and axial resolutions were 5.1 and 5.5 respectively. The CT mode was used for attenuation correction. All patient fasted 6 hours; fasting blood sugar was less than 200 mg%. Patients were injected with a dosage of 0.14 mCi/Kg of ^{18}FDG. Then after resting for 1 hour, the study was begun. The field of study included the base of the skull down to the upper thighs. CT scan technique: Detector type was cadmium tungstate (CdWO4) with 16 slices; 120 kV, 250 mA.; slice thickness 5 mm. Immediately after CT scan was done, PET scan was performed with total 6 - 7 bed positions. The raw data of PET study was attenuation corrected by using the CT scan, then reformatted into trans axial, coronal and sagittal views.

Interpretations of PET/CT scan

The PET/CT scan was reviewed by one nuclear medicine professional, who had no prior patient detail such as diagnosis of any previous PET/CT scans.The report was interpreted from the SUV of lymph nodes. Moreover, we also had the report on the SUV of primary tumor(s).

Table 1: Demographic data of colorectal cancer patients.

Factor	Sample Size	
Sex	Male (20)	Female (10)
Age	46 - 83 years (mean = 63)	43 - 99 years (mean = 64.3)
Nationality	Thai (13)	Foreigner (17)
Site of primary tumor		
Ascending colon	Male (3)	Female (0)
Transverse colon	Male (2)	Female (0)
Descending colon	Male (4)	Female (2)
Sigmoid colon	Male (4)	Female (5)
Rectum	Male (7)	Female (3)

Statistical Analysis

An association between SUV of lymph node and result from final histopathology was calculated using by Student's t-test. A corrected $p < 0.05$ was considered evidence of statistical significance. Comparison of SUV between each cell types of primary tumor was done, using one-way analysis of variance (ANOVA).[4]

Results

From the review, we have found that the CT scan could identify 24 out of 30 patients with pre-operative lymphadenopathies.The final histopathology showed 14 out of 24 patients (58.3%) with metastatic lymphadenopathies (Figure 1). In addition, there were 6 out of 30 patients whereby the ^{18}FDG PET/CT scan was unable to identify pre-operative lymphadenopathies. The final histopathology showed that 2 out of those 6 patients (33.3%) did have metastatic lymphadenopathies, but the PET could not detect them (Figure 2). The imaging of CT showed no demonstrated regional node enlargement (Figure 3). The mean of the SUV in malignant lymphadenopathies (1.18 ± 0.69) together with benign lymphadenopathies (0.59 ± 0.54) in primary colorectal cancer patient had the significant differentiation ($p = 0.014$) which was shown in Table 2. The mean total of malignant lymph nodes found per patient during colorectal surgery was 13 (range 3 - 25).

The correlation between SUV and cell type of primary tumor, we found that there was no significant difference in the statistic between cell types (well, moderately and poorly differentiated) and SUV ($p = 0.304$) (Table 3). There was only one patient whose the final histopathology of primary tumor revealed lymphoma and we did not include this patient's results for the evaluation.

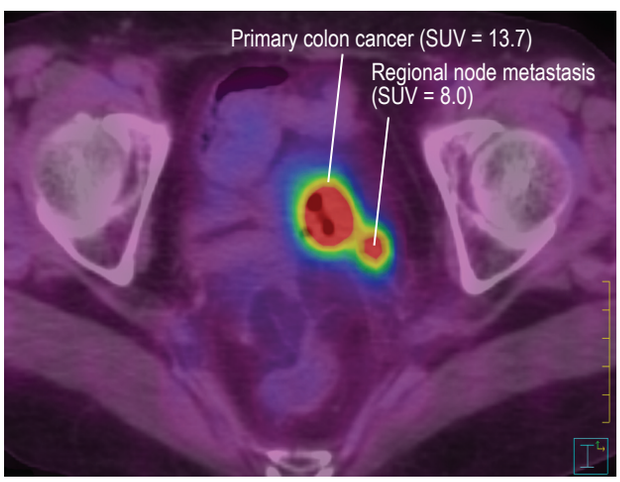

Figure 1 : *True positive PET-CT. This case of primary CA Colon with regional node metastasis SUV 8.0 at right pelvic cavity shows increased uptake.*

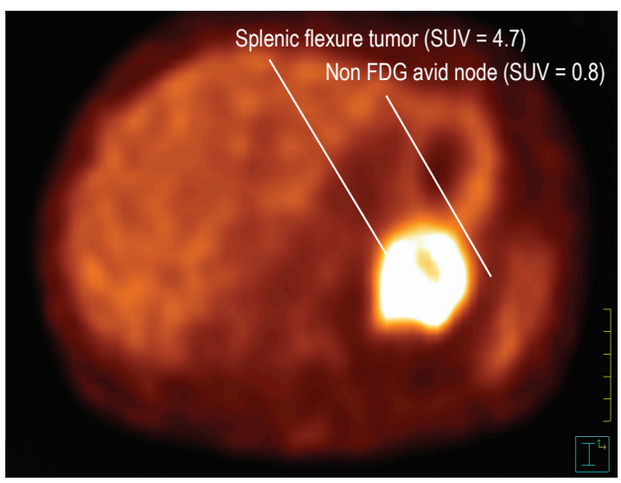

Figure 2 : *False negative PET. This case of primary CA Splenic flexor shows at primary site but regional node has not increased uptake SUV 0.8.*

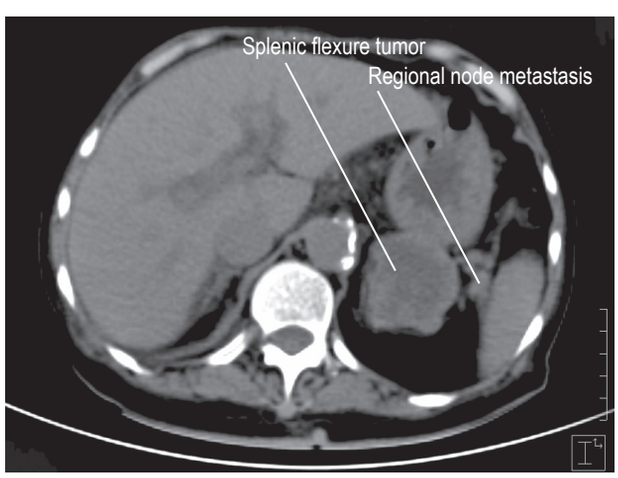

Figure 3 : *False negative CT. This case of primary CA Splenic flexor, only CT study shows no demonstrated regional node enlargement.*

Table 2: Pathological lymph nodes detected by PET/CT.

Characteristic	Malignant LN* (n = 16)	Benign LN* (n = 14)	*p* value
Range SUV	0 - 2.4	0 - 1.8	0.014
Mean ± SD	1.18 ± 0.69	0.59 ± 0.54	

Note_Data was analyzed by Student's t-test ($p < 0.05$)

*LN = Lymph node

Table 3: Comparison of standardized uptake value (SUV) between each cell type of primary tumor.

Characteristic	Pathological diagnosis of each cell type of primary tumor			
	Well differentiated (n = 6)	Moderately differentiated (n = 20)	Poorly differentiated (n = 3)	*p* value
Range SUV	0 - 2.4	0 - 1.8	3.9 - 4.6	0.304
Mean ± SD	1.18 ± 0.69	0.59 ± 0.54	4.2 ± 0.35	

Discussion

The hypothesis is that cancer cells will have a higher glycolysis metabolic rate than normal cells.[5] Given that assumption, using PET scan for ^{18}F-fluorodeoxyglucose (^{18}FDG) detection to count the glucose uptake on the cellular level will help the detection of primary tumors and metastatic lesions. However, different primary tumors have different uptakes of ^{18}FDG. It is believed that important enzymes for glucose uptake in cancer cells are hexokinase and glucose transporters (Gluts), which are located on the cell membrane.[6] Gauthier's study of mitrochondrial hexokinase found that it accounted for 75-80% of total intracellular enzyme activity.[7] Different cell types in colorectal cancer tumors-well, moderate and poorly differentiated - have different enzyme activities, meaning there is a diversity of ^{18}FDG uptake.

Our study however, did not show significant difference of ^{18}FDG uptake between cell type ($p = 0.304$ as shown in Table 3), presumably because of our small sample size. Furthermore, there are many other factors that impact on and account for the variation in ^{18}FDG uptake, which include ^{18}FDG quantity, the time period between ^{18}FDG injections and actual time of PET scan, base line blood sugar before injection of ^{18}FDG, as well as patients' weight and PET scan model used. Other enzyme activities can affect ^{18}FDG uptake, for example glucose phosphatase. Due to the abovementioned factors, it is important to set up the criteria which take these factors into account, in order to reduce the deviation on the ^{18}FDG uptake (SUV) calculation.

Yoshioka's study[8] found that the trend of ^{18}FDG uptake in histological cancer cell line (which is less differentiated in terms of using PET/CT scan to evaluate lymph node metastasis) is close to the primary tumor, if using SUV for the detection. Yoshiyuki also found that there should be more than 1.5 on cut-off point in metastatic lymph node in colorectal cancer.[3] PET/CT scan results in this study, then, also showed the trend of higher uptake of ^{18}FDG in metastatic lymph nodes, compared with non-metastatic lymph nodes. This can be confirmed by the significant result from final histopathology ($p = 0.014$). However, as study was retrospective, it still had the constraint of not being able to exactly confirm that the lymph nodes identified as positive by the ^{18}FDG PET/CT scan, actually matched those lymph nodes detailed in the final histotathology. The size of lymph node is another factor that affects the evaluation of ^{18}FDG PET/CT scan results. It was found that the lymph nodes that may cause metastasis are usually larger than 1 cm.[9, 10]

Conclusion

We show a clear correlation between ^{18}FDG PET/CT diagnoses of suspicious malignancies and final histopathological lymphadenopathies. It is therefore clearly beneficial to further document the pre-operative predictive role of the ^{18}FDG PET/CT scan in diagnosing lymph node metastasis in colorectal cancer patients. One of the constraints of this study, being retrospective, is that we could not confirm the exact correlation between the location of the malignant nodes identified by PET/CT, and those in the final histopathology report.

The pre-operative ^{18}FDG PET/CT scan shows the tendency of malignant lymph nodes to have a higher uptake of FDG than is seen in benign lymph nodes. However, due to our small sample size, the cutoff point of significant SUV could not be exactly calculated. This report will be the basis for further studies in the future.

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