Positron Emission Tomography with F-18 Fluorodeoxyglucose in Evaluating Colorectal Hepatic Metastasis Down-staged by Chemotherapy

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Abstract. Background: The efficacy of positron emission tomography with ¹⁸F fluoro-2-deoxy-D-glucose (FDG-PET) is obscure in evaluating viability or the extent of colorectal hepatic metastasis (CHM), down-staged by chemotherapy. Patients and Methods: A retrospective lesion-by-lesion analysis was performed for seven consecutive patients, who had received rescue hepatectomy for initially unresectable CHM, in order to evaluate the correlation between results of imaging modalities and the corresponding pathology. Results: The sensitivity and positive predictive value of the conventional modalities (CT and MRI) were 92% and 42%, respectively, while the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were 58%, 100%, 100% and 75% respectively. The sensitivity of FDG-PET was 100% in evaluating the viability of tumors >2 cm, however, this fell to 17% in tumors <2 cm. Conclusion: FDG-PET is effective in assessing the viability of tumors >2 cm, but not those <2 cm, in patients with CHM down-staged by chemotherapy.

Unresectable hepatic metastasis is one of the major obstacles in the treatment of colorectal cancer. Systemic chemotherapy for unresectable colorectal cancer has improved recently with the introduction of new effective agents (1-4). Even so, chemotherapy is rarely curative. Rescue hepatectomy after down-staging by chemotherapy is a potential treatment for unresectable colorectal hepatic metastasis (CHM) (5-8). However, pre-operative evaluation of tumor extent or viability is one of the issues in this strategy. The indication for rescue hepatectomy is based on the interpretation of the imaging of tumor extent or viability after down-staging by chemotherapy, however, evaluating the viability of hepatic tumors treated with chemotherapy is sometimes difficult by conventional imaging methods, such as computed tomography (CT) or magnetic resonance imaging (MRI), especially when the tumors have shrunk remarkably or exhibit notable calcification, after chemotherapy. Therefore, an effective diagnostic imaging modality to evaluate the viability of hepatic tumors after chemotherapy is needed.

Positron emission tomography with ¹⁸F fluoro-2-deoxy-D-glucose (FDG-PET) is a functional imaging technique based on the increased utilization of glucose by tumor cells, and is effective for staging colorectal cancer (9, 10). Furthermore, the ability of FDG-PET to assess the pathological response to chemotherapy has been suggested in various malignant tumors (11-15). The correlation in CHM between FDG-PET findings and those of corresponding pathology has not been fully examined.

The present study was conducted to examine whether FDG-PET was able to assess tumor viability, before rescue surgery, for initially unresectable CHMs down-staged by chemotherapy and indicate which tumors should be resected.

Patients and Methods

Patient population. Seventy-four patients underwent hepatic resection for CHM at the National Cancer Center Hospital East, Japan, between January 2004 and July 2005, and 10 out of these underwent hepatic resection, after down-staging by chemotherapy. Since January 2004, all patients about to undergo rescue surgery are examined using FDG-PET pre-operatively, when informed consent is granted. Consequently, seven consecutive patients, who had been examined by CT, MRI and FDG-PET, were included in the present study. The patients were four men and three women, ranging from 44 to 70 years old. The location of the primary colorectal tumor was the colon in five patients and the rectum in two patients. All the
primary tumors were well- or moderately-differentiated adenocarcinomas. The primary tumors were staged as II (n=2), III (n=2), and IV (n=3) according to the TNM classification.

Chemotherapy. The reasons for choosing chemotherapy instead of curative resection, initially, were multiple bilobar tumors in five patients, invasion to the bilateral bile ducts and portal veins in one and invasion to the 3 major hepatic veins in one. The chemotherapies performed for the unresectable tumors were 5-fluorouracil-leucovorin combined with irinotecan in four patients, 5-fluorouracil-leucovorin alone in one, oral uracil/tegafur in one and capectabine in one. Five patients experienced a partial response and two patients had stable disease, based on the Response Evaluation Criteria in Solid Tumors.

Conventional imaging (CT, MRI). All patients underwent contrast-enhanced CT and MRI before hepatectomy. Multi slice CT with 16 DAS was used for this study (Aquillion, Toshiba Medical Systems, Japan). CT images were obtained using 5 mm collimation after administration of 100 ml of nonionic iodine intravenous contrast medium injected at 3 ml/sec with a 70-sec delay (portal-dominant phase). Images were reconstructed at 5 mm intervals using a standard soft-tissue algorithm.

MR images were acquired using a 1.5-T MR imager (Gyroscaon Intera, Philips Medical Systems, Netherlands) with a phased array coil. A section thickness of 7 mm with a 1 mm gap was used for all sequences. T1-weighted fast field-echo image, T2-weighted fast spin-echo image and diffusion-weighted image with b factor 500 sec/mm² were performed. After gadodiamide injection, T1-weighted fast field-echo dynamic image were also obtained during the hepatic arterial, portal venous and delayed phases.

FDG-PET. Whole body FDG-PET was performed in five patients using a GE Advance Scanner (General Electric Medical System, Milwaukee, WI, USA), which has an axial field of view of 15 cm and a spatial resolution of 4.5 mm full-width-half-maximum. All patients fasted for at least 4 h prior to scanning. Sixty min after intravenous injection of 300 MBq of F18-FDG, emission scanning was performed in 5 min and transmission scanning in 1 min. Data acquisition was performed in 7 bed positions.

In the remaining two patients, PET/CT scanning was performed using a Discovery LS PET/CT system (General Electric Medical Systems, Waukesha, WI, USA) because our PET system had been replaced by PET/CT. The CT component was performed using a multi-detector scanner. The parameters were 140 kV, 80 Ma, 0.8 s/CT rotation, a pitch of 6, and a table speed of 22.5 mm/s. Scans were acquired from the skull base to mid-thigh level, in 7 bed positions, with a total acquisition time of 31.9 sec to 37 sec. CT data was resized from a 512x512 matrix to a 128x128 matrix to match the PET data, to allow for image fusion and generation of CT transmission maps. The PET data were also acquired in the same anatomic positions; in 7 bed positions at 5 min per position.

All PET studies were performed at least 4 weeks after completion of chemotherapy.

Rescue hepatectomy. At the National Cancer Center Hospital East, Japan, all lesions considered positive for malignancy, by any pre-operative diagnostic imaging evaluation, were resected by rescue hepatectomy. During this operation, all the tiny suspicious lesions that were definitive metastases before chemotherapy were resected.

In our patients, a careful search was performed after laparotomy for local recurrence, extrahepatic metastases and peritoneal dissemination in the abdominal cavity. Any suspicious lesions were examined by biopsy. Intra-operative bimanual liver palpation and ultrasonography were performed to confirm tumor location and size, in all seven patients and all of the resections were ultrasound-guided procedures. Hepatic resection was performed with tumor-free resection margins, by the forceps fracture method, under inflow occlusion (Pringle’s maneuver). When small lesions that had been detected by pre-operative imaging could not be recognized by either palpation or intra-operative ultrasonography, the estimated part or segment of the liver occupied by the lesions was resected.

Extended lobectomy and multiple partial resections were performed on two patients each, and central bisegmentectomy, lobectomy, and segmentectomy were performed on one patient each, according to Couinaud’s anatomical classification.

Assessment of tumor viability with FDG-PET. In our hospital, when interpreting conventional CT and MRI findings, any hepatic lesions are classified according to the degree of confidence that a metastatic tumor is present, as follows: definitely present, probably present, possibly present, probably absent and definitely absent. Lesions that fall into the definitely present, probably present and possibly present categories are considered positive for malignancy, while lesions that fall into the other categories are considered negative. Lesions which are positive, by either CT or MRI, are considered positive by conventional examination.

In the present study, the category "possibly present" included the small lesions, detected using conventional imaging, that were used to indicate definitive metastasis, but which then could not be determined as viable or otherwise, due to a reduction in size or remarkable calcification after chemotherapy (Figure 1).

All lesions considered positive by conventional examination were compared with their corresponding pathology findings, as the standard reference and the sensitivity and positive predictive value were then calculated. Furthermore, these lesions were also assessed by FDG-PET according to the degree of confidence of malignancy, i.e. definitely present, probably present, possibly present, probably absent, and definitely absent. A discrete focus with increased FDG accumulation, markedly greater than that in the hepatic parenchyma, was interpreted as malignancy, being definitely present or probably present. Focally increased FDG uptake, minimally greater than in the liver, was considered possibly positive for malignancy, but heterogeneous uptake in the hepatic parenchyma without a focal lesion was considered to indicate that malignancy was probably absent. Lesions in the definitely present, probably present and possibly present categories were considered positive for malignancy, while those in the probably absent and definitely absent categories were considered negative.

FDG-PET findings were also compared with the pathology findings, as the reference, and then sensitivity, specificity, positive predictive value and negative predictive value were calculated according to tumor size: <2 cm and ≥2 cm.

Finally, the sensitivities, specificities, positive predictive values and negative predictive values were compared between the subgroups according to tumor size. The results of each imaging test were interpreted by at least two experienced radiologists.

Pathological examination. The resected hepatic specimens were fixed in 10% phosphate-buffered formalin, sliced at 5 mm intervals and embedded in paraffin. The findings of all lesions, considered positive
by any diagnostic imaging or intra-operative examination, were confirmed macroscopically and the lesions were then examined microscopically to evaluate viability. Serial sections 3 µm thick were stained with hematoxylin and eosin (H&E) for morphological examination. Histological diagnoses were based on the World Health Organization classification (16).

Statistical analysis. \( \chi^2 \) analysis was used to assess sensitivity, specificity, positive predictive value and negative predictive value between subgroups according to tumor size. A \( p \)-value of less than 0.05 was considered to denote statistical significance.

Results

In the seven patients with CHMs down-staged by chemotherapy, 27 lesions were resected, all of which were considered positive for malignancy by pre-operative diagnostic imaging or intra-operative examination. Among the 27 lesions, 26 were deemed positive by at least one imaging modality, while the other could not be evaluated using imaging and was diagnosed by intra-operative examination. Twelve lesions were histologically diagnosed as adenocarcinoma, but no malignancies were demonstrated in the remaining 15 lesions.

CT and MRI led to 26 lesions being diagnosed as malignant, while only 7 of these 26 lesions were considered positive by FDG-PET (Figure 2). No lesion was positive only by FDG-PET.

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<tr>
<th>Pathological findings</th>
<th>Imaging finding</th>
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<td></td>
<td>Malignancy (12)</td>
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<td>CT and MR Imaging</td>
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<tr>
<td>Positive (26)</td>
<td>11</td>
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<td>Negative (1)</td>
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<td>FDG-PET</td>
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<td>Positive (7)</td>
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<td>Negative (20)</td>
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The interpretations of the conventional (CT/MRI) findings and FDG-PET findings were compared with the results of pathology in Table I. The sensitivity and positive predictive value of the conventional modalities were 92% (95% CI=0.73-1.00) and 42% (0.22-0.63), respectively, while the sensitivity, specificity, positive predictive value and negative predictive value of FDG-PET were 58% (95% CI=0.26-0.91), 100% (1.00-1.00), 100% (1.00-1.00) and 75% (0.54-0.96), respectively.

An assessment of the accuracy of conventional imaging and FDG-PET, according to tumor size (Table II), revealed that interpretation of the conventional findings and FDG-PET was highly accurate in lesions >2 cm. However, in lesions <2 cm, the positive predictive value for conventional imaging was only 26%, while the sensitivity for FDG-PET was only 17%, both of which were significantly lower than in lesions >2 cm. The specificity and negative predictive value of conventional imaging were not calculated, because lesions negative by both CT and MRI, were not resected, except for one which was diagnosed as positive by intra-operative examination. The viability of the 27 tumors could not be determined by any cut-off value of tumor-size (data not shown).

**Discussion**

We assessed the efficacy of FDG-PET in evaluating the tumor viability of CHM down-staged by chemotherapy, before rescue surgery. Our results indicate that FDG-PET is only effective in assessing the viability of hepatic lesions >2 cm after chemotherapy.
The ability to use FDG-PET to assess the pathological tumor response to pre-operative chemotherapy, radiation or other treatment has been suggested in several tumors (11-15). In addition, correlation between decreased uptake in FDG-PET and histopathological response in the resected specimen was observed in patients, who underwent pre-operative chemotherapy or chemoradiotherapy for esophageal squamous cell carcinoma (17, 18), rectal cancer (19) and gastric carcinoma (20). However, the correlation between uptake in FDG-PET and the corresponding pathological findings has not been studied fully in CHM.

In the present study, portal phase helical CT and MRI were used as the conventional modalities. In our institution, diagnosis based on either, is routinely performed before hepatic resection for CHM, because portal phase helical CT has shown excellent sensitivity in detecting CHM and is considered as the standard pre-operative examination for CHM (21-23). Furthermore, SPIO-enhanced MRI and diffusion-weighted sensitivity encoding MRI have demonstrated high sensitivity equal to that of portal phase helical CT, and have excellent specificity in detecting CHM (24-26).

The present lesion-by-lesion analysis demonstrated that only 11 out of the 26 lesions that had pathological malignancy, considered positive for malignancy by conventional imaging. In the conventional examinations, the sensitivity of 92% for detecting hepatic viable CHMs was similar to that in the aforementioned studies, but the positive predictive value in tumors <2 cm was only 26%. Thus, CT and MRI were able to detect even small tumors, but could hardly evaluate the viability of small tumors after down-staging by chemotherapy.

On the other hand, FDG-PET showed excellent specificity (100%) and positive predictive value (100%), irrespective of tumor size. In tumors >2 cm, the sensitivity and negative predictive value for FDG-PET were both 100%. However, in tumors <2 cm, sensitivity was extremely low (17%). Thus, many of the tumors that shrunk to <2 cm by chemotherapy were undetectable by FDG-PET.

The reasons for this low sensitivity of FDG-PET in tumors <2 cm may be low spatial resolution, the partial volume effect and decreased FDG uptake in tumor tissue, after chemotherapy. Several groups reported that the sensitivity of FDG-PET for CHM was related to tumor size (27, 28). Lower sensitivity to smaller tumors was shown to be caused by the relatively low spatial resolution of FDG-PET and decreased measured activity concentration owing to the partial volume effect (29, 30). The partial volume effect reduces the measured activity concentration to a greater extent in smaller tumors.

Low sensitivity in FDG-PET has also been ascribed to the effects of chemotherapy itself. Chemotherapy may alter FDG uptake in two ways. First, the chemotherapy may reduce FDG uptake, by causing functional changes in tumor glucose metabolism. Spaepen et al. demonstrated that changes in tumor glucose metabolism occurred rapidly after chemotherapy, as demonstrated using transplants of Daudi cells in SCID mice (31). Second, a decrease in viable cells by necrosis or apoptosis induced by chemotherapy may diminish FDG uptake in the tumor. Swisher et al. studied the correlation between the percentage of residual tumor and standardized uptake value (SUV) of FDG-PET after pre-operative chemoradiation in patients with esophageal cancer (18). They found that patients with >50% histological tumor viability had a significantly higher average SUV compared with those with <50% histological tumor viability. However, the SUV of tumors with no viability was similar to that of tumors with 10-50% tumor viability. Accordingly, when chemotherapy shows excellent efficacy in CHMs, it is extremely difficult to detect the resulting low FDG uptake by PET.

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<th>Table II. Accuracies of CT, MRI, and FDG-PET in evaluation of tumor viability according to tumor size.</th>
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<td>Sensitivity (%)</td>
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<tr>
<td>CT, MRI tumor size</td>
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<td>&lt;2 cm</td>
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<td>≥2 cm</td>
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<tr>
<td>FDG-PET tumor size</td>
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<td>&lt;2 cm</td>
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<td>≥2 cm</td>
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Numbers in parentheses are the data used to determine the percentages and the 95% confidence intervals. *Difference between positive predictive value of CT and MRI in tumor <2 cm and that in tumor ≥2 cm. †Difference between sensitivity of FDG-PET in tumor <2 cm and that in tumor ≥2 cm.
Our results suggest that the viability of small tumors that have been down-staged by chemotherapy can hardly be evaluated by CT, MRI or FDG-PET. Thus, at the moment, lesions considered positive by either CT or MRI should be treated by surgical resection in order to avoid leaving viable metastases in the residual liver. When surgical resection is not suitable for the specific lesion, perhaps due the small amount of residual liver, locoregional therapy, such as radiofrequency ablation or cryosurgery may become the preferred treatment options (6, 7).

The present study has nevertheless some limitations. The number of subjects in our study was relatively small, although the results have significant implications for rescue surgery for CHMs after chemotherapy. Furthermore, only two of the seven patients underwent PET/CT. The recent introduction of combined FDG-PET and CT has improved imaging accuracy by allowing accurate anatomical localization of FDG uptake. The sensitivity of PET/CT may be superior to that of FDG-PET for the detection of viable CHMs after chemotherapy. However, a major improvement in sensitivity is not expected, because the fundamental problem of detecting small viable tumors in PET is not resolved even using PET/CT.

New functional imaging with higher sensitivity for detecting small viable tumors is necessary to improve rescue surgery for CHM.

FDG-PET can be used to accurately assess the viability of CHMs >2 cm, before rescue surgery for initially unresectable CHMs down-staged by chemotherapy, but cannot be used for hepatic tumors <2 cm, because of the extremely low sensitivity of FDG-PET for such tumors.

Acknowledgements

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References


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