PET scanning is not superior to whole-body multi-detector helical computed tomography in the preoperative staging of colorectal cancer

Hiroyoshi Furukawa, Hiroki Ikuma, Akihiko Seki, Koiku Yokoe, Sachiko Yuen, Takeshi Aramaki, and Shigeki Yamaguchi

Hiroyoshi Furukawa, Hiroki Ikuma, Akihiko Seki, Koiku Yokoe, Sachiko Yuen, Takeshi Aramaki, Division of diagnostic radiology,
Shigeki Yamagushi, Division of colorectal surgery.
Shizuoka Cancer Center Hospital,
1007, Nagaizumi-cho, Suntogun, Shizuoka, 411-8777, Japan.
E-mail: H Furukawa, h.furukawa@scchr.jp (corresponding author); H Ikuma, h.ikuma@scchr.jp; A Seki, a.seki@scchr.jp; K Yokoe, k.yokoe@scchr.jp; S Yuen, s.yuen@scchr.jp; T Aramaki, t.aramaki@scchr.jp; S Yamaguchi, s.yamaguchi@scchr.jp

Key words: positron emission tomography, colorectal surgery, spiral computed tomography, colorectal neoplasms, neoplasm staging

Abstract

Background: The role of positron emission tomography with glucose analog [18F] fluoro-2-deoxy-D-glucose (FDG-PET) in the initial staging of disease in patients with primary CRC has not been adequately assessed.

Aims: To evaluate the additional value of FDG-PET as a staging modality complementary to routine multidetector-row computed tomography (MDCT) in patients with CRC.

Methods: Forty-four patients with CRC underwent preoperative MDCT and FDG-PET. The accuracy of intraoperative macroscopic staging was also investigated compared with histopathological diagnosis. All FDG-PET images were evaluated with respect to detectability of primary tumour, lymph node involvement, and distant metastases. Both MDCT and FDG-PET diagnoses and treatment plan were compared with followed surgical and histopathological results.

Results: Thirty-seven patients underwent surgery. The tumour detection rate was 95% (42/44) in MDCT, 100% (44/44) in FDG-PET, and 100% (37/37) in intraoperative macroscopic diagnosis. Pathological diagnosis of T factor was T1 in 5, T2 in 4, T3 in 24, and T4 in 4. The concordance rate with the pathologic findings of T factor was 57% (21/37) in MDCT and 62% (23/37) in macroscopic diagnosis. Lymph node involvement was pathologically positive in 19 cases. Regarding N factor, the overall accuracy was 62% (23/37) in MDCT, 59% (22/37) in FDG-PET, and 70% (26/37) in macroscopic diagnosis. Of all 44 patients, FDG-PET findings resulted in treatment changes in only one (2%) patient.

Conclusion: FDG-PET is not superior to routine MDCT in the initial staging of primary CRC.

Introduction

Colorectal cancer is an important cause of morbidity and mortality in Japan as well as other countries.[1] The prognosis of CRC directly relates to extramural tumour spread, the ability to achieve surgical clearance, and the presence of lymph node and distant metastases.[2][3] The optimal management of individual patients requires detailed assessment of the locoregional and distant extent of disease.

Conventional preoperative staging of CRC has been abdominal computed tomography (CT) and chest radiography to rule out liver, lung or lymph node metastases and invasion to the surrounding organs, respectively. The introduction of multidetector-row CT (MDCT) provides high resolution imaging and shortens the examination time.[4] This becomes an effective diagnostic technique in the evaluation of preoperative staging of CRC.

Positron emission tomography with glucose analog [18F] fluoro-2-deoxy-D-glucose (FDG-PET) is a sensitive diagnostic test that images tumours based on the increased utilization of glucose by tumour cells.[5][6] FDG-PET has been demonstrated to be more sensitive than conventional imaging in the detection of recurrent or metastatic CRC.[7][8][9][10][11][12][13] One meta-analysis revealed an overall sensitivity of 97% and an overall specificity of 76% for FDG-PET in detecting recurrent CRC.[14]

However, reports of FDG-PET dealing with the staging of primary CRC were few.[15][16] [17] [18] But in these reports had some limitation; patient numbers were small[15][16] or diagnostic accuracy of FDG-PET was compared with conventional abdominal CT[17] or CT performed at different hospital.[18] A comparison of state-of-art FDG-PET with CT using variable techniques and qualities is not meaningful. Thus, the role of FDG-PET in the initial staging of disease in patients with primary CRC has not yet been fully and fairly investigated.[19]

The purpose of this study was to prospectively evaluate the additional value of

FDG-PET as a staging modality complementary to routine MDCT in patients with primary CRC. In patients receiving surgery, the accuracy of intraoperative macroscopic staging was also investigated compared with histopathological diagnosis, as well as those of preoperative imagings. All studies were performed in a single Japanese hospital.

Methods

Patients

Between September 2002 and January 2004, 44 consecutive patients with CRC who

approved of this study were enrolled after giving written informed consent in accordance with the regulations of the institutional review board. There were 33 men and 11 women with a mean age of 61.4 years (range 38-82). The primary tumour originated from the right colon (n=2), sigmoid colon (n=4), or rectum (n=38). Histological diagnosis was performed in all patients by colonoscopy. All patients underwent preoperative MDCT and FDG-PET within 1 month (median 9 days, range 0-26).

MDCT

The diagnosis and location were established by barium enema and/or colonoscopy before CT scanning. The time interval between barium enema and/or colonoscopy and MDCT was within 1 week. No specific preparation, such as laxative, enema, or oral contrast agent, was performed before MDCT examination.

We used an Aquiline 16 CT scanner (Toshiba medical systems, Tokyo, Japan). For imaging the whole body, we used the 16 high-resolution central detectors. From these detectors we selected a 2 mm slice thickness and reconstructed the data at 5 mm intervals. The other parameters were a 0.5 second helical rotation time, 135 kVp, and 300 mAs. One hundred milliliters of iopamidol (Iopamiron; Nihon Schering, Tokyo, Japan) was administered through a peripheral venous line at 3 ml/sec using a power injector (Autoenhance A-50; Nemoto Kyorindo, Tokyo, Japan). The CT scanning began 120 seconds after the start of injection of the contrast medium and scan data were acquired from the neck to the upper femur within one breath hold in approximately 20 seconds. Multiplanar reformation was reconstructed by a freestanding workstation (ZAIO, Tokyo, Japan) if diagnostic radiologists considered it necessary.

FDG-PET

Patients fasted for at least 4 hrs before the examination. Patients received an intravenous injection of 200 to 250 MBq of [18F] fluoro-2-deoxy-D-glucose and then rested for approximately 60 minutes before undergoing imaging. Image acquisition was performed with use of an Advance NXi (GE Medical System). Two-dimensional emission scanning from the groin to the base of the skull (6-7 bed positions) was performed, lasting 5 min per bed position, in combination with a transmission scan lasting 1.5 min per bed position (transmission scanning time was corrected to allow for decay of the transmission sources). The data acquired were reconstructed by iterative ordered-subsets expectation maximization (21 subsets, 2 iterations).

Image analysis

At first, MDCT images were prospectively evaluated by two radiology physicians in consensus. They were assessed for detectability of the tumour, depth of tumour infiltration (T factor), regional lymph node involvement (N factor), and distant metastasis (M factor).

T factor on MDCT was defined by a modified TNM stage: tumour confined to the bowel wall was classified as T1 or T2. T1 was defined as an intraluminal elevated mass without thickening of the bowel wall. T2 was defined as thickening of the bowel wall (>5mm) without invasion into the surrounding tissue. Tumour exposed out of the bowel wall but no extension to the surrounding organs was considered as T3. Tumour infiltration into adjacent organs was considered T4. Lymph nodes were considered positive when the short axis was greater than 1cm in diameter or clusters of three or more smaller nodes (each <1 cm). Lesions in the liver not characteristic of a cyst or hemangioma were considered suspicious of metastases. Also in the lung, pulmonary nodules without calcification were suspicious of metastases.

All FDG-PET images were interpreted with knowledge of patient's medical history and the MDCT findings, and were evaluated with respect to detectability of primary tumour, lymph node involvement, and distant metastases by two nuclear-radiology physicians. T factor was not evaluated because the layers of intestinal wall and neighboring structures can not be differentiated on FDG-PET. Uptake higher than background was considered to be increased. The physicians interpreted the FDG-PET images by visually correlating the FDG-PET and MDCT images.(Fig.1) This approach was chosen because it represents the routine practice of combined reading of FDG-PET and MDCT images in our hospital. On the basis of their visual correlation, the physicians assigned a TNM stage on FDG-PET. Regarding N factor, we chose to analyze the imaging studies on a nodal station bases and not on an individual lymph node basis. It seemed impossible for us to make a precise correlation between individually sampled and mapped lymph nodes on imaging studies.

Decision of preoperative staging

Both MDCT and FDG-PET results were presented at the colorectal cancer conference consisting of surgeons, medical oncologists, endoscopists, nuclear-radiology physicians, and radiation oncologists. All conference members confirmed the MDCT and FDG-PET findings. When a clear differentiation between different tumour stages on MDCT and FDG-PET was not possible, both stages were noted and confirmed after surgery. According to the consensus of the conference, the patients were divided into 2 groups.

Patients considered as unresectable were referred to division of gastrointestinal medical oncology, where chemotherapy, chemo-radiotherapy, or best supportive care was performed. If unresectable factors were negative, the patient was admitted to a surgical ward and curative resection was attempted. In our hospital, neoadjuvant therapy was not routinely performed. These decisions of diagnosis and treatment plan were recorded and compared with surgical and pathological results.

Macroscopic diagnosis

For the 37 patients who proceeded to surgery, the detection of the primary tumour, its depth of invasion, lymph node status, and liver metastases were macroscopically diagnosed either during surgery or through a node collection-and-classification procedure immediately after resection. These procedures were performed with knowledge of the preoperative imaging findings.

Data analysis

Resected specimens were examined by pathologists without knowing the preoperative MDCT and FDG-PET findings. The diagnostic accuracy of MDCT, FDG-PET, and macroscopic diagnosis of T and N factors were assessed using the histopathologic findings as the gold standard. Comparison of diagnostic and pathological parameters was performed using McNemar test. The level of statistical significance was determined at 5% in all cases.

Results

All 44 patients tolerated both MDCT and FDG-PET examinations without any complications. According to both MDCT and FDG-PET, 10 lesions of distant metastases were revealed in 5 patients and defined as unresectable: 3 bone metastases, 3 lung metastases, 2 liver metastases, and 2 distant lymph node metastases. MDCT showed 8 of 10 lesions and one of each of bone and distant lymph node metastasis were missed. FDG-PET showed 9 of 10 lesions and one lung metastasis was missed. These 5 patients did not receive surgical resection. Two patients were refused any anti-cancer treatment and left our hospital, although their tumours were potentially resectable. Thus, the remaining 37 patients were defined as resectable and received surgery. As expected, all lesions were resected with regional lymph node dissection.

The tumour detection rate was 95% in MDCT, 100% in FDG-PET, and 100% in intraoperative macroscopic diagnosis. The two cases which were not detected on MDCT were 0.7 and 1.8 cm adenocarcinomas, both limited to the submucosal layer.

Regarding T factor, the concordance rate with the pathologic findings was 57% in MDCT and 62% in macroscopic diagnosis (Table 1). The difference was not significant (p=0.813). In 3 of 7 cases, tumours were diagnosed as T4 in surgery, but histopathologically with no evidence of the invasion to the adjacent organ. In contrast, in one case, MDCT showed no evidence of invasion to the adjacent organ, but the tumour was found to have invaded to the vagina at surgery and combined resection was performed. The invasion was histopathologically confirmed.

Table 1 Comparisons of MDCT and macroscopic diagnosis in staging depth of tumor invasion with colorectal carcinoma.

Pathologic	MDCT diagnosis					Macroscopic diagnosis			
staging	Tx	T1	T2	T3	T4	T1	T2	T3	T4
T1	2	0	2	1	0	1	4	0	0
T2	0	0	1	3	0	1	0	3	0
T3	0	0	5	17	2	0	3	18	3
T4	0	0	0	1	3	0	0	0	4

MDCT=multidetector-row computed tomography

Regarding N factor, the overall accuracy was 62% in MDCT, 59% in FDG-PET, and 70% in macroscopic diagnosis (Table 2). The sensitivity, specificity, positive predictive value, and negative predictive value were calculated as 58%, 67%, 65%, and 60%, respectively, in MDCT; 37%, 83%, 70%, and 43%, respectively, in FDG-PET; and 68%, 72%, 72%, and 68%, respectively, in macroscopic diagnosis. Macroscopic diagnosis showed a slightly higher accuracy, but the values were not significantly different between these modalities (p=0.624 in MDCT vs. macroscopic diagnosis, p=0.466 in FDG-PET vs. macroscopic diagnosis).

Table 2 Comparisons of MDCT, PET, and macroscopic diagnosis in staging lymph node metastasis with colorectal carcinoma.

	Sensitivity(%)	Specificity(%)	Positive predictive value(%)	Negative predictive value(%)	Accuracy(%)
MDCT	58(11/19)	67(12/18)	65(11/17)	60(12/20)	62(23/37)
PET	37(7/19)	83(15/18)	70(7/10)	43(15/27)	59(22/37)
Macroscopic diagnosis	68(13/19)	72(13/18)	72(13/18)	68(13/19)	70(26/37)

MDCT=multidetector-row computed tomography; PET=positron emission tomography

Of all 44 patients, FDG-PET findings resulted in treatment changes in only one (2%) patient, who had bone and distant lymph node metastases detected only by FDG-PET. Although MDCT detected lung metastases that were not demonstrated on FDG-PET in one patient, the patient had other distant metastases and treatment plan was not influence by MDCT findings.

Discussion

CT examination is an established method in staging of colorectal carcinoma. But recent studies showed low accuracy rates due considerably to low sensitivity for detection of lymph node metastases and to local tumour extension.[20][21][22][23] MDCT is expected to improve the diagnostic accuracy to scan the wide range of region with a better resolution. To evaluate the usefulness of FDG-PET, we compared the diagnostic accuracy of FDG-PET to that of this up-to-date technology.

The utility of imaging techniques is usually evaluated by radiologists' retrospective reading blinded to the clinical information. However, this is not a practical situation and many physicians often feel that actual diagnostic results are different from the results reported. We intended to evaluate the usefulness of FDG-PET in clinical setting. Recently, integrated PET-CT scanners have been introduced into the clinical situation.[24] In this technique, PET, CT, and integrated PET-CT images are displayed together on the monitor. This type of PET scanner and reading style will become routine. Thus, in this study, FDG-PET images were interpreted with knowledge of patient's medical history and the MDCT images.

For detection of a primary tumour, FDG-PET was positive in all 44 lesions but MDCT had 2 false negative lesions. We did not perform any preparation before MDCT studies. If sufflation of air or water into the bowel cavity and administration of anti-peristaltic drug were carried out, the detection rate might be improved. Whereas, FDG-PET was positive in all lesions including MDCT negative ones. Such high sensitivity confirms the results of previous reports.[15][16][17] The injected activity we used was lower than the conventional dose reported. But we confirmed that the image quality of this dose was not deteriorated in our preliminary study. We suppose that it is chiefly due to the difference of physique between Japanese and western. We should try to reduce the radiation exposure preserving the diagnostic accuracy.

CT studies from the last decade showed accuracy rates of 41-82% in T staging.[20][21][22][23] Our result of 57% was compared with that of these reports. Even with improved imaging resolution of MDCT, it is still difficult to discriminate bowel wall layers as conventional single detector spiral CT. MDCT did not demonstrate satisfactory results for diagnosis of N factor as reported in the previous studies.[25][26][27] Microscopic metastasis or uninvolved swelling of lymph nodes results in misdiagnosis. As long as diagnosis is made based on the size of lymph nodes, a certain percentage of false positive and negative lymph nodes are not inherently avoidable. In this study, FDG-PET had low sensitivity (37%) and high specificity (83%) as reported in the previous studies.[16][17][18] It was no better than MDCT. The high false-negative rate was attributed to limited spatial resolution which was disadvantage for detecting micrometastases and the dose proximity of the primary tumour to the lymph node metastases.

Accuracy of intraoperative macroscopic diagnosis was superior but not statistically significant to that of MDCT and FDG-PET. By palpation and inspection, lymph nodes in the immediate vicinity of the primary tumour could be differentiated easier than by MDCT and FDG-PET. Moreover, macroscopic diagnosis was made with information of MDCT and FDG-PET. Nevertheless, accurate diagnosis of lymph node metastasis is difficult even at surgery.

FDG-PET has had the advantage of studying the whole body at one examination and synchronous tumours have been identified on FDG-PET. But MDCT can also scan the whole body in a shorter time than FDG-PET needs. In this study, distant metastases were revealed only 10 lesions in 5 patients. While patient's number was too small to compare the usefulness of diagnostic modalities, MDCT and FDG-PET showed various metastatic lesions complementary.

In assessing the influence of FDG-PET findings on clinical management, we

found only 2% (1/44) of changes in therapeutic decision making, which was fewer than other investigators. The incidence of management alterations due to FDG-PET was reported as 16-50%.[8][13][18][28][29] The reason might be the selection of patients in the other studies, because many of other patients had already been known to have advanced disease and FDG-PET was performed to detect the recurrences or metastases.

According to the results of this study, the diagnostic accuracy of FDG-PET for the initial staging of CRC did not overcome that of routine MDCT and was not influential with patient's management. We think routine evaluation of patients suspicious of CRC by FDG-PET is not necessary; it should be performed on selected patients who have a suggestive but unconclusive metastatic lesion by other modalities.

Acknowledgements

This work was supported by Foundation for Promotion of Cancer Research in Japan.

Competing interests: None declared.

References

1 Nomura K, Sobue T, Honma I, et al. Mortality from malignant neoplasms by age group and sex in Japan. In: The editorial board of the cancer statistics in Japan. Cancer statistics in Japan 2003. Tokyo: Foundation for promotion of cancer research, 2003:40-1.

2 Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994;344:707-11.

3 de Haas-Kock DF, Baeten CG, Jager JJ, et al. Prognostic significance of radial margins of clearance of rectal cancer. Br J Surg 1996;83:781-5.

4 Hu H, He HD, Foley WD, et al. Four multidetector-row helical CT: image quality and volume coverage speed. Radiology 2000;215:55-62.

5 Som P, Atkins HL, Bandoypadhyay D, et al. A fluorinated glucose analog, 2-fluoro-2-deoxy-D-glucose (F-18): nontoxic tracer for rapid tumor detection. J Nucl Med 1980;21:670-5.

6 Flier JS, Mueckler MM, Usher P, et al. Elevated levels of glucose transport and transporter messenger RNA are induced by ras or src oncogenes. Science 1987;235:1492-5.

7 Topal B, Flamen P, Aerts R, et al. Clinical value of whole-body emission tomography in potentially curable colorectal liver metastases. Eur J Surg Oncol 2001;27:175-9.

8 Arulampalam T, Costa D, Visvikis D, et al. The impact of FDG-PET on the management algorithm for recurrent colorectal cancer. Eur J Nucl Med 2001;28:1758-65.

9 Delbeke D, Vitola JV, Sandler MP, et al. Staging recurrent metastatic colorectal carcinoma with PET. J Nucl Med 1997;38:1196-201.

10 Flamen P, Stroobants S, Van Cutsem E, et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894-901.

11 Johnson K, Bakhsh A, Young D, et al. Correlating computed tomography and positron emission tomography scan with operative findings in metastatic colorectal cancer. Dis Colon Rectum 2001;44:354-7.

12 Lai DT, Fulham M, Stephen MS, et al. The role of whole-body positron emission tomography with [18F]fluorodeoxy-glucose in identifying operable colorectal cancer metastases to the liver. Arch Surg 1996;131:703-7.

13 Ogunbiyi OA, Flanagan FL, Dehdashti F, et al. Detection of recurrent and metastatic colorectal cancer: comparison positron emission tomography and computed tomography. Ann Surg Oncol 1997;4:613-20.

14 Huebner PH, Park KC, Shepherd JE, et al. A meta-analysis of the literature for whole body FDG PET detection of recurrent colorectal cancer. J Nucl Med 2000;41:1177-89.
15 Gupta NC, Falk PM, Frank AL, et al. F-18 fluorodeoxyglucose (FDG) PET for preoperative staging of colorectal carcinoma (abstr). J Nucl Med 1992;33:975.
16 Abdel-Nabi, Doerr RJ, Lamonica DM, et al. Staging of primary colorectal carcinomas with fluorine-18 Fluorodeoxyglucose whole-body PET: correlation with histopathologic and CT findings. Radiology 1998;206:755-760.
17 Mukai M, Sadahiro S, Yasuda S, et al. Preoperative evaluation by whole-body 18F-fluorodeoxyglucose positron emission tomography in patients with primary colorectal cancer. Oncol Rep 2000;7:85-87.
18 Kantorová I, Lipská L, Bělohlávek O, et al. Routine 18F-FDG PET preoperative staging of colorectal cancer: comparison with conventional staging and its impact on treatment decision making. J Nucl Med 2003;44:1784-1788.
19 Arulampalam THA, Costa DC, Loizidou M, et al. Positron emission tomography and colorectal cancer. Br J Surg 201;88:176-189.
20 Thoeni RF. Colorectal cancer: radiological staging. Radiol Clin N Am 1997;35:457-458.
21 Hundt W, Braunschweig R, Reiser M. Evaluation of spiral CT in staging of colon and rectum carcinoma. Eur J Radiol 1999;9:78-84.
22 Angelelli G, Macarini L, Lupo L, et al. Rectal carcinoma: CT staging with water as contrast medium. Radiology 1990;177:511-514.
23 Chiesura-Corona M, Muzzio PC, Giust G, et al. Rectal cancer: CT local staging with histopathologic correlation. Abdom Imaging 2001;26:134-138.
24 Cohade C, Osman M, Leal J, et al. Direct comparison of 18F-FDG PET and PET/CT in patients with colorectal carcinoma. J Nucl Med 2003;44:1797-1803.
25 Matsuoka H, Nakamura A, Masaki T, et al. Preoperative staging by multidetector-row computed tomography in patients with rectal carcinoma. Am J Surg 2002;184:131-135.
26 Klinna C, Eibel R, Matzek W, et al. Staging of rectal cancer: diagnostic potential of multiplanar reconstructions with MDCT. AJR 2004;183:421-427.
27 Flippone A, Ambrosini R, Fuschi M, et al. Preoperative T and N staging of colorectal cancer: accuracy of contrast-enhanced multidetector-row CT colonography-initial experience. Radiology 2004;231:83-90.
28 Boykin KN, Zibari GB, Lilien DL, et al. The use of FDG-positron emission tomography for the evaluation of colorectal metastases of the liver. Am Surg 1999;65:1183-1185.

29 Ruers TJ, Langenhoff BS, Neeleman N, et al. Value of positron emission tomography with (F-18)fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002;20:388-395.

Figure legends

Figure 1. (A) Primary rectal tumour was exposed to the rectal wall but no extension to the pelvic side walls on computed tomography (CT) (arrow). (B) At the same level of (A), avid uptake was demonstrated on positron emission tomography (PET) (arrow). (C) A superior rectal lymph node was greater than 1cm on CT (arrow). (D) At the same level of (C), PET showed an uptake corresponded to the lymph node demonstrated on CT (arrow). This case was preoperatively diagnosed as TNM stage T3N1 and confirmed at surgery and histopathological examination.