Cardiac 18F-FDG uptake and new-onset rectal cancer

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Abstract. The present study aimed to investigate the factors affecting the cardiac uptake of 18F-fluorodeoxyglucose (18F-FDG) during 18F-FDG positron emission tomography (PET) for new-onset rectal cancer and new-onset colon cancer (ascending, transverse, descending, sigmoid colon cancer) and to examine the association between the cardiac uptake of 18F-FDG and prognosis. The participants were diagnosed with new-onset rectal cancer and new-onset colon cancer (ascending, transverse, descending, sigmoid cancer) at the Iga City General Hospital (Iga, Japan) between January 1, 2013, and March 31, 2018, and underwent an 18F-FDG PET scan for pretreatment staging. The relationship between cardiac maximum standard uptake value (SUVmax), the presence/absence of distant metastasis and prognosis was examined. A total of 26 patients (14 men and 12 women) aged 72.0±10 years with new-onset rectal cancer were selected for the study. No patients had multiple simultaneous cancers. The median cardiac SUVmax was 3.8 and 2.5 in patients with no distant metastasis and distant metastasis, respectively, revealing a statistically significant difference (P<0.01). The median tumor volume on PET-computed tomography (CT) images was 7,815 cm^2 and was 66,248 cm^2 in patients with no distant metastasis and distant metastasis, respectively, revealing a statistically significant difference (P<0.01). Echocardiography findings revealed no significant difference between patients with and without distant metastasis. The correlation coefficient between cardiac SUVmax and total tumor volume on PET/CT images (primary + lymph + distant metastases) was statistically significant (r=-0.42, P=0.03). Analysis of the association between the occurrence of distance metastasis and cardiac SUVmax as a continuous variable gave a statistically significant result [hazard ratio (HR): 0.30, 95% confidence interval (CI): 0.09-0.98, P=0.045]. Receiver operating characteristic analysis showed a cardiac SUVmax of 2.6 with an area under the curve of 0.86 for determining the presence of distant metastasis (95% CI: 0.70-1.00). The median observation time was 56 months, and nine patients died during observation. Analysis of the association between the overall survival and cardiac SUVmax (cutoff: 2.6) showed 95% CI: 0.01-0.45 and HR: 0.06 (P<0.01); that between the overall survival and total tumor volume on PET images showed 95% CI: 1.00-1.00 and HR: 1.00 (P<0.01); and that between the overall survival and presence of distant metastasis showed 95% CI: 1.72-116.4 and HR: 14.1 (P<0.01). Furthermore, 25 patients (16 men and nine women) aged 71.4±14.2 years with new-onset colon cancer were selected for the study. Analysis of new-onset colon cancer revealed no statistically significance between the cardiac SUVmax and distant metastasis.

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Abbreviations: SUVmax, maximum standard uptake value; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-CT; 18F-FDG, 18F-fluorodeoxyglucose; GLUT, glucose transporter; 123I-BMIPP, 123I-β-methyl-P-iodophenyl-pentadecanoic acid; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction; E/e, maximum value of early diastolic filling velocity/maximum value of mitral annulus velocity; E/A, maximum value of early diastolic filling velocity/maximum value of atrial filling wave velocity; CEA, carcinoembryonic antigen; AUC, area under the curve; ROC, receiver operating characteristic; HR, hazard ratio; CI, confidence interval; MST, mean survival time; BSC, best supportive care; SD, standard deviation

In conclusion, cardiac SUVmax data from patients with new-onset rectal cancer and distant metastasis suggested that increased glucose uptake by tumors may reduce glucose uptake by the heart. Cardiac SUVmax may also be related to the occurrence of distant metastases and prognosis.

Introduction

Rectal cancer and colon cancer refer to malignant tumors of the large intestine, which are usually treated with surgery if found early, or with chemotherapy and surgery at later stages (1). Thus, accurate staging is essential in rectal cancer and colon cancer. Endoscopy is used for staging rectal cancer and colon cancer, and computed tomography (CT) is used for whole-body screening. Magnetic resonance imaging (MRI) may be used to evaluate local progression, for tumor staging and to evaluate lymph node metastasis in rectal cancer (2).

Positron emission tomography (PET)-CT is sometimes used for whole-body screening in cases of rectal cancer and colon cancer, and it allows PET images and CT images to be combined. PET-CT uses 18F-fluorodeoxyglucose (18F-FDG), a radiolabeled glucose analog, as a radiopharmaceutical. Compared with CT and MRI, PET-CT sometimes detects additional lesions when used in the diagnosis of new-onset rectal cancer (3). In addition, PET-CT can improve staging in cases of lower rectal cancer (4), and has a reported sensitivity of 93.7% in the detection of distant metastasis (5). When PET is performed before chemoradiation therapy for rectal cancer, the response to chemoradiation and prognosis can be predicted based on the 18F-FDG uptake (6). Pathological remission, in particular, can be predicted based on the 18F-FDG uptake (7,8).

Numerous studies have shown the use of PET-CT in rectal cancer. However, 18F-FDG is also taken up by non-tumor tissue, including the physiological uptake of 18F-FDG by the brain and heart. Multiple glucose transporters are present in the body, including GLUT1, GLUT2, GLUT3, GLUT4 and GLUT5; GLUT1 transports glucose into the tumor tissue and GLUT4 transports glucose into the myocardial tissue (9).

Although the heart can use both glucose and fatty acids as an energy, it mainly uses fatty acids due to the higher amount of ATP produced; fatty acid uptake in the heart can be detected using 123I-β-methyl-P-iodophenyl-pentadecanoic acid (123I-BMIPP) cardiac scintigraphy. Notably, ischemia and other events cause a rapid decline in fatty acid uptake in the heart, which is difficult to recover from; therefore, 123I-BMIPP scintigraphy also reveals reduced uptake at sites of ischemia. The heart can shift to the glycolytic system and glucose metabolism when it becomes ischemic (10). It has been reported that 18F-FDG accumulates in the heart in cases of unstable angina, and this uptake indicates ischemia (11). Thus, the heart and tumors may be in competition for the metabolism of glucose. Nevertheless, to the best of our knowledge, studies have found no association between cardiac uptake of 18F-FDG and glucose, fatty acids, body weight or other factors (12-14). At present, the factors affecting cardiac 18F-FDG uptake in patients with malignant tumors remain unknown. The glycolytic system is enhanced due to the Warburg effect in cancer cells, and glucose metabolism is increased (15). It may be hypothesized that the more advanced the cancer, the less glucose can be supplied to the heart (15). A previous study treated patients with rectal cancer with chemoradiotherapy, and reported a higher likelihood of metastasis and a poorer prognosis in patients with elevated levels of GLUT1 expression following treatment (16). From this molecular biology research and 18F-FDG PET imaging, it was hypothesized that cardiac 18F-FDG uptake may vary depending on the extent of rectal cancer and colon cancer, and that this change in uptake may affect prognosis and other factors. The present study aimed to investigate the factors that affect the degree of cardiac 18F-FDG uptake, and the effect of this uptake on the pathology and prognosis in patients with rectal cancer and colon cancer.

Patients and methods

Study design and participants. The present study is a single-center, case-control, retrospective study. The study retrospectively enrolled patients diagnosed with new-onset rectal cancer and new-onset colon cancer (ascending, transverse, descending, sigmoid cancer) at the Iga City General Hospital (Iga, Japan) between January 1, 2013 and March 31, 2018, who underwent an 18F-FDG PET scan for pretreatment staging. The patients were selected using the reporting terminal system (PSP, Japan Tokyo) and patient data were checked using the electronic medical records. Rectal cancer and colon cancer were diagnosed based on imaging, endoscopic and pathological findings, and clinical course.

For the present study, it was considered that the rectum is under the promontory of the sacrum and above the anal canal. From this definition, rectal cancer was defined as: i) Adenocarcinoma (pathologically diagnosed) and ii) occurring at recto sigmoid, above peritoneal reflection and below peritoneal reflection. Moreover, in the present study, colon cancer was defined as: i) Adenocarcinoma (pathologically diagnosed) and ii) occurring at the ileocecal, ascending, transverse, descending and sigmoid colon but not the rectum. Medical imaging, endoscopic and pathological findings, and the clinical information obtained from the medical records (clinical diagnosis and medical reports) were referred to for this definition.

The inclusion criteria for the present study were as follows: i) Patients had new-onset rectal cancer and colon cancer (pathologically diagnosed and matched clinical course) and ii) patients underwent PET-CT for initial staging prior to therapy. The exclusion criteria were as follows: i) Patients also diagnosed with other types of new onset cancer (with untreated new onset other types of cancer) and ii) patients undergoing treatment for other types of cancer.

PET-CT evaluation. PET-CT was performed using a Discovery ST Elite equipped with an 8-row or 16-row multi-slice CT (GE Healthcare). The patients scheduled to undergo PET-CT fasted for 5-6 h, were administered 18F-FDG based on their body weight, and then remained at rest for 1 h before PET-CT imaging. PET images, CT images and fusion images were prepared from the PET-CT scan. PETCT images were visually assessed by a radiologist (author Yukinori Okada) with experience the PET research (17), a boardcertified radiologist and radiation oncologist (Japan Radiological Society and Japanese Society for Radiation Oncology) and a boardcertified nuclear medicine specialist (Japan Society of Nuclear Medicine).

The images were viewed simultaneously by a radiologist and a gastroenterologist, who visually assessed the extent of the lesions and cardiac uptake. The radiologist defined the regions of interest (ROIs) for the heart and the primary lesion, and measured the maximum standard uptake value (SUVmax) on the reading monitor. The ROI was set over the whole heart, and included the left ventricle and the SUVmax was calculated for each slice including the heart. The maximum was used as the cardiac SUVmax. The 18F-FDG uptake value at the aorta inducing the arteriosclerosis was not selected.

The presence or absence of lymph node metastasis and distant metastasis was assessed visually by the radiologist compared with CT images obtained in parallel, recent CT and MRI images, and the clinical course. The radiologist defined the ROIs on the reading monitor for the principal lesion, lymph node metastases and distant metastases, measured and summed these areas, and used them to calculate the tumor volumes. The iliopsoas muscle area at the L3 level was also measured on the CT images obtained by PET-CT.

Echocardiography. Left atrial diameter (LAD) (mm), left ventricular end-diastolic diameter (LVDd) (mm), left ventricular end-systolic diameter (LVDs) (mm), ejection fraction (EF) (%), E/e and E/A were obtained from the echocardiography (iE33, Philips Healthcare) performed at the same time as the PET-CT.

Carcinoembryonic antigen (CEA) detection. The CEA levels were detected from a blood (200 μl of serum) by the hospital performed simultaneously as PET-CT.

Evaluation of survival. Survival was evaluated starting from the day of the PET-CT scan up until the final observation day on September 30, 2021. For dropouts during this period, the final observation day was taken as the date of the last visit.

Statistical analysis. Statistical analysis was performed using EZR software developed by the Jichi Medical University Saitama Medical Center (Saitama, Japan) (18). Comparisons between the two groups were made using the Mann-Whitney U-test or Fisher's exact test. The correlation between two variables was evaluated using the Spearman's rank correlation coefficient. A logistic model was used for single variate analysis and multi variate analysis. A receiver operating characteristic (ROC) analysis was used to analyze the cutoff values. The survival data were analyzed using the Kaplan-Meier method and log-rank test, or Cox proportional hazards model. P<0.05 was considered to indicate a statistically significant difference.

Results

Patients. A total of 50 patients were selected in the present study; 26 patients with new-onset rectal cancer and 24 patients with new-onset colon cancer.

Rectal cancer
Participants. A total of 26 patients (14 men and 12 women) aged 72.0±10 years were enrolled in the present study. Of the 26 patients, one had previously had a myocardial infarction

and been diagnosed with gastric cancer >20 years ago. The histopathological results of these 26 patients confirmed that they all had tubular adenocarcinoma (one patient had combined cancer (main tubular adenocarcinoma and partly mucinous adenocarcinoma).

Three patients had stage I rectal cancer, eight patients had stage II, five patients had stage III and 10 had stage IV. One patient with stage III rectal cancer had multiple small lung metastases that increased in size during the course of observation; hence, the patient was characterized as having distant metastasis. A total of 15 patients had no distant metastasis and 11 patients had distant metastasis (lung, bone, liver and peritoneal dissemination).

The 18F-FDG dose was 231.3±44.1 MBq and the blood glucose level was 103.1±23.7 mg/dl. The SUVmax of the primary lesion was 18.9±8.8 and the cardiac SUVmax was 4.3±4.1. The SUVmax values of the heart were detected at left ventricle. The tumor volume on PET images (sum of primary lesion+lymph nodes + distant metastases) was 74,990.1±148,317.1 cm^2 (range 704-639,740 cm^2), The tumor volume on PET images (only primary lesion) was 47,616.0±93,659.0 cm^2 (range 704-455,162 cm^2). The tumor volume on PET images (only lymph nodes) was 1,547.2±3,091.0 cm^2 (range 0-11,331 cm^2).The tumor volume on PET images (only distant metastases) was 25,825.5±111,639.0 cm^2 (range 0-56,9012 cm^2). The iliopsoas muscle area at the L3 level was 1,090.9±455.6 cm^2.

Echocardiography was performed on 24 patients, giving a LAD (mm) of 37.4±6.1, LVDd (mm) of 44.4±5.0, LVDs (mm) of 30.1±4.6, EF (%) of 65.6±7.6, E/e of 8.3±3.0 and E/A of 1.2±1.8. CEA was measured as 844.9±3,128.1 ng/ml in 24 patients. The results are shown in Table I.

Absence/presence of distant metastasis and investigation of various factors. The median cardiac SUVmax was 3.8 and 2.5 in patients with no distant metastasis and distant metastasis, respectively, revealing a statistically significant difference (P<0.01; Fig. 1).

The median total tumor volume was 7,815 cm^2 and was 66,248 cm^2 in patients with no distant metastasis and distant metastasis, respectively, revealing a statistically significant difference (P<0.01; Fig. 2). However, two patients had lung metastases with small tumor volumes that proved difficult to measure.

The median CEA was 3.3 and 79.3 ng/ml in patients with no distant metastasis and distant metastasis, respectively, revealing a statistically significant difference (P<0.01). No other factors revealed a statistically significant difference. The results are shown in Table II.

Correlation between tumor volume and cardiac SUVmax. The correlation coefficient between cardiac SUVmax and total tumor volume (sum of primary lesion tumor volume + lymph nodes tumor volume + distant metastases tumor volume) was statistically significant (correlation coefficient=-0.42, P=0.03; Fig. 3). There was a statistically significant correlation between the total volume of lymph node metastases (0 in patients with no lymph node metastasis) and cardiac SUVmax (correlation coefficient=-0.46, P=0.02; Fig. 4), and between the total volume of distant metastases (0 in patients with no distant

Table I. Characteristics of patients with rectal cancer.

Characteristic	Value (mean ± SD)
Number of patients	26
Age, years	72±10
Staging	
I	3
II	8
III	5
IV	10
Therapy	
Surgery (no distant metastasis)	15
Chemotherapy (distant metastasis)	6
Surgery at primary site (distant metastasis)	1
Surgery at primary site + liver radiofrequency ablation (distant metastasis)	1
Surgery at the primary site + moved to a different institute	1
Supportive care	2
Pathology	
Tubular adenocarcinoma	26[a]
Distant metastasis	
Absent	15
Present	11
PET- CT (mean ± SD)	
18F-FDG dose, MBq	231.3±44.1
Blood glucose, mg/dl	103.1±23.7
Primary lesion SUVmax	18.9±8.8
Cardiac SUVmax	4.3±4.1
Tumor volume on PET images, cm^2	74,990.1±148317.1
L3 iliopsoas muscle area, cm^2	1,090.9±455.6
Echocardiography (mean ± SD)	
LAD, mm	37.4±6.1
LVDd, mm	44.4±5.0
LVDs, mm	30.1±4.6
EF, %	65.6±7.6
E/e	8.3±3.0
E/A	1.2±1.8
Carcinoembryonic antigen (mean ± SD)	
ng/ml	844.9±3,128.1

[a]One patient had combined carcinoma (main tubular adenocarcinoma and partly mucinous adenocarcinoma. PET, positron emission tomography; CT, computed tomography; 18F-FDG, 18F-fluorodeoxyglucose; SUVmax, maximum standard uptake values; CEA, carcinoembryonic antigen; LAD, left anterior descending coronary artery; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; EF, ejection fraction; E/e, maximum value of early diastolic filling velocity/maximum value of mitral annulus velocity; E/A, maximum value of early diastolic filling velocity/maximum value of atrial filling wave velocity.
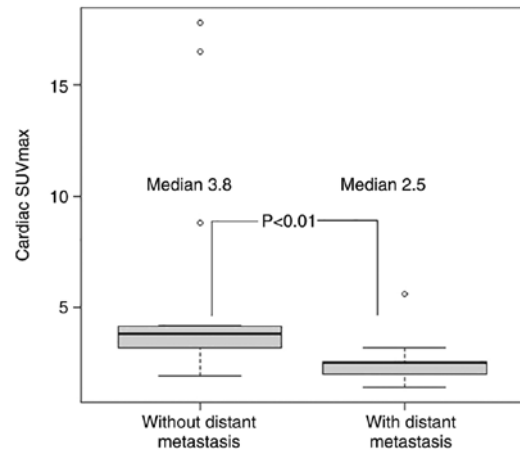

Figure 1. Presence or absence of distant metastasis and Cardiac SUVmax. SUVmax, maximum standard uptake value.
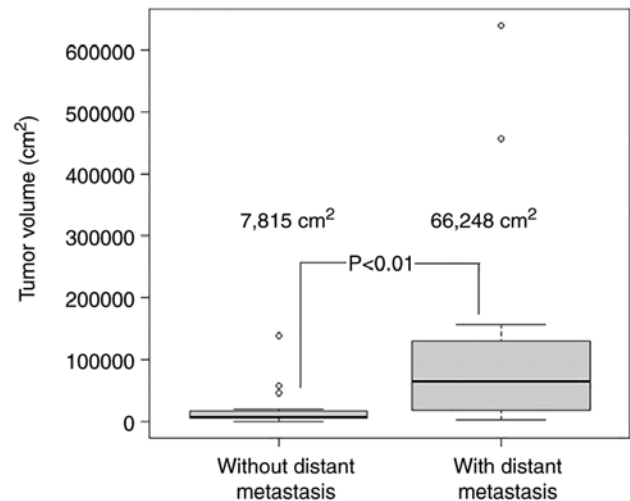

Figure 2. Presence or absence of distant metastasis and the positron emission tomography-computed tomography tumor volume.

metastasis) and cardiac SUVmax (correlation coefficient=-0.6, P<0.01; Fig. 5).

Factors related to the occurrence of distant metastasis. Analyzing cardiac SUVmax as a continuous variable showed a significant association between the occurrence of distant metastasis and cardiac SUVmax [Odds ratio (OR): 0.30, 95% confidence interval (CI): 0.09-0.98, P=0.045] (Table III). ROC analysis showed that a cardiac SUVmax of 2.6 had the best an area under the curve (AUC) for predicting the presence of distant metastasis.

By using the cut off value 2.6 of cardiac SUVmax, the AUC value was 0.86, specificity 0.933, sensitivity 0.818 and 95% CI: 0.70-1.00 for predicting the presence of distant metastasis (Fig. 6). Analyzing primary tumor SUVmax as a continuous variable showed a significant association between the occurrence of distant metastasis and primary tumor SUVmax (HR: 0.89, 95% CI: 0.78-1.00, P=0.049). ROC analysis showed that a primary tumor SUVmax of 21 had an AUC of 0.82 for determining the presence of distant metastasis (specificity 0.533, sensitivity 1.000; 95% CI:

Table II. Presence/absence of distant metastasis and investigated factors in rectal cancer.

Factor	No metastasis	Metastasis	P-value
Age, years	72	67	0.09
Sex male/female	6/9	8/3	0.13
18F-FDG, MBq	216.9	229.1	0.63
Glucose, mg/dl	99	98	0.47
Primary lesion SUVmax	22.2	16.3	0.10
Cardiac SUVmax	3.8	2.5	<0.01
Total tumor volume on PET images	7,815	66,248	<0.01
L3 iliopsoas muscle area	1,105	1,069	0.90
LAD	38.0	36.1	0.73
LVDd	47.5	47.8	0.78
LVDs	29.0	28.7	0.69
EF	67.5	66.2	0.39
E/e	8.5	7.6	0.18
E/A	0.8	0.8	0.66
CEA	3.3	79.3	<0.01

18F-FDG, 18F-fluorodeoxyglucose; CEA, carcinoembryonic antigen; EF, ejection fraction; LAD, left anterior descending coronary artery; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; PET, positron emission tomography; SUVmax, maximum standard uptake values.
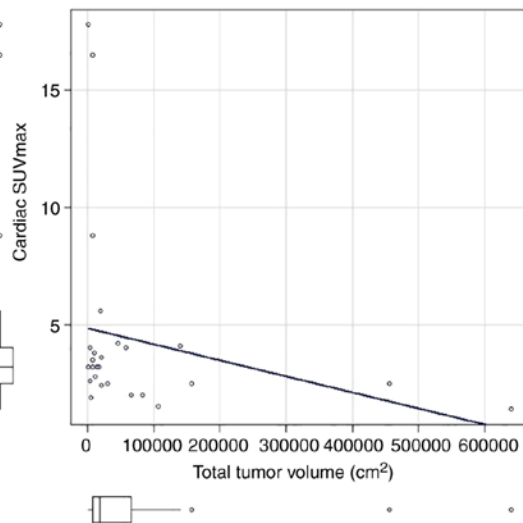

Figure 3. Correlation between Cardiac SUVmax and total tumor volume. SUVmax, maximum standard uptake value.
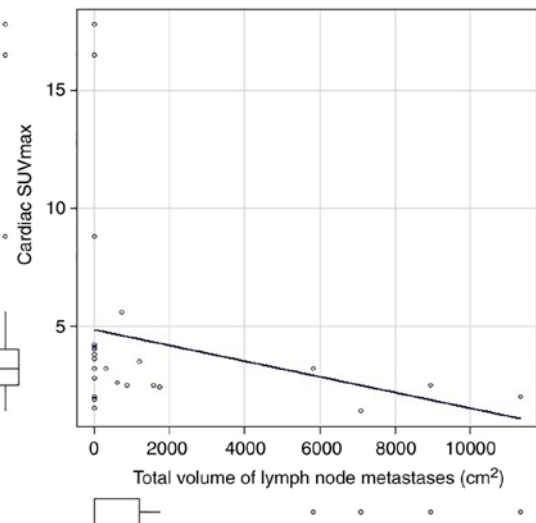

Figure 4. Correlation between Cardiac SUVmax and total volume of lymph node metastases. SUVmax, maximum standard uptake value.

0.46-1.00). No other factor produced a statistically significant result (Table III).

Investigation of overall survival. The median observation time was 56 months, and nine patients died during observation. Four patients were lost from follow up.

Two of the 15 patients without distant metastasis and seven of the 11 patients with distant metastasis died during the observation period. Two patients with distant metastases received only best supportive care (BSC) and died ~1 month after staging. A total of 24 patients received standard therapy (surgery and/or chemotherapy). All patients without distant metastases underwent surgery for primary tumor. Six patients with distant metastases received first line Folinic acid, Fluorouracil and Oxaliplatin (FOLFOX) treatment. One patient with distant metastases underwent surgery at the primary site, another underwent surgery at the primary site and radiofrequency ablation (RFA) for liver metastasis and another underwent surgery at the primary site before moving to a different hospital.

Analyzing the association between overall survival (including the two patients that received BSC) and cardiac SUVmax (cutoff: 2.6) showed 95% CI: 0.01-0.45, HR: 0.06, and P<0.01(Table IV). The Kaplan-Meier method

Table III. Factors related to the occurrence of distant metastasis in rectal cancer.

Factor	Odds ratio	95% CI	P-value
Age	0.90	0.84-1.01	0.09
Sex	4.00	0.74-21.5	0.11
Primary lesion SUVmax	0.89	0.78-1.00	0.049
Cardiac SUVmax	0.30	0.09-0.98	0.045
Total tumor volume on PET images	1.00	1.00-1.00	0.10
L3 iliopsoas muscle area	1.00	0.99-1.00	0.69
LAD	0.97	0.85-1.13	0.75
LVDd	1.05	0.88-1.25	0.59
LVDs	1.13	0.92-1.39	0.23
EF	0.89	0.77-10.0	0.16
E/e	0.79	0.55-1.15	0.23
E/A	0.18	0.00-9.13	0.39
CEA	1.04	1.00-1.08	0.051

CEA, carcinoembryonic antigen; CI, confidence interval; EF, ejection fraction; LAD, left anterior descending coronary artery; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; PET, positron emission tomography; SUVmax, maximum standard uptake values.
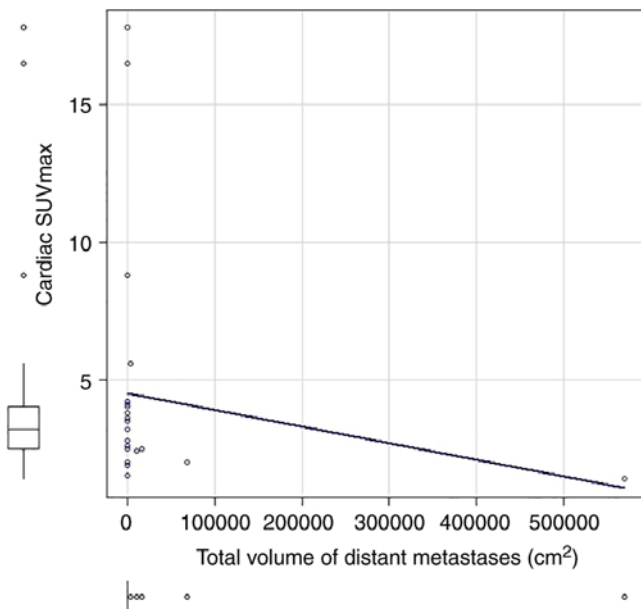

Figure 5. Correlation between Cardiac SUVmax and the volume of distant metastases. SUVmax, maximum standard uptake value.
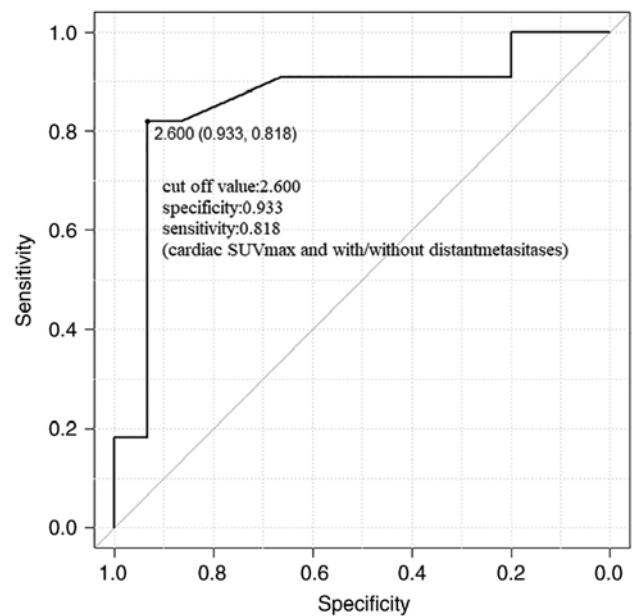

Figure 6. Receiver operating characteristic curve of Cardiac SUVmax and distant metastasis (cut off value, specificity and sensitivity).

and log-rank test showed that there was a statistically significant difference in overall survival between the cardiac SUVmax ≥2.6 group (n=17; three patients died; median follow-up time, 60 months) and the cardiac SUVmax <2.6 group (n=9; six patients died; median follow-up time, 14 months). The SUVmax ≥2.6 group did not achieve median survival time (MST), whereas in the SUVmax <2.6 group the MST was 17 months (P<0.01; Fig. 7). Analyzing the association between overall survival (including the two patients that received BSC) and distant metastasis showed 95% CI: 1.72-116.4, HR: 14.1, and P<0.01 (Table IV). The Kaplan-Meier method and log-rank

test showed that there was a statistically significant difference in overall survival between the group without distant metastasis (n=15; two patients died; median follow up time, 60 months) and the group with distant metastasis (n=11; seven patients died; median follow up time, 18 months). The group without distant metastasis did not achieve MST, whereas in the group with distant metastasis the MST was 32 months (P<0.01; data not shown).

Subsequently, the patients were classified into four groups: Group A (cardiac SUVmax ≥2.6+ without distant metastasis; n=14; two patients died; median follow-up time, 60 months), group B (cardiac SUVmax ≥2.6+ with distant metastasis;

Table IV. Factors related to overall survival in 26 patients with rectal cancer (including two patients treated with best supportive care).

Factor	Hazard ratio	95% CI	P-value
Age	1.00	0.94-1.07	0.96
Sex	1.05	0.25-4.43	0.95
Primary lesion SUVmax	0.98	0.90-1.06	0.63
Cardiac SUVmax	0.45	0.17-1.17	0.10
Cardiac SUVmax			
(2.6 cutoff)	0.06	0.01-0.45	<0.01
CEA	1.00	1.00-1.00	0.01
Total tumor volume on PET images	1.00	1.00-1.00	<0.01
L3 iliopsoas muscle area	0.99	0.99-1.01	0.38
Presence/absence of distant metastasis	14.10	1.72-116.40	<0.01

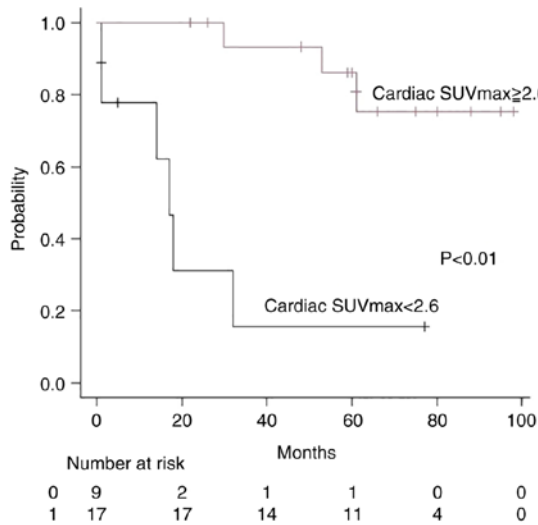CEA, carcinoembryonic antigen; CI, confidence interval; SUVmax, maximum standard uptake values.

Figure 7. Kaplan-Meier curve analysis of 26 patients with new-onset rectal cancer according to cardiac SUVmax (cutoff value: 2.6). SUVmax, maximum standard uptake value.
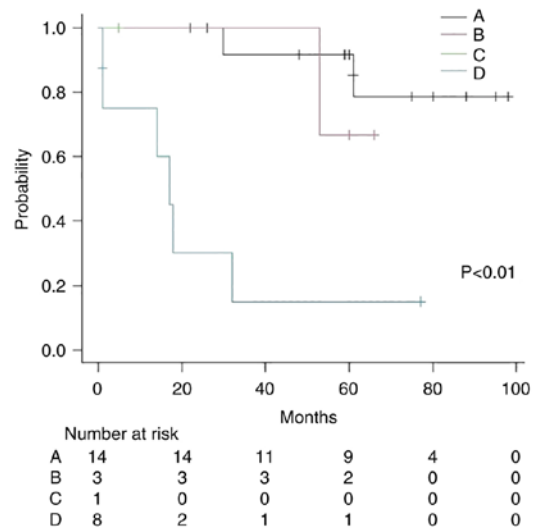

Figure 8. Kaplan-Meier curve analysis of 26 patients with new-onset rectal cancer separated into groups according to cardiac SUVmax (cutoff value: 2.6) and distant metastasis. SUVmax, maximum standard uptake value.

n=3; one patient died; median follow-up time, 60 months), group C (cardiac SUVmax <2.6+ without distant metastasis; n=1; median follow-up time, 5 months) and group D (cardiac SUVmax <2.6+ with distant metastasis; n=8; six patients died; median follow-up time, 15.5 months). The Kaplan-Meier method and log-rank test showed that there was a statistically significant difference between the four groups; groups A, B and C did not achieve MST, whereas group D had an MST of 17 months (P<0.01; Fig. 8).

Analyzing the association between overall survival (excluding the two patients that received BSC) and cardiac SUVmax (cutoff: 2.6) showed 95% CI: 0.02-0.53, HR: 0.12 and P<0.01 (Table V). The Kaplan-Meier method and log-rank test showed that there was a statistically significant difference between the cardiac SUVmax ≥2.6 group (n=17; three patients died; median follow-up time, 60 months) and the cardiac SUVmax <2.6 group (n=7; four patients died; median follow-up time, 17 months). The SUVmax ≥2.6 group did not achieve MST, whereas the MST in the SUVmax <2.6 group was 17 months (P<0.01; Fig. 9). Analyzing the association between overall survival (excluding the two patients that received BSC) and distant metastasis showed 95% CI: 1.13-30.5, HR: 5.88 and P=0.03 (Table V). The Kaplan-Meier method and log-rank test showed that there was a statistically significant difference between the group without distant metastasis (n=15; two patients died; median follow-up time, 60 months) and the group with distant metastasis (n=9; five patients died; median follow-up time, 32 months). The group without distant metastasis did not achieve MST, whereas the group with distant metastasis had an MST of 42.5 months (P<0.01; data not shown).

The patients (exclude two BSC patients) were then classified into the following four groups: Group A (cardiac SUVmax ≥2.6+ without distant metastasis; n=14; two patients died; median follow-up time, 60 months), group B (cardiac SUVmax ≥2.6+ with distant metastasis, n=3; one

Table V. Factors related to overall survival in 24 patients with rectal cancer (excluding two patients that received best supportive care).

Factor	Hazard ratio	95% CI	P-value
Age	0.98	0.91-1.06	0.66
Sex	0.81	0.18-3.66	0.79
Primary lesion SUVmax	0.97	0.88-1.06	0.45
Cardiac SUVmax	0.68	0.32-1.48	0.33
Cardiac SUVmax (2.6 cutoff)	0.12	0.02-0.53	<0.01
CEA	1.01	0.99-1.03	0.23
Total tumor volume on PET images	1.00	1.00-1.00	0.13
L3 iliopsoas muscle area	1.00	1.00-1.00	0.96
Presence/absence of distant metastasis	5.88	1.13-30.5	0.03

CEA, carcinoembryonic antigen; CI, confidence interval; SUVmax, maximum standard uptake values.
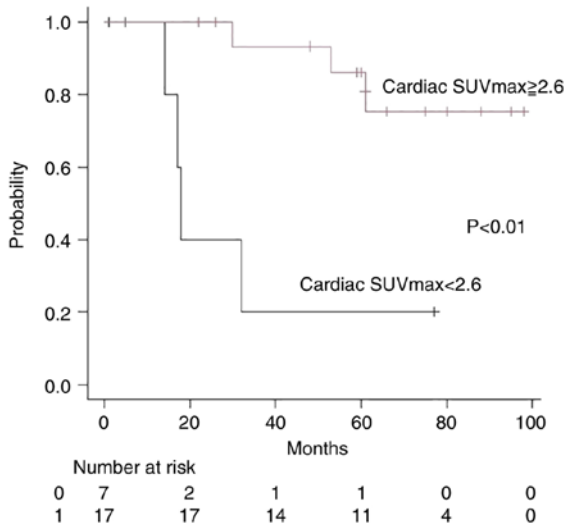

Figure 9. Kaplan-Meier curve analysis of 24 patients with new-onset rectal cancer according to cardiac SUVmax (cutoff value: 2.6). Two patients that received best supportive care were not included. SUVmax, maximum standard uptake value.
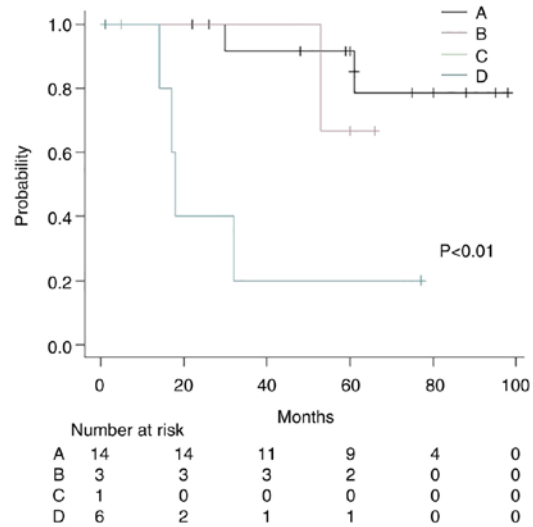

Figure 10. Kaplan-Meier curve analysis of 24 patients with new-onset rectal cancer separated into groups according to cardiac SUVmax (cutoff value: 2.6) and distant metastasis. Two patients that received best supportive care were not included. SUVmax, maximum standard uptake value.

patient died; median follow-up time, 60 months), group C (cardiac SUVmax <2.6+ without distant metastasis; n=1; median follow-up time, 5 months) and group D (cardiac SUVmax <2.6+ with distant metastasis; n=6; four patients died; median follow-up time, 17.5 months). The Kaplan-Meier method and log-rank test showed that there was a statistically significant difference between the four groups; groups A, B and C did not achieve MST; group D had an MST of 17 months (P<0.01; Fig. 10).

Colon cancer
All patients. A total of 24 patients had colon cancer in a region other than the rectum. The 24 patients included 16 men and eight women with a mean age of 72.5±14.0 years. Distant metastasis was absent in 14 patients and present in 10 patients. Colon cancer was located in the ileocecal region in three patients, the ascending colon in five patients, the transverse

colon in one patient, the descending colon in two patients and the sigmoid colon in 13 patients. Histopathological results were as follows: 22 cases of tubular adenocarcinoma, one case of tubular adenocarcinoma + poorly differentiated adenocarcinoma combined, and one case of poorly differentiated adenocarcinoma. Double colon/rectum cancer was detected in three patients (two patients in the sigmoid colon and rectum and one patient in the ascending colon and appendiceal mucinous adenocarcinoma).

All of the 14 patients without distant metastasis underwent primary tumor resection and four patients received adjuvant chemotherapy (two patients received capecitabine and four tegafur-uracil (UFT). Of the 10 patients with distant metastasis, one patient received FOLFOX6 + bevacizumab, one patient received modified FOLFOX, five patients underwent surgery at the primary site + FOLFOX6, one patient underwent surgery at the primary site + capecitabine, one

patient underwent surgery at the primary site + RFA (liver metastasis) + 5-fluorouracil + Bevacizumab, and one patient received BSC.

The 18F-FDG dose was 237.3±43.0 MBq, and the blood glucose level was 97.1±15.5 mg/dl. The SUVmax of the primary lesion was 18.7±6.0 and the cardiac SUVmax was 4.5±4.4. The iliopsoas muscle area at the L3 level was 1,279.6±539.6 cm^2.

Echocardiography was performed on 22 patients, giving a LAD (mm) of 37.7±5.0, LVDd (mm) of 47.1±4.3, LVDs (mm) of 30.4±3.8, EF (%) of 63.6±10.0, E/e of 9.8±3.4 and E/A of 1.0±0.4.

The median L3 iliopsoas muscle area was 1,042 and 1,410 cm^2 in patients with no distant metastasis and with distant metastasis, respectively; this difference was statistically significant (P=0.04). The median E/e was 10.8 and 7.3 in patients with no distant metastasis and distant metastasis, respectively, revealing a statistically significant difference (P=0.01). When patients with colon cancer in regions other than the rectum were grouped based on the presence or absence of distant metastasis, no statistically significant difference was found in terms of age, sex, 18F-FDG dose, blood glucose level, primary lesion SUVmax, cardiac SUVmax, LAD, LVDd and EF. The distant metastasis group was compared with the non-distant metastasis group and the results for age, sex, 18F-FDG dose, glucose, Primary lesion SUVmax, Cardiac SUVmax, L3 iliopsoas muscle area, LAD, LVDd, LVDs, EF, E/A and E/e are shown in Table VI.

Analysis excluding the three patients with double colon or rectum cancer. A total of 21 patients had colon cancer in a region other than the rectum. Colon cancer was located in the ileocecal region in three patients, the ascending colon in four patients, the transverse colon in one patient, the descending colon in two patients and the sigmoid colon in 11 patients. The 21 patients included 13 men and 8 women with a mean age of 69.9±14.9 years. Distant metastasis was absent in 12 patients and present in nine patients. Histopathological results were as follows: 19 cases of tubular adenocarcinoma and two cases of poorly differentiated adenocarcinoma.

The 18F-FDG dose was 238.3±43.0 MBq, and the blood glucose level was 97.3±16.5 mg/dl. The SUVmax of the primary lesion was 18.5±6.4 and the cardiac SUVmax was 4.7±4.7. The iliopsoas muscle area at the L3 level was 1,274.4±536.6 cm^2.

Echocardiography was performed on 19 patients, giving a LAD (mm) of 37.3±5.1, LVDd (mm) of 46.6±4.1, LVDs (mm) of 30.2±4.0, EF (%) of 63.4±10.9, and E/A of 1.0±0.5.

The median L3 iliopsoas muscle area was 1,042.5 and 1,455 cm^2 in patients with no distant metastasis and with distant metastasis, respectively, revealing a statistically significant difference (P=0.01). The median E/e was 10.7 and 7.1 in patients with no distant metastasis and with distant metastasis, respectively, revealing a statistically significant difference (P=0.04). When patients with colon cancer in regions other than the rectum were grouped based on the presence or absence of distant metastasis, no statistically significant difference was found in terms of age, sex, 18F-FDG dose, blood glucose level, primary lesion SUVmax, cardiac SUVmax, LAD, LVDd and EF. The distant metastasis group was compared with the non-distant metastasis group and the results for age, sex, 18F-FDG dose, glucose, Primary lesion SUVmax, Cardiac SUVmax, L3 iliopsoas muscle area, LAD, LVDd, LVDs, EF, E/A, E/e are shown in Table VII.

Discussion

The present study aimed to investigate the factors affecting 18F-FDG uptake in the heart in patients with new-onset rectal cancer and new-onset colon cancer. In new-onset rectal cancer, compared with the patients with distant metastasis, the patients without distant metastasis had a i) statistically higher cardiac SUVmax and ii) statistically smaller tumor volume. A statistically significant association was found between the occurrence of distant metastasis and cardiac SUVmax; however, no statistically significant association was found between the occurrence of distant metastasis and tumor volume. The correlation coefficient between cardiac SUVmax and tumor volume was also statistically significant. The results revealed that cardiac SUVmax decreased with an increasing volume of lymph node metastases and an increasing volume of distant metastases. Thus, the present study indicated the probability that heart metabolic mechanism is affected by cancer burden, especially distant metastasis. A high GLUT1 expression following chemoradiotherapy in rectal cancer has been associated with a large number of distant metastases and a poor prognosis (16). In addition, although not related to rectal cancer, a previous study showed that the prognosis of neuroblastoma may be improved by GLUT1 inhibitors (19). It may be hypothesized that as cancer cells and tumor volume increase, the demand of glucose by cancer cells expands, thus the glucose supply in the body becomes smaller and less available for use by the heart, thus heart metabolism changes from using glucose to fatty acids. This may be the mechanism underlying the change in cardiac SUVmax. Diabetes mellitus has also been associated with reduced glucose uptake by the heart (20). However, in the present study, the blood glucose levels were normal in all patients, and since the blood glucose levels were strictly managed and averaged ~102 mg/dl before the examination, the possibility of the blood glucose levels affecting the findings appears to be low. In addition, 18F-FDG uptake by the heart could potentially be affected by a history of angina pectoris or myocardial infarction. However, the presence or absence of distant metastasis had no significant effect on the echocardiography findings; therefore, the uptake was unlikely to be affected by cardiac function or other causes originating in the heart. The cardiac uptake in cases of malignant lymphoma has also been weakly correlated with free fatty acids in the blood (21). Furthermore, cardiac uptake has been shown to be stronger in cases of Hodgkin lymphoma than in cases of non-Hodgkin lymphoma, where the involvement of tumor-related factors has been reported as a possible cause (22). Accordingly, cardiac uptake may be affected by the tumor or associated factors.

In new-onset rectal cancer, distant metastasis and cardiac SUVmax were considered as prognostic factors of overall survival. Cardiac 18F-FDG accumulation is not used for staging but cardiac 18F-FDG accumulation and cardiac SUVmax may be indicators for disease characteristics, especially glucose demand by cancer. In the present study, cardiac SUVmax and distant metastasis were considered prognostic

Table VI. Presence/absence of distant metastasis and investigated factors in 24 patients with colon cancer

Factor	No metastasis	Metastasis	P-value
Age	75.5	65.0	0.11
Sex	Men:8		
Women:6	Men:8		
Women:2	0.39		
18F-FDG, MBq	227.0	242.5	0.48
Glucose, mg/dl	96	90	0.77
Primary lesion SUVmax	19.5	18.0	0.58
Cardiac SUVmax	2.9	2.8	0.36
L3 iliopsoas muscle area	1,042	1,410	0.04
LAD	37.0	37.5	0.79
LVDd	47	48	0.57
LVDs	30	31	0.35
EF	66	62	0.13
E/A	0.9	0.8	0.47
E/e	10.8	7.3	0.01

18F-FDG, 18F-fluorodeoxyglucose; EF, ejection fraction; LAD, left anterior descending coronary artery; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; PET, positron emission tomography; SUVmax, maximum standard uptake values.

Table VII. Presence/absence of distant metastasis and investigated factors in 21 patients with colon cancer (ascending, transverse, descending, sigmoid cancer) excluding three patients with double colon/rectal cancer.

Factor	No metastasis	Metastasis	P-value
Age	75.6	65.0	0.13
Sex male/female	6/6	6/2	0.36
18F-FDG, Bq	96	89	1.00
Glucose, mg/dl	224.8	253.9	0.24
Primary lesion SUVmax	19.6	17.0	0.59
Cardiac SUVmax	3.05	2.70	0.15
L3 iliopsoas muscle area	1,042.5	1,455.0	0.01
LAD	37.0	37.5	0.77
LVDd	47	47	0.36
LVDs	28.0	30.5	0.23
EF	66.0	61.0	0.17
E/A	1.1	0.8	0.17
E/e	10.7	7.1	0.04

18F-FDG, 18F-fluorodeoxyglucose; EF, ejection fraction; LAD, left anterior descending coronary artery; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; PET, positron emission tomography; SUVmax, maximum

factors. Although only three patients, the patients with cardiac SUVmax ≥2.6 and with distant metastasis had a longer prognosis compared with patients with cardiac SUVmax <2.6 and with distant metastasis. When excluding the two patients treated with BSC, cardiac SUVmax (cutoff 2.6) was more significantly associated with survival (Table V). Although the sample size was limited, cardiac SUVmax may be a prognostic factor at new onset rectal cancer.

Notably, analysis of patients with new-onset colon cancer found no statistically significant difference in cardiac SUVmax or other factors between the patients with and without distant metastasis, suggesting that the pathophysiology of rectal cancer differs from that of colon cancer. The reason for differences between new-onset rectal cancer and new-onset colon cancer regarding the association between cardiac SUVmax and distant metastases are unclear.

It has been reported that patients with advanced rectal cancer have a poor prognosis due to cachexia (23), raising the potential involvement of inflammatory substances, such as cytokines. Furthermore, rectal cancer with high GLUT1

expression treated with chemoradiotherapy was associated with a poor progress (16). It was hypothesized that rectal cancer has a specific metabolic change, such as strong demand of glucose with distant metastasis, especially the correlation between the GLUT-1 expression and tumor volume. This glucose metabolic change induces this cardiac 18F-FDG accumulation change correlated to the distant metastasis and tumor volume. The reason may be that the disease uniformity (ascending, transverse, descending, sigmoid) and GLUT 1,4 uniformity may cause these results. However no studies were on this were or any studies on the correlation between GLUT1 and GLUT 4 with cancer and *in vivo*.

The present study considered that 18F-FDG PET-CT can evaluate GLUT1 expression pattern at tumor and whole-body organs such as brain, heart and muscle, which express GULT 1, 2, 3 and 4. PET-CT has semi quantitative indicators such as SUV. Semi quantitative evaluation of GLUT expression is possible by using PET-CT and was used PET-CT in the present study.

There are reports on GLUT-1 expression in cancer (16,19). Moreover, GLUT1 expression is not only detected in rectal cancer but also in neuroblastoma (16,19). PET-CT data from other types of gastroenterological cancer were checked; however, the sample size was small, especially for esophageal carcinoma, gastric carcinoma, pancreas carcinoma, bile duct carcinoma and hepatocellular carcinoma. In addition, the frequency of 18F-FDG PET-CT use for hepatocellular carcinoma staging is rare, due to the low uptake of 18F-FDG. However, we reported the research about rectal cancer and colon cancer from our institute before (24-28), and investigated the rectum and colon cancer in this PET-CT study.

Commonly, overall survival rate and 5-year survival rate are used as indicators of survival, whereas the present study used MST. As the median follow-up time was 56 months (4 years and 6 months) in rectum cancer, the 5-year survival rate could not be evaluated. In addition, some patients were lost during the follow-up, thus making it difficult to evaluate the true overall survival rate. Moreover, a long time is necessary to calculate overall survival rate. The present study is retrospective in design; therefore, the timing for follow-up examination (such as blood test, CT, MRI, PET) was not constant. This variation may induce bias when assessing progression-free survival rate and disease-free survival rate. Thus, MST was used as an indicator of survival.

The limitations of the present study include the retrospective study design and the enrollment of a limited number of individuals from a single study site. In addition, cytokines, other humoral factors and fatty acid were not evaluated. There was difficulty in the evaluation about the percentage of colon and rectum cancer patients received PET-CT in all colon and rectum cancer patients Moreover, the cardiac 18F-FDG accumulation in other types of cancer was not assessed. Furthermore, the treatment strategy was heterogeneous and the probability of treatment bias which affect the overall survival rate cannot be excluded. The present study also did not evaluate the 18F-FDG accumulation in the brain. Initially, we aimed to evaluate brain 18F-FDG accumulation by visual evaluation; however, visual evaluation is subjective and cannot indicate minor changes. 18F-FDG metabolism in the brain in each segment may change by physiological changes caused by non-small lung cancer (NSCLC) (29). In this previous retrospective study (29), they compare the brain 18F-FDG uptake pattern between normal group and cancer group by statistical parametric mapping 8 (29), Increased 18F-FDG uptake was detected at the insula, putamen, pallidum, thalamus, hippocampus and amygdala, whereas decreased 18F-FDG uptake was detected at the inferior parietal lobule, left superior parietal lobule and left fusiform gyrus in the NSCLC patient group (29). This may be induced by lung-cancer related visceral sympathetic activation and a decrease in dorsal attention network function (29). This mechanism is still hypothetical but this research is important. Paradoxically, there is difficulty setting a suitable ROI in the brain (stable area) by PET-CT. In addition, 18F-FDG accumulation in the brain is affected by other factors, such as aging and dementia. Three-dimensional stereotactic surface projection (3D-SSP; Nihon Medi-Physics Co., Ltd.) is used for brain 18F-FDG accumulation. 3D-SSP uses Z score, which is an index showing the difference in patient data from the standard deviation in a database of normal subjects (30). In Lewy body disease, N-isopropyl-(123I)-p-iodoamphetamine (cerebral blood) accumulation at frontal lobe is decreased in visual hallucination patients (31). As the present study did not evaluate the 18F-FDG accumulation in the brain, this should be evaluated in future studies, perhaps using a larger group of patients with different types of cancer and prospective multicenter study design

In conclusion, cardiac SUVmax data in patients with rectal cancer and distant metastasis suggested that increased glucose uptake by tumors may reduce glucose uptake by the heart. Cardiac SUVmax may be related to the occurrence of distant metastases and could influence the prognosis of rectal cancer.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

KS and YuO initially designed the present study (KS, gastroenterology; YuO, radiology), collected data, analyzed data, performed visual evaluation of PET-CT and wrote

the manuscript. KS and YuO confirm the authenticity of all the raw data. YA, RyoY, ST, RyuY, TMi, HF, TMo, MH, KH and HS designed and advised the present study based on clinical practice (gastroenterology), interpreted data, checked and revised the manuscript. NT contributed experience of PET-CT, designed and advised the present study on radiology, interpreted data and checked and revised the manuscript. SS and KT reported on related previous research (GLUT-1), designed and advised the present study on molecular biology (GLUT-1), checked the manuscript, interpreted data and revised the manuscript. YoO checked and corrected the initial design, interpreted data and checked and revised the manuscript. YT, KO and MN designed the present study, interpreted data and checked and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was reviewed and approved by the Ethical Review Board of the Iga City General Hospital (approved in February 2022; approval no. 785). Study opt-out was implemented through the hospital website.

Patient consent for publication

Not applicable.

Competing interests

Iga City and the Iga City General Hospital have established endowed chairs with the Department of Gastroenterology and Hepatology at the Kansai Medical University and with the Departments of Gastroenterology and Pediatric Surgery at Mie University. This study was conducted as a research project with Department of Gastroenterology and Hepatology at the Kansai Medical University, Departments of Gastroenterology and Pediatric Surgery at Mie University, and Iga city General Hospital at Iga city General Hospital. YO received a lecture fee (not related this research) and is an officer of EIIS (Expert Imaging and Interventional Support) which charges for the imaging reading at Iga city General Hospital (no reward as an officer). However, the authors declare that they have no competing interests.

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