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ORIGINAL ARTICLE

^{18}F-Fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET) for the early detection of response to neoadjuvant chemotherapy for locally advanced rectal cancer

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Abstract
Purpose Early detection of a response to neoadjuvant chemotherapy for locally advanced rectal cancer may spare patients from additional toxic but ineffective chemotherapy. Using ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG PET), we evaluated tumor response prospectively in the early course of preoperative chemotherapy.
Methods The subjects were 15 patients who received neoadjuvant chemotherapy (XELOX or XELOX plus bevacizumab) for locally advanced rectal cancer. Patients underwent ^{18}F-FDG PET before chemotherapy, at the end of the first cycle of chemotherapy, and before surgical resection. Magnetic resonance imaging (MRI) was performed before chemotherapy, after the second cycle of chemotherapy, and before resection. After resection, the SUVmax and diameter were compared and graded according to the tumor regression grade (TRG).
Results The TRG was assessed as TRG1 in one patient, TRG2 in five patients, and TRG3 in nine patients. We divided the patients into two groups: non-responders (NR) included the TRG1 and TRG2 patients, and responders (R) included the TRG3 patients. The tumor size before surgery was significantly smaller in the R group than in the NR group. The SUVmax at the end of the first cycle of chemotherapy and before surgical resection was significantly lower in the R group than in the NR group.
Conclusion Performing ^{18}F-FDG PET at the end of the first cycle of chemotherapy allowed us to predict the pathological response of locally advanced rectal cancer.

Keywords Rectal cancer · Neoadjuvant chemotherapy · FDG-PET

Introduction

Local recurrence of rectal cancer is difficult to treat and often carries a dismal prognosis. In recent years, surgical and multimodal treatments have been combined to reduce locoregional recurrence. While total mesorectal excision (TME) has dramatically improved oncologic and functional outcomes following surgery for rectal cancer [1–3], the risk of local recurrence continues to threaten patients with locally advanced rectal cancer. As surgery alone is often not curative, preoperative treatment is required to achieve radial resection and to improve the local control rate [4]. A recent report reviewed the strategy of neoadjuvant treatment for locally advanced rectal cancer [5]. Neoadjuvant chemoradiotherapy (CRT) has become standard treatment for locally advanced rectal cancer to prevent local recurrence [6, 7]; however, the adverse effects of radiotherapy compromise the patient's quality of life. Radiation enterocolitis, chronic cystitis, and sexual dysfunction have all been reported to be associated with CRT following TME resection [8–10]. The recent availability of new agents, including capecitabine, irinotecan, and oxaliplatin, has substantially expanded the options available for

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the management of recurrent and unresectable colorectal cancer. Several studies indicate that new chemotherapy regimens can omit radiotherapy from the neoadjuvant settings [11–14]. However, neoadjuvant therapy is not beneficial for all patients. The treatment response ranges from pathological complete response to resistance and favorable regression of advanced rectal cancer is not always achieved with neoadjuvant chemotherapy [11, 14]. Moreover, it is challenging to identify which patients have had no or minimal tumor response to neoadjuvant therapy before or during treatment.

The ^{18}F-FDG PET scan is more accurate than any other technique for detecting residual tumors. Several studies have found that ^{18}F-FDG PET performed after neoadjuvant CRT for rectal cancer can predict patient prognosis [15–17]. However, Leibold et al. reported that early response could not be detected by ^{18}F-FDG PET during preoperative CRT [18]. Aiba et al. suggested that MRI scans before and after neoadjuvant chemotherapy can be helpful to predict treatment response. However, to our knowledge, there are no reports on the early detection of ^{18}F-FDG PET response during neoadjuvant chemotherapy for locally advanced rectal cancer. There is a clear need for a reliable and noninvasive method for predicting treatment response. Thus, we conducted this study to investigate the use of ^{18}F-FDG PET for predicting the pathological grade of rectal cancer.

Patients and methods

Patient selection

Patients with biopsy-proven locally advanced resectable rectal adenocarcinoma (T3 or T4 and N0-N2) diagnosed between 2011 and 2013, were enrolled in this study. Other eligibility criteria were as follows: the tumor was located within 12 cm of the anal verge (mid/lower rectum), as defined by colonoscopy; the patient was 75 years or younger at the time of enrollment; there was no severe impairment of major organ function, including the heart, liver, kidney, and lung; the performance status was 0–1 on the Eastern Cooperative Oncology Group (ECOG) scale; and the fasting blood sugar level did not exceed 150 mg/dl.

Written informed consent was obtained from all patients according to the study protocol. The protocol was approved previously by the institutional review board at the Osaka Rosai Hospital in Sakai, Japan. Table 1 summarizes the clinicopathological characteristics of the patients. The contributions to this study were as follows: conception and design, JN, JH, YO, HM, HY, IT, TM, RN, YD, and MM; patient recruitment, JN, JH, and RN; and analysis and interpretation of data, JN, JH, YO, HM, MU, NH, TH. All authors were involved in the preparation and revision of this report for submission.

Table 1 Clinicopathological characteristics of patients with locally advanced rectal cancer ($n = 15$)

Parameters	
Age, years (mean)	49–73 (64)
Sex, male/female	4/11
Tumor size, mm (mean)	35–110 (58)
Stage	
IIA	2
IIB	1
IIC	1
IIIB	9
IIIC	2
Neoadjuvant CTx	
XELOX	6
XELOX + BV	9

BV bevacizumab, *CTx* chemotherapy, *XELOX* capecitabine and oxaliplatin

Treatment protocols

XELOX consisted of a 2-h intravenous infusion of oxaliplatin, 130 mg/m^2 on day 1, plus oral capecitabine, 1000 mg/m^2 twice daily for 2 weeks of a 3-week cycle. In some patients, bevacizumab 7.5 mg/kg was administered as a 30- to 90-min intravenous infusion before oxaliplatin on day 1 of the 3-week cycle. Preoperative chemotherapy was continued for four cycles. For the bevacizumab-treated patients, bevacizumab was omitted from the last cycle. All patients completed the chemotherapy regimen without grade 4 side effects developing.

^{18}F-FDG PET scan procedure and data interpretation

^{18}F-FDG PET was performed before neoadjuvant chemotherapy (first PET), after one cycle of chemotherapy (second PET), and before surgery (third PET). After the patient had fasted for 5 h, ^{18}F-FDG, 3.083 MBq/kg, was injected intravenously and images were obtained using a combined PET/CT scanner (SET-3000GCT/M, Shimazu, Kyoto, Japan). Image emission data were acquired over approximately 20 min. After attenuation corrections were performed on the obtained data, images were reconstructed using a dynamic row-action maximum likelihood algorithm. The reconstructed sectional images were evaluated visually and quantitatively using the maximum standardized uptake value (SUVmax) inside a volume of interest (VOI) on the lesion. SUVmax was calculated as follows: [(maximum activity in VOI)/(volume of VOI)]/[(injected FDG dose)/(patient weight)]. ΔSUVmax was calculated as follows: [SUVmax (the first PET) − SUVmax (the second or third PET)] × 100/[SUVmax (the first PET)].

MRI scan procedure

MRI scanning was performed before chemotherapy (first MRI), after the second cycle of chemotherapy (second MRI), and before surgery (third MRI). All MRI scans were reviewed by a radiologist (YO). T stage was assessed by MRI T2-weighted images. The longest diameter of the tumor was measured on MRI T2-weighted images.

Histology

The primary tumor and harvested lymph nodes were analyzed microscopically. Slices were stained with hematoxylin-eosin and an experienced pathologist (MH) reviewed all the patient specimens. Pathologic staging of the tumors was done according to the TNM system, as recommended by the AJCC Cancer Staging Manual, 7th edn. [19]. The chemotherapy response was evaluated using the tumor regression grade (TRG) system proposed by Rodel et al. [20] as follows: TRG 0, no regression; TRG 1, minor regression (dominant tumor mass with obvious fibrosis in 25 % or less of the tumor mass); TRG 2, moderate regression (dominant tumor mass with obvious fibrosis in 26–50 % of the tumor mass); TRG 3, good regression (dominant fibrosis outgrowing the tumor mass, representing more than 50 % tumor regression; and TRG 4, total regression (no visible tumor cells, only fibrotic mass).

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for continuous variables and as numbers and percentages for categorical variables. The relationship between the pathologic response as assessed by TRG during or after chemotherapy and the clinical parameters in the responder and non-responder patient groups was established using Fisher's test. The tumor size and SUVmax values were compared among the groups using the paired *t* test. $p < 0.05$ was considered significant.

Results

Primary tumor size

All patients completed the course of neoadjuvant chemotherapy following complete resection. The second MRI was performed 4–8 weeks (mean 6 weeks) after the first round of chemotherapy and the third MRI was performed 12–15 weeks after the first round of chemotherapy. The tumor size was 35–110 mm (median 58 mm) at the first MRI, 18–90 mm (median 35 mm) at the second MRI, and 15–46 mm (median 24 mm) at the third MRI (Fig. 1a). In all patients, the tumor size was smaller at the second and third MRI than at the first MRI.

Time course of SUVmax in the primary tumors

The first PET scan was performed 0–5 weeks (median 1.9 weeks) before chemotherapy was started. The second PET scan was performed 12–38 days (median 15 days) after the start day of the first course of chemotherapy. The third PET scan was performed 9–24 days (median 13 days) after the last chemotherapy was completed. There was a significant decrease in the SUVmax value in the second and third PET scans compared with the first PET scan (Fig. 1b). However, there was no significant decrease from the second to the third PET scans.

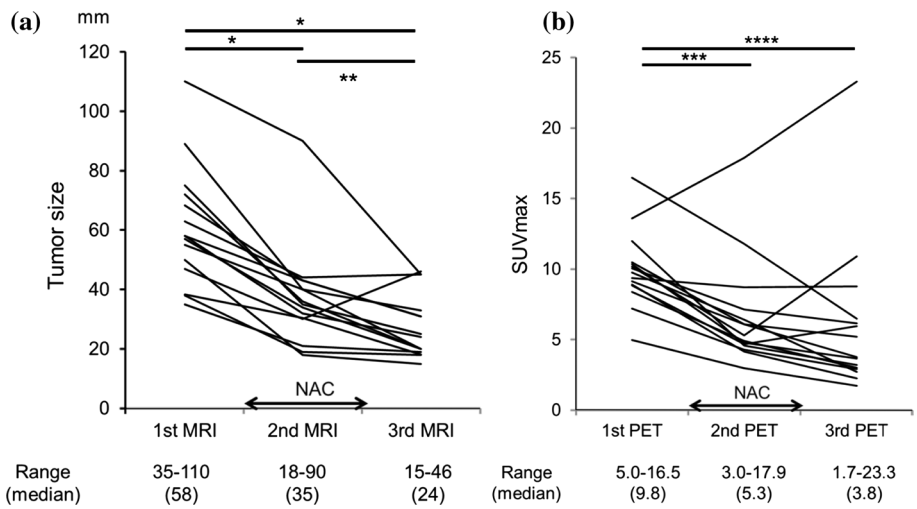

Fig. 1 Tumor size (**a**) and maximum standardized uptake value (SUVmax) (**b**) of the primary tumor. Each *thin line* indicates the tumor size or SUVmax for each patient. *$p < 0.0001$, **$p = 0.012$, ***$p = 0.0002$, ****$p = 0.006$

Table 2 Comparison of clinicopathological parameters in the responder (R) and non-responder (NR) groups

Parameters	R group	NR group	*p* value
Age	49–71 (64)	60–73 (64)	ns
Male/female	5/4	6/0	0.10
Tumor size (mm)	35–110 (55)	47–89 (60.5)	ns
CEA (ng/ml)	1.6–54.9 (5.15)	2.2–30.1 (6.95)	ns
CT classification			
T3	5	3	ns
T4a	3	1	
T4b	1	2	
Stage			
IIA	0	1	ns
IIB	1	0	
IIC	0	1	
IIIB	6	3	
IIIC	1	1	
IIA/IIB/IIC	1	2	ns
IIIB/IIIC	7	4	
Neoadjuvant chemotherapy			
XELOX	3	3	ns
XELOX + BV	6	3	
Histological type			
Well differentiated	6	0	0.028
Moderately differentiated	3	6	
Pre treatment SUV_{max}	4.98–12 (9.14)	8.86–16.5 (10.13)	0.085

Histological chemotherapy response of the primary tumor

After resection, the histopathological response was evaluated according to the TRG. There was one patient with TRG1, five with TRG2, and nine with TRG3. Before chemotherapy, there were no significant correlations between the histological response and any clinicopathological characteristic, including age, sex, tumor size, CEA level, TNM stage, chemotherapy regimen, histological type, or SUVmax (Table 2). The final ypTNM staging was stage I in five patients, stage IIA in six patients, stage IIIA in one patient, and stage IIIB in two patients (supplementary Table 1).

MRI and PET scan results analyzed according to chemotherapy response

The patients were divided into two groups according to their response to chemotherapy. The non-responder (NR) group included TRG1 and TRG2 patients, and the responder (R) group included TRG3 patients. The tumor size on the first and second MRI was not significantly different between the two groups (Fig. 2a). However, the tumor size on the third MRI was significantly smaller in the R group than in the NR group (mean 22.2 vs. 35.0 mm, respectively; $p = 0.017$). We compared the chemotherapy response and SUVmax in the two groups (Fig. 2b). There was no significant difference in SUVmax between the groups before chemotherapy, but it was significantly greater in the NR group on the second PET (4.9 vs. 9.3; $p = 0.023$) and on the third PET (3.2 vs. 10.3; $p = 0.007$).

Tumor shrinkage and ΔSUVmax analyzed according to chemotherapy response

The tumor shrinkage ratio did not differ significantly between the two groups during chemotherapy (Fig. 3a); however, the tumor shrinkage ratio was significantly greater on the third MRI than on the second MRI (60.8 vs. 42.2 %; $p = 0.046$). The ΔSUVmax between the first and second PET scans and the first and third PET scans was compared

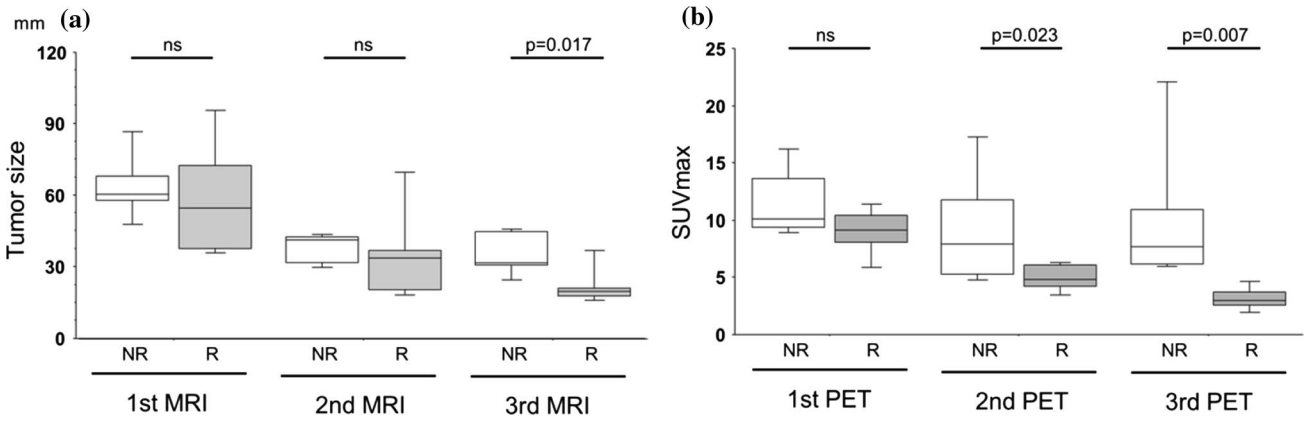

Fig. 2 Box plots of tumor size (**a**) or maximum standardized uptake value (SUVmax) (**b**) in each group. Tumor size and SUVmax were compared between the non-responder (NR) and responder (R) groups

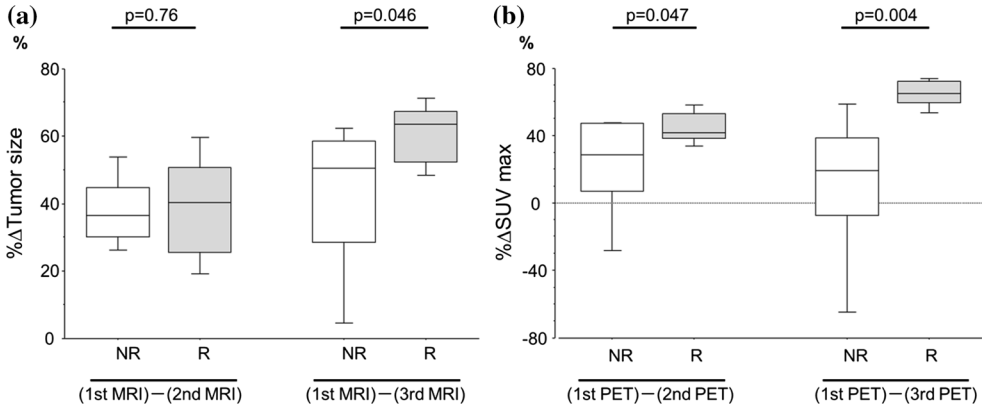

Fig. 3 Box plots of tumor shrinkage ratio (%Δtumor size) (**a**) or reduction rate of SUVmax (%ΔSUVmax) (**b**) for each group. %Δtumor size was calculated as follows: [tumor size in baseline (the first MRI) − tumor size post chemotherapy (the second or third MRI)] × 100/[tumor size in baseline (the first MRI)]. %ΔSUVmax was calculated as follows: [SUVmax (the first PET) − SUVmax (the second or third PET)] × 100/[SUVmax (the first PET)]

in the two groups (Fig. 3b). The ΔSUVmax was significantly higher in the R group than in the NR group after the first round of chemotherapy (44.5 vs. 21.3 %; $p = 0.047$) and before resection (64.8 vs. 10.2 %; $p = 0.004$). After a median follow-up period of 32 months, all patients in the R group remained disease-free; however, two patients in the NR group showed metastatic progression, lung metastasis (DFS 8 months), and liver metastasis (DFS 11 months).

Discussion

This study showed that ^{18}F-FDG PET can predict chemotherapy response after the first chemotherapy course given to patients with locally advanced rectal cancer. In contrast, MRI imaging failed to predict early chemotherapy response.

Neoadjuvant CRT has proven successful for treating locally advanced rectal cancer. Preoperative CRT for rectal cancer has been reported to improve local control and to minimize treatment toxicity more effectively than postoperative CRT [21]. In Western countries, neoadjuvant CRT is used as a standard combined modality treatment for treating locally advanced rectal cancer [21]. XELOX treatment is superior to bolus 5-FU/LV (Mayo Clinic or Roswell Park) as adjuvant treatment, and XELOX chemotherapy has been shown to benefit patients with unresectable metastatic colorectal cancer [22, 23]. The advantages of XELOX or XELOX + BV treatment include that there is no need for a central venous port [24] and that it has been associated with lower rates of neutropenia than FOLFOX [25]. Several groups have looked at omitting radiotherapy from the treatment regimen for locally advanced rectal cancer [11–14]. Several studies of neoadjuvant chemotherapy without radiation for rectal cancer are planned or ongoing (NCT01650428, NCT01515787, and NCT01211210). Thus, preoperative multimodal treatments are still being developed. As for CRT and chemotherapy, tumor responses to neoadjuvant treatment vary considerably. Some patients experience serious side effects and not all patients benefit equally [26]. Moreover, pelvic radiotherapy has been reported to affect sexual function and cause urinary and fecal incontinence [27–29]. There is clinical interest in preventing side effects in patients who are not responding to neoadjuvant treatment.

In this study, the longest tumor diameter measured by MRI was significantly shorter in the R group than in the NR group before resection, whereas the change in diameter did not predict histological response at the end of two cycles of chemotherapy. The RECIST criteria are widely accepted, but the correlation between morphologic tumor response and patient outcome is weak [30]. Several studies have analyzed the tumor volume change on MRI after preoperative CRT as a parameter of treatment response [31–33]. Musino et al. reported that diffusion-weight MRI during preoperative CRT can be used to evaluate the early response of primary rectal tumors [34]. Nougaret et al. reported that MRI volumetry can predict the histological response after four cycles of FOLFOX plus irinotecan chemotherapy [35]. Recently, Aiba et al. reported the usefulness of the MRI calculated total volume before and after neoadjuvant chemotherapy [36]. These reports indicate that two or three dimensional volumes measured by diffusion-weight MRI can be used to predict neoadjuvant-therapy response. Thus, MRI might be a reliable tool for predicting the final clinical T and N stages.

Recent studies have looked at the use of ^{18}F-FDG PET for the early prediction of neoadjuvant CRT response. In the early phase, 8–14 days after starting preoperative CRT, ^{18}F-FDG PET does not predict the pathological response well

enough to justify an early change in therapy [18]. However, 3 weeks after starting CRT, ^{18}F-FDG PET is a reliable and accurate diagnostic tool for assessing response to neoadjuvant treatment [37]. These results indicate that there is an optimal time frame for evaluating treatment response; however, no studies have evaluated ^{18}F-FDG PET as a tool for early prediction of the response to neoadjuvant chemotherapy. In this study, ^{18}F-FDG PET scanning was done at the end of the first cycle of chemotherapy and in all except one patient, the SUVmax had decreased (range −31.6 to 61.7 %). These decreases continued to the time of the preoperative PET scan in the R group. In the NR group, a relapse, indicated by an increasing SUVmax, was noted in three of six patients. Comparing the tumor size as measured by MRI, the SUVmax was significantly decreased in the R group at the end of the first cycle of chemotherapy. Thus, we could detect the decrease in the SUVmax of the primary tumor early in treatment in the R group. Early identification of inadequate response to neoadjuvant treatment could spare the patients from the toxicity of ineffective treatment. If the decrease in the SUVmax was poor, neoadjuvant therapy could be changed to a more powerful chemotherapy regimen including targeted therapy or additional radiotherapy during the neoadjuvant chemotherapy. However, the true ability of the ^{18}F-FDG PET scan to detect early tumor response cannot be confirmed based on the limited number of patients in this series, so further studies are warranted. While the median follow-up period was short, distant metastases developed in two patients from the NR group developed, but in none from the R group. These outcomes might suggest that the primary tumor response to neoadjuvant chemotherapy reflects the response to distant micrometastasis. From this viewpoint, ^{18}F-FDG PET scan results at the end of the first cycle of chemotherapy could be a prognostic factor for locally advanced rectal cancer. Thus, when the SUVmax does not decrease, treatment for primary tumor or adjuvant chemotherapy should be changed to more powerful systemic chemotherapy.

In conclusion, our data show that the ^{18}F-FDG PET scan may be a useful tool for predicting primary tumor early response to neoadjuvant chemotherapy.

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Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

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