Preoperative Diagnosis of Lymph Node Metastases of Colorectal Cancer by FDG-PET/CT

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Purpose: The purpose of this study was to assess the diagnostic value of 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) for lymph node (LN) metastasis of colorectal cancer.

Methods: FDG-PET/CT was used to preoperatively evaluate 88 patients with colorectal cancer. In this study, LN sites were divided into proximal and distant according to their distance from the primary tumor. The FDG-PET/CT images were evaluated by three criteria; nodal diameter, abnormal uptake and maximum standardized uptake value (SUV). We compared the diagnostic ability of these methods for LN metastasis at proximal and distant sites.

Results: The mean SUV of the malignant LNs was significantly higher than that of the benign LNs. The sensitivity, specificity and accuracy of diagnosis by abnormal uptake were 28.6, 92.9 and 75.0%, those by nodal diameter using cutoff value of 10 mm were 30.6, 95.3 and 74.4% and those by SUV using cutoff value of 1.5 were 53.1, 90.6 and 80.1%, respectively. The sensitivity, specificity and accuracy of diagnosis based on optimal SUV were 51.2, 85.1 and 69.3% in the proximal site and 62.5, 92.5 and 89.7%, respectively, in the distant site.

Conclusions: FDG-PET/CT is useful for preoperative diagnosis of distant LN metastases of colorectal cancers.

Key words: FDG-PET/CT – colorectal cancer – lymph node metastasis

INTRODUCTION

Computed tomography (CT), magnetic resonance imaging (MRI) and endorectal ultrasonography (EUS) are commonly used for preoperative diagnosis of lymph node (LN) metastasis in colorectal cancer. However, many investigators have reported low sensitivity for LN diagnosis using these modalities (1,2) and that is the main reason for being unable to tailor the extent of LN dissection according to the results of these diagnoses.

18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) has been reported to be an effective method of diagnosing malignant disease (3,4). FDG-PET has often been used to diagnose postoperative recurrence (5,6) and distant metastasis (7,8) of colorectal cancer. However, FDG-PET has also been reported to have low sensitivity for the detection of LN metastasis (9,10), and FDG-PET could not determine the anatomical location for small lesions, such as LNs.

In this respect, 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), which combines the use of a full-ring-detector PET scanner and multidetector-row helical CT scanner, has been developed and introduced widely into clinical practice (11,12). To our knowledge, there has been little information reported on the value of FDG-PET/CT preoperative nodal diagnosis in colorectal cancer.

The purpose of this study was to assess the diagnostic value of FDG-PET/CT for LN metastases of colorectal cancer.

PATIENTS AND METHODS

Patients

The subjects of this study were 88 patients diagnosed with primary colorectal cancer between May 2004 and May
FDG-PET/CT

The FDG-PET/CT examinations were performed with a Discovery LS8 (GE Healthcare, Milwaukee, WI, USA). The axial field of view (FOV) is 15.2 cm, and the system produces 35 images with a slice thickness of 4.25 mm using 2D mode. The matrix size is 128 × 128 with a 50 cm transaxial FOV. All patients fasted for at least 6 h before the injection of FDG. The dose of FDG was 370 MBq, and the FDG-PET/CT examination was started 60 min after taking the dose of FDG. First, the CT scan was performed from the base of the skull to the pelvic floor with the following settings: 140 kV, 100–380 mA, 0.6 s per CT rotation, pitch 1.35:1, table rotation 22.5 mm/s, and slice thickness 5.0 mm. A whole-body PET scan was performed immediately after the CT scan was completed. The emission time was set at 4 min per bed position, and a total of six incremental bed positions were scanned. PET images were corrected for attenuation by using the CT data. The PET images were reconstructed by an iterative reconstruction with ordered-subset expectation maximization algorithm (two iterations, 14 subsets) and reformatted into transverse, coronal and sagittal views.

CLASSIFICATION OF LNS

The intra-abdominal LNs were divided into two groups according their anatomical location. The first group consisted of LNs along the vascular arcades of marginal vessels, which were proximal to the primary tumor and will be referred to as proximal group (PG). The second group consisted of LNs along the superior mesenteric artery, inferior mesenteric artery, ileocolic artery, right colic artery, middle colic artery, left colic artery, sigmoid arteries or superior rectal artery and in the para-aortic region and will be referred to as the distant group (DG).

RESULTS

PATHOLOGICAL DIAGNOSIS FOR LN METASTASIS

Surgical resection and regional LN dissection were performed in 88 patients. In 43 patients, malignant LNs were diagnosed by pathological examination in 49 groups of LNs. Of these 49 groups of LNs, 41 were PG and 8 were DG. Six patients had malignant LNs in both PG and DG.
FDG-PET/CT FINDINGS

Table 1 shows rates of malignant LNs according to SUV and nodal diameter in 176 LN groups in 88 patients. LNs < 10 mm in diameter were found in 153 groups, whereas LNs ≥ 10 mm in diameter were in 23 groups. Rates of malignancy were 20.9% (32/153) of LNs < 10 mm in diameter and 73.9% (17/23) of LNs ≥ 10 mm in diameter. Of 153 LNs < 10 mm in diameter, rate of LN metastases were 16.8% (23/137) in 0–1.5 of SUV; 57.1% (4/7) in 1.5–2.5 of SUV; 42.9% (3/7) in 2.5–3.5 of SUV; and 100% (2/2) in more than 3.5 of SUV, respectively. Of 23 LNs ≥ 10 mm in diameter, there were no malignant LNs in 0–1.5 of SUV, and the rates were 60.0% (3/5) in 1.5–2.5 of SUV; 57.1% (4/7) in 2.5–3.5 of SUV; and 100% (10/10) in more than 3.5 of SUV, respectively.

In 43 LNs that were detected, the mean SUV of the malignant LN was 6.3 (range: 1.1–33.8), and the mean SUV of the benign LNs was 2.5 (range: 1.3–3.3). The mean maximum axial diameters of the malignant and benign LNs were 11.6 mm (range: 5.5–25.6 mm) and 9.7 mm (range: 5.0–15.0 mm), respectively. The difference between the SUVs was significant (P = 0.01), however, the difference in maximum axial diameter was not (P = 0.3) (Table 2).

Table 2. Comparison of SUV and nodal diameter between malignant and benign LNs

<table>
<thead>
<tr>
<th>Pathological diagnosis of detected lymph nodes</th>
<th>Malignant LNs (n = 30)</th>
<th>Benign LNs (n = 13)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean SUV</td>
<td>6.3</td>
<td>2.5</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean diameter (mm)</td>
<td>11.6</td>
<td>9.7</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Diagnostic Ability of FDG-PET/CT

The sensitivity, specificity and accuracy by visual diagnosis of FDG-PET/CT images were 28.6, 92.9 and 75.0%, respectively (Table 3). The receiver operating characteristic (ROC) curve analysis is shown in Fig. 1. The best combination between sensitivity and specificity, and thus the highest accuracy to distinguish benign from malignant LNs, was found at an SUV cutoff value of 1.5, and the optimal SUV cutoff value of 1.5 was chosen. At the cutoff value, the sensitivity, specificity and accuracy of SUV diagnosis were 53.1, 90.6 and 80.1%, respectively, and the sensitivity, specificity and accuracy of size diagnosis were 30.6, 95.3 and 74.4%, respectively. SUV diagnosis showed the best result in sensitivity among three methods of diagnosis, and demonstrated about 25% improvement of sensitivity compared to size or visual diagnosis.

Table 4 shows the results of the SUV diagnosis, which were assessed at each LN group. In the PG, the sensitivity, specificity and accuracy of SUV diagnosis were 51.2, 85.1 and 69.3%, respectively, and in the DG, 62.5, 92.5% and 89.7%, respectively. The results in the DG were superior to those in the PG. A representative image with LN metastasis in DG is shown in Fig. 2.

Next, we assessed influence of inflammation on diagnosis by FDG-PET/CT, because we had the impression that a false-positive accumulation of FDG was often seen at the proximal LN group. Figure 3 showed one of the false-positive cases. There was a huge tumor that invaded directly into the urinary bladder with abnormal white blood cell (WBC) counts. We could see the swollen LNs with abnormal uptake of FDG near primary tumor.

When FDG-PET/CT examinations were performed, the mean WBC count and C-reactive protein (CRP) values were 11 225 (range: 7700–14 600) and 3.6 (range: 0.09–8.20) in the four false-positive cases in the PG. In the true-positive
cases, the WBC and CRP values were 6157 (range: 3600–10 800) and 1.1 (range: 0.06–4.3), respectively. The difference in WBC count in both false- and true-positive cases was statistically significant ($P = 0.001$) (Table 5). In patients with normal WBC counts, the diagnostic ability of SUV diagnosis was better than in those with abnormal WBC counts, in terms of specificity (85.1 versus 91.9) and PPV (75.0 versus 85.7) in the PG (Table 6). In the DG, only slightly improvements of specificity and PPV were found.

**DISCUSSION**

The results of this study indicated that FDG-PET/CT was a useful modality for preoperative diagnosis of LN metastases of colorectal cancer. Especially, the superiority was shown in the diagnosis of distant LNs, by using optimized cutoff value of SUV.

We compared the diagnostic abilities for LN metastasis among three methods based on different criteria; abnormal uptake, nodal diameter and SUV. The conventional evaluation of LN metastasis has mainly been based on nodal size. The widely accepted size criterion for LN metastasis by gastrointestinal tumors is ≥10 mm in diameter (13). Monig et al. (14) reported a significant difference in the average size of metastatic and non-metastatic LNs in colon cancer patients, but those up to 90% of the metastatic LNs were <10 mm in diameter, and Herrera-Ornelas et al. (15) reported similar results. The present study also described that malignant LNs were included at rates of 20.9% of LNs <10 mm in diameter. Moreover, in such small LNs, we could catch many malignant LNs by using SUV diagnosis, and in LNs ≥10 mm in diameter, SUV of all malignant LNs was >1.5. These results indicated that size criterion was not reliable in correctly assessing the nodal status.
The presence of abnormal FDG uptake on FDG-PET or FDG-PET/CT images has been widely accepted as a criterion for differentiation between benign and malignant disease. FDG uptake has been evaluated mainly by visual inspection or calculation of the SUV. The value of the SUV has been reported to be affected by the size of the lesion and not to be very accurate in small lesions <15 mm (16), so each investigator has been applied his or her own visual criteria for diagnosis of LN metastasis (17–20). In the present series, although some malignant LNs did not have abnormal uptake, the mean SUV of malignant LNs was significantly higher than that of benign LNs. Consequently, SUV diagnosis yielded more accurate results than the visual or size diagnosis. Diagnosis using SUV could be the most valuable method of assessing FDG uptake objectively to diagnose LN metastasis of colorectal cancer.

In this study, diagnostic ability for metastasis at the distant sites showed better results than that at the proximal sites. FDG-PET/CT provided very low sensitivity at sites near the primary tumor, the same as that reported in

| Table 6. Nodal diagnosis in patients with normal WBC |
|---------------------------------|------------------|------------------|------------------|
|                                | PG               | DG               |
|                                | All cases        | Cases with normal WBC | All cases        | Cases with normal WBC |
| Sensitivity (%)                | 51.2             | 50.0             | 62.5             | 57.1             |
| Specificity (%)                | 85.1             | 91.9             | 92.5             | 93.9             |
| PPV (%)                        | 75.0             | 85.7             | 45.5             | 50.0             |
| NPV (%)                        | 66.7             | 65.4             | 96.1             | 95.4             |
| Accuracy (%)                   | 69.3             | 71.2             | 89.7             | 90.4             |

FPV, positive predictive value; NPV, negative predictive value.

exactly, and SUV showed great benefit in accurately diagnosing LNs in colorectal cancer.

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| Table 5. Differences of WBC count and CRP between patients with true positive LNs and with false positive LNs |
|-------------------------------------------------------------|-------------|-------------|-------------|
|                                                             | True-positive (n = 14) | False-positive (n = 4) | P value |
| Mean WBC (/μl)                                              | 6157        | 11 225      | 0.001      |
| Mean CRP (mg/dl)                                            | 1.1         | 3.6         | 0.2        |

Mean WBC (/μl) 6157 11 225 0.001 6480 7800 0.4
Mean CRP (mg/dl) 1.1 3.6 0.2 1.4 2.8 0.7

WBC, white blood cell; CRP, C-reactive protein.

Figure 3. A 60-year-old man with sigmoid colon cancer that had directly invaded the urinary bladder. The white blood cell count and C-reactive protein value were 14 600 and 4.3, respectively. (A) Computed tomography transaxial image. (B) PET transaxial image. (C) FDG PET/CT transaxial image. LN metastases near the tumor were diagnosed by all three studies, but no LN metastases were demonstrated histologically. This is an example of false-positive results because of an inflammatory reactive change.
previous studies of FDG-PET (9,10). The low sensitivity at the proximal sites in the present study may be explained by LNs near a primary tumor that cannot be distinguished from the tumor or physiological uptake on FDG-PET/CT images.

Inflammatory change by the primary colorectal cancer may have affected the results of our study. In the PG, the mean WBC count in the false-negative cases by SUV diagnosis was significantly higher than in the true-positive cases. The specificity and PPV of SUV diagnosis in the patients with a normal WBC count were better in the PG. No such difference was seen in the DG. This suggests that LNs near a primary tumor with inflammation often appear to have abnormal FDG uptake and are diagnosed as false positive. This is one of the limitations caused by the properties of FDG. FDG is a glucose analog that is taken up into cells by the large number of GLUT-1 transporters located on the cell membrane. Macrophages and neutrophils, whose numbers are increased in inflamed tissue, use glucose as an energy source and have an increased level of FDG uptake, the same as cancer cells. Several new tracers have been developed in recent years as agents to image tumor cells through different and specific aspects of malignant metabolism (21–23).

A sensitivity of 63% and an accuracy of 90% based on SUV-based diagnosis for distant LN are much better than those reported by CT, MRI or PET alone (1,2,9,10). SUV diagnosis in this study improves sensitivity by approximately 20–30% compared to sensitivity that has been reported by other modalities of images. Thus, FDG-PET/CT has a great ability to detect for small malignant lesions. However, this result is not still enough to tailor the range of LN dissection in the surgical treatments of colorectal cancer patients. More studies are needed using other imaging agents to achieve higher sensitivity.

In conclusion, FDG-PET/CT is a powerful tool for detection of distant LN metastases in colorectal cancer patients. SUV is a better criterion for detection of malignant LNs than abnormal FDG uptake or the nodal diameter. On the other hand, the inflammation near primary tumor yields false-positive accumulation of FDG to proximal nodes.

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Conflict of interest statement
None declared.

References

