Cancer Chemother Pharmacol (2017) 80:1219–1226
DOI 10.1007/s00280-017-3442-2

ORIGINAL ARTICLE

The potential usefulness of the Response Index in positron emission tomography assessing the therapeutic effect of pre-operative chemotherapy for advanced colorectal cancer

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Received: 10 February 2017 / Accepted: 22 September 2017 / Published online: 26 October 2017

Abstract

Background and purpose Pre-operative chemotherapy is an option for patients with local advanced rectal cancer, but the response rate to pre-operative chemotherapy with oxaliplatin is still low. If the therapeutic effect of pre-operative chemotherapy could be assessed, we may be able to convert to surgery early. The purpose of the present study was to validate the correlation between the maximum standardized uptake value (SUV_{max}) in 18F-fluorodeoxyglucose positron emission tomography–computed tomography (PET–CT) of the primary tumor and the therapeutic effect of pre-operative chemotherapy in advanced colorectal cancer.

Patients and methods Retrospective cohort study from January 2011 to October 2015. We examined 28 patients with pathologically confirmed sigmoid or rectal cancer that underwent pre-operative chemotherapy and surgery. The correlation between Response Index (RI), calculated as (SUV_{max} after chemotherapy)/(SUV_{max} before chemotherapy), and the therapeutic effect on the primary tumor in advanced colorectal cancer.

Results The degree of differentiation ($p = 0.04$), SUV_{max} in the primary tumor after chemotherapy ($p = 0.02$), and RI ($p = 0.008$) were significant predictors of the therapeutic effect in univariate analysis. The areas under the ROC curve constructed with RI and therapeutic effect was 0.77. The optimal cut-off values for the RI in the responder group was < 0.32.

Conclusion RI calculated as (SUV_{max} after chemotherapy)/(SUV_{max} before chemotherapy) in the primary tumor significantly correlated with the therapeutic effect of chemotherapy on advanced colorectal cancer. Thus, RI is potentially useful for predicting the therapeutic effect in advanced colorectal cancer.

Keywords Colorectal cancer · Pre-operative chemotherapy · PET–CT · Therapeutic effect · SUV_{max}

Introduction

Colorectal cancer is the third most common cancer in the world, with nearly 1.4 million new cases diagnosed in 2012 [1]. The prognosis of rectal cancer is generally poorer than that of colon cancer, but it was recently improved by progress in chemotherapy, radiotherapy, and surgical techniques, such as total mesorectal excision and tumor-specific mesorectal excision [2]. Pre-operative therapy for local advanced rectal cancer is recommended to reduce the risk of local recurrence, improve resectability, and preserve anal, sexual, and urinary function [3]. Neoadjuvant chemoradiotherapy (CRT) is effective for reducing the local recurrence rate in local advanced rectal cancer [4–8]. However, the recurrence rate is still ~ 30% at 5 years, higher than that of colon cancer, mainly because of recurrence of distant metastases [9]. In addition, radiotherapy has adverse effects, such as intestinal obstruction and sexual and urinary dysfunction. Therefore, chemotherapy is used as a pre-operative therapy.

The total clinical response rate is approximately 70% for local advanced rectal cancer when the capecitabine + oxaliplatin (XELOX) regimen is used as neoadjuvant chemotherapy [10]. For patients with rectal cancer, poorly reactive to pre-operative therapy, pre-operative therapy could

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not only be not effective but also harmful. Furthermore, the rate of patient completion of adjuvant chemotherapy with oxaliplatin is low [11]. Therefore, an accurate in vivo assessment of the response to pre-operative therapy is essential to determine which patients have poorly reactive rectal cancer.

We usually perform ^{18}F-fluorodoxyglucose positron emission tomography–computed tomography (PET–CT) to stage colorectal cancer and confirm tumor location and the extent of colorectal cancer in our department. Recently, we began administering neoadjuvant chemotherapy for patients with rectal cancer clinical suspected of lymph node metastasis or clinical T3 and T4, performing PET–CT before and after treatment to evaluate rectal cancer stage. Previous studies demonstrated that PET–CT for the recurrence of rectal cancer after surgery [12, 13] is useful for assessing therapeutic effects after neoadjuvant CRT [14], but few reports address the usefulness of pre-operative chemotherapy for colorectal cancer.

The aim of this study was to investigate a novel in vivo indicator of the chemotherapeutic effect on histopathology in advanced colorectal cancer patients using PET-related parameters, such as the maximum standardized uptake value (SUV_{max}).

Patients and methods

Study design and patient characteristics

The present retrospective study was approved by our Institutional Review Board (approval number 15144). Table 1 provides the clinicopathological characteristics of the patients. From January 2011 to October 2015, 65 patients < 75 years of age with pathologically confirmed sigmoid colon cancer or rectal cancer underwent their first operation after pre-operative chemotherapy at our department. Their performance status was 0–1 on the Eastern Cooperative Oncology Group (ECOG) Scale. Of these patients, 28 underwent PET–CT before and after pre-operative chemotherapy and were enrolled in this study. Four patients were eliminated because they also underwent radiotherapy; 33 patients did not undergo PET–CT twice. One of the 28 enrolled patients

Table 1 Clinicopathological characteristics of responders and non-responders

Characteristic	All patients ($n=28$)	Responders ($n=13$)	Non-responders ($n=15$)	p value
Age (years)	63 ± 7.8	62 ± 8.0	64 ± 7.8	0.46
Male/female	21/7	8/5	13/2	0.12
Clinical T stage				
cT1/T2/T3/T4	0/4/15/10	0/1/7/5	0/3/8/4	–
Location of tumor				
Sigmoid colon/rectum	1/27	1/12	0/15	–
Adjuvant chemotherapy				
XELOXIRI/XELOX/XELOX + Bev/FOLFOX/FOLFOX + Bev	10/13/3/1/1	5/5/2/0/1	5/8/1/1/0	–
Serum CEA levels				
Before chemotherapy	11 ± 27	4.3 ± 3.0	16 ± 36	0.23
After chemotherapy	4.8 ± 5.8	4.1 ± 3.6	5.4 ± 7.2	0.63
Ratio	1.0 ± 0.79	1.1 ± 0.79	0.96 ± 0.80	0.55
Pathological T stage				
ypT0/T1/T2/T3/T4	2/1/12/12/1	2/0/6/4/1	0/1/6/8/0	–
Degree of differentiation				
tub/por, muc	25/3	13/0	12/3	**0.04**
SUV_{max} in the primary tumor				
Before chemotherapy	12 ± 4.4	12 ± 4.6	12 ± 4.1	0.99
After chemotherapy	6.7 ± 6.7	3.8 ± 3.8	9.3 ± 7.6	**0.02**
RI	0.58 ± 0.43	0.36 ± 0.37	0.77 ± 0.39	**0.008**

Data are presented as mean ± SD or number of patients

Significant values are in bold

XELOXIRI capecitabine, oxaliplatin, and irinotecan, *XELOX* capecitabine and oxaliplatin, *Bev* bevacizumab, *FOLFOX* 5-fluorouracil, oxaliplatin, and levofolinate calcium, *CEA* carcinoembryonic antigen, *tub* tubular adenocarcinoma, *por* poorly differentiated adenocarcinoma, *muc* mucinous adenocarcinoma, SUV_{max} maximum standardized uptake value, *RI* Response Index

had both rectal and esophageal cancer, and rectal cancer was operated on first.

T stage refers to the UICC TNM classification of colorectal carcinoma. Quantitative values were expressed as mean ± standard deviation (SD). The serum carcinoembryonic antigen (CEA) ratio was defined as the ratio of serum CEA levels before and after chemotherapy. The degree of differentiation was classified into two groups: well- and moderately differentiated tubular adenocarcinoma, or others.

Treatment and imaging schedule

Patients received one of five oxaliplatin-based regimens as pre-operative chemotherapy: XELOXILI [130 mg/m^2 oxaliplatin and 150 mg/m^2 irinotecan on day 1, oral capecitabine (1000 mg/m^2) twice daily for a week in a 2-week cycle] in ten patients, XELOX (1000 mg/m^2 capecitabine twice daily for 2 weeks and 130 mg/m^2 oxaliplatin on day 1 of a 3-week cycle) in 13 patients, XELOX + bevacizumab (XELOX regimen and 7.5 mg/kg bevacizumab before oxaliplatin on day 1 of a 3-week cycle) in 3 patients, FOLFOX (85 mg oxaliplatin on day 1, 200 mg/m^2 levofolinate calcium on day 1, 400 mg/m^2 5-fluorouracil via rapid intravenous infusion after oxaliplatin and levofolinate calcium on day 1, and 2400 mg/m^2 continuous intravenous infusion during days 1–2 of a 2-week cycle) in 1 patient, or FOLFOX + Bev (FOLFOX regimen and 5 mg/kg bevacizumab via intravenous infusion on day 1 of a 2-week cycle) in 1 patient. Fundamentally, XELOXILI was carried out for six cycles and XELOX for four cycles before surgery. The number of cycles for the other chemotherapies was determined by each physician.

PET–CT

All patients underwent PET–CT before and after pre-operative therapy. The time elapsed between the PET–CT evaluations, pre-operative therapy, and surgery are provided in Table 2. All patients fasted for at least 4 h before injection of ^{18}F-FDG (3.7 MBq/kg). Blood glucose levels were measured systematically before ^{18}F-FDG injection. PET–CT was performed using a Discovery PET/CT 710 (GE Healthcare, Little Chalfont, UK) 60 min after ^{18}F-FDG injection. The reconstructed sectional images were evaluated using SUV_{max} inside a volume of interest (VOI) on the lesion.

SUV_{max} was calculated as (maximum activity in VOI/volume of VOI)/(injected FDG dose/patient weight). This value was used to assess the response to pre-operative chemotherapy by calculating a Response Index (RI). The RI is calculated as the ratio of SUV_{max} after and before chemotherapy.

Chemotherapy grade

We investigated the correlation between RI and the therapeutic effect of chemotherapy on pathology. The therapeutic effect referred to the classification of chemotherapy grade. Chemotherapy grade are classified according to five-point grades based on residual tumor. Chemotherapy grade 0: there is almost no change due to treatment on cancer cells, grade 1a: a slight change is observed in cancer cells and a high degree of change is observed in cancer cells of about less than 1/3, grade 1b: a high degree of change is observed in cancer cells of about more than 1/3 and less than 2/3, grade 2: about 2/3 or more of the cancer cells show a high degree of change, but obvious cancer lesions remained, grade 3: all cancer cells are necrosed or disappeared.

We defined grade 0 and 1a are non-responders, and grades 1b, 2, and 3 are responders. In this study, pathologists were not specified and did not know the result of PET–CT.

Statistical analysis

We assessed whether the non-responder and responder groups correlate with clinicopathological factors. Age, serum CEA levels, SUV_{max}, RI, and the duration were compared among groups using t test. We investigated the correlation between therapeutic effect and sex or tumor differentiation using Fisher's test. Receiver operating characteristic (ROC) curves were constructed with the RI; we determined cut-off values for the RI and examined their correlation with therapeutic effect. The statistical tests were performed using JMP Pro 11.2.0 (SAS Institute Inc., Cary, NC, USA). $p < 0.05$ was considered significant.

Table 2 Time between first PET and chemotherapy, chemotherapy and second PET, and second PET and surgery

	All patients ($n = 29$)	Responders ($n = 13$)	Non-responders ($n = 15$)	p value
First PET-chemotherapy (days)	27 ± 15	26 ± 12	29 ± 18	0.59
Chemotherapy-second PET (days)	17 ± 13	21 ± 12	14 ± 13	0.17
Second PET-surgery (days)	21 ± 16	15 ± 7.0	25 ± 21	0.10

Data are presented as mean ± SD

Results

Therapeutic effect in the primary tumor

The grade of the therapeutic effect in the primary tumor was 0 in 1 patient (3.5%), 1a in 14 patients (50%), 1b in 9 patients (32%), 2 in 2 patients (7.1%), and 3 in 2 patients (7.1%). Therefore, the responder group included 13 patients and the non-responder group 15 patients. The therapeutic effect of each regimen is provided in Table 1. A complete response was achieved only with the XELOX regimen.

Comparison of responders and non-responders

In the univariate analysis, we found no significant difference between age, sex, serum CEA levels before and after chemotherapy, CEA ratio, SUV_{max} in the primary tumor before chemotherapy, and the therapeutic effect, whereas the degree of differentiation, SUV_{max} in the primary tumor after chemotherapy, and RI were significantly associated with the therapeutic effect (Table 1). Figure 1 summarizes the SUV_{max} in the primary tumor before and after chemotherapy in the non-responder and responder groups.

RI cut-off values

The ROC curve constructed with the RI and therapeutic effect is shown in Fig. 2. The area under the curve was 0.77. The optimal criterion for separating the responders from the non-responders was RI = 0.31 (62% sensitivity and 93% specificity). In the case of a cut-off of 0.32, the therapeutic effect, sex, and serum CEA levels after chemotherapy significantly correlated with RI (Table 3). The RI for one non-responder in the low RI group was 0.27.

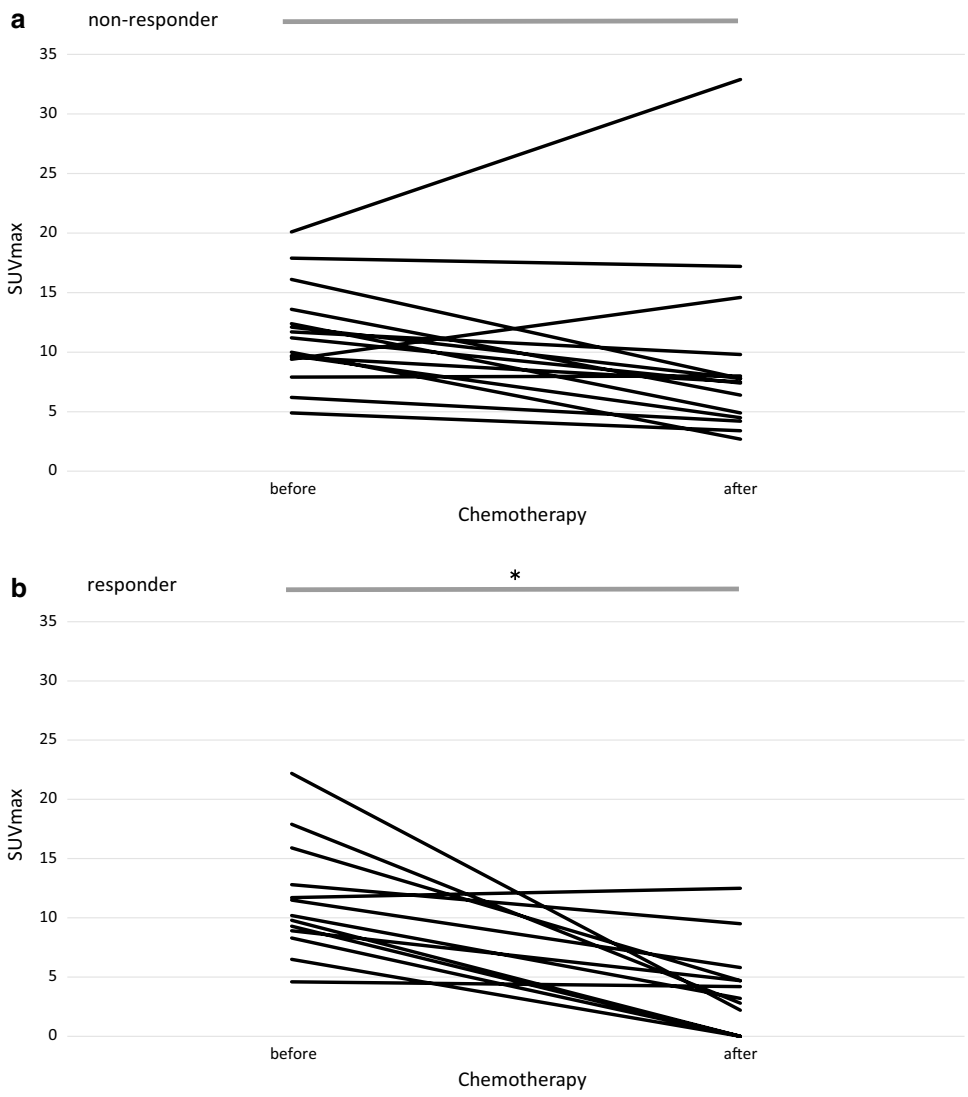

Fig. 1 Maximum standardized uptake value in the primary tumor before and after preoperative chemotherapy in **a** the non-responder group (grade 0, 1a) and **b** responder group (grade 1b, 2, and 3). *$p = 0.0004$

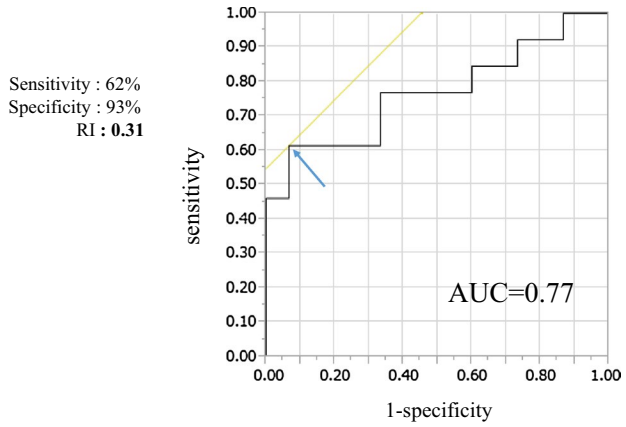

Fig. 2 ROC curve using SUVmax to predict the effect of chemotherapy. The RI cut-off is indicated by a blue arrow

Discussion

This study indicates that SUV_{max} is potentially useful for predicting the therapeutic effect of pre-operative chemotherapy on local advanced colorectal tumors. Moreover, if the RI is ≥0.32, the patient may be a non-responder.

In Europe and the US, neoadjuvant CRT is commonly used in the treatment of local advanced rectal cancer. Neoadjuvant CRT decreases the local recurrence rate of local advanced rectal cancer compared to adjuvant CRT and has a lower risk of complications, such as diarrhea and anastomotic stenosis, than adjuvant CRT [15]. However, neoadjuvant CRT did not improve overall survival (OS) and relapse-free survival (RFS) [15]. In other words, neoadjuvant CRT may not be enough to improve long-term outcomes. In addition, neoadjuvant radiotherapy has a higher risk of complications, such as urinary and sexual dysfunction and bowel problems [16–18]. Fibrosis of surrounding tissue by radiation may make it more difficult to operate, causing these complications [19].

Hasegawa et al. reported a response rate of 78.3% for neoadjuvant XELOX combined with bevacizumab for high-risk rectal cancer. In addition, major complications did not occur; five patients exhibited metastatic progression, including one case involving local failure. However, anemia, neutropenia, arterial hypertension, bleeding, asthenia, emesis, obstruction, thromboembolic events, and fistula/pelvic abscess of grade 3 or greater were each observed in one patient. Bevacizumab may be associated with hypertension, bleeding, thromboembolic events, and pelvic infection. Two patients (8.0%) could not undergo resection because of tumor progression [20]. Uehara et al. also administered XELOX + bevacizumab to advanced rectal cancer, with a completion rate of 84.4% and pathological complete response (pCR) rate of 13.3% [21]. This completion rate is markedly superior to that of adjuvant chemotherapy after surgery [11]. Deng et al. reported modified FOLFOX 6 with and without radiation for local advanced rectal cancer. Neoadjuvant chemotherapy had a

Table 3 Clinicopathological characteristics according to Response Index (RI) group

Characteristic	All patients ($n=28$)	Low RI (<0.32) ($n=9$)	High RI (≥0.32) ($n=19$)	p value
Age (years)	63 ± 7.8	62 ± 7.0	63 ± 8.4	0.88
Male/female	21/7	4/5	17/2	**0.01**
T stage before any therapy				
cT1/T2/T3/T4	0/4/15/9	0/2/6/2	0/2/9/7	–
Location of tumor				
Sigmoid colon/rectum	1/27	0/10	1/17	–
Serum CEA levels				
Before chemotherapy	11 ± 27	3.7 ± 3.3	14 ± 33	0.18
After chemotherapy	4.9 ± 5.7	2.2 ± 1.5	6.2 ± 6.5	**0.02**
Ratio	1.0 ± 0.79	0.89 ± 0.60	1.1 ± 0.87	0.43
Pathological T stage				
ypT0/T1/T2/T3/T4	2/1/12/12/1	2/0/5/3/0	0/1/7/9/1	–
Degree of differentiation				
tub/por, muc	25/3	9/0	16/3	0.11
SUV_{max} in the primary tumor				
Before chemotherapy	12 ± 4.4	12 ± 5.2	11 ± 4.0	0.60
After chemotherapy	6.7 ± 6.7	1.7 ± 1.8	9.1 ± 6.8	**0.004**
Chemotherapy effect				
Responder/non-responder	13/15	8/1	5/14	**0.001**

Data are presented as mean ± SD or number of patients. Significant values are in bold

lower pCR rate than neoadjuvant CRT, but the T down-staging was comparable to neoadjuvant CRT [18].

Fernandez et al. reported short disease-free survival with neoadjuvant chemotherapy (XELOX + bevacizumab) for intermediate-risk rectal adenocarcinoma [22]. However, Schrag et al. reported a 4-year disease-free survival of 84% in intermediate-risk rectal cancer patients after neoadjuvant chemotherapy (FOLFOX + bevacizumab) [23]. For local advanced rectal cancer, long-term outcome trials, such as NCT01515787, are ongoing. The long-term outcomes of neoadjuvant chemotherapy with or without radiation therapy remain unclear for local advanced rectal cancer [24]. In our study, the clinical response rate was 93%, with two patients having endoscopically confirmed progressive disease before surgery.

Therefore, we need to administer neoadjuvant chemotherapy without bevacizumab, such as XELOX and XELOXIRI. Furthermore, we must evaluate the therapeutic effect of neoadjuvant chemotherapy in the early cycles in terms of adverse events and tumor progression. We validated that SUV_{max} can serve as a barometer of the therapeutic effect of pre-operative chemotherapy on colorectal cancer.

The response rates in the XELOX and XELOXIRI groups are given in Table 4. In the XELOX group, three patients were administered less than four cycles, and their therapeutic effect grade was 1a. In the XELOXIRI group, only one patient was administered less than six cycles, achieving a therapeutic effect grade of 0. In terms of the RI, the XELOXIRI group had significantly lower values than the XELOX group, though no significant difference was found in terms of therapeutic effect grade.

Serum CEA levels before chemotherapy tended to be higher in non-responder, it might be thought that high serum CEA levels caused the therapeutic effect to be low. However, there were cases of serum CEA levels decreased by chemotherapy remarkedly in non-responder, in contrast there were cases of serum CEA levels increased by chemotherapy in responder. Tumor marker value is in normal level in many cases, furthermore, it is not useful for therapeutic effect of primary tumor in stage IV cases.

The advantage of RI can show the metabolism in each tumor and estimate the state of each tumor objectively. PET–CT has been reported to be able to detect an early response of chemotherapy in rectal cancer [25]. RI can evaluate early response of chemotherapy, therefore, RI is useful for the judgement of the therapeutic effect in early cycle of chemotherapy. If we judge as non-responder according to RI, we must consider another chemotherapy, in addition of radiotherapy, or early surgery. In some cases, even if SUV_{max} decreases in early PET–CT, it may increase in late PET–CT [25]. Thus, it is necessary to perform PET–CT before surgery. If possible, PET–CT must be performed three times. If early and late PET–CT are performed, the therapeutic effect can be determined more exactly and non-responders

Table 4 Clinicopathological characteristics of the XELOX and XELOXIRI groups

Characteristic	All patients ($n=23$)	XELOX ($n=13$)	XELOXIRI ($n=10$)	p value
Age (years)	63 ± 8.3	61 ± 8.6	65 ± 7.6	0.23
Male/female	18/5	10/3	8/2	0.86
T stage before any therapy				
cT1/T2/T3/T4	0/4/14/5	0/3/7/3	0/1/7/2	–
Location of tumor				
Sigmoid colon/rectum	0/23	0/13	0/10	–
Serum CEA levels				
Before chemotherapy	5.2 ± 7.5	6.3 ± 9.7	3.7 ± 2.8	0.37
After chemotherapy	3.6 ± 3.9	3.4 ± 4.1	3.8 ± 3.9	0.81
Ratio	1.1 ± 0.81	1.0 ± 0.79	1.2 ± 0.86	0.63
Pathological T stage				
ypT0/T1/T2/T3/T4	2/1/11/9/0	2/1/3/7/0	0/0/8/2/0	–
Degree of differentiation				
tub/por, muc	21/2	11/2	10/0	0.12
SUV_{max} in the primary tumor				
Before chemotherapy	11 ± 4.7	12 ± 4.5	11 ± 5.2	0.70
After chemotherapy	6.8 + 7.3	9.5 ± 8.6	3.3 ± 2.9	**0.03**
RI	0.58 ± 0.47	0.76 ± 0.49	0.35 ± 0.33	**0.03**
Chemotherapy effect				
Responder/non-responder	13/10	8/5	5/5	0.13

Data are presented as mean ± SD or number of patients. Significant values are in bold

RI Response Index

detected. In addition, therapy without radiotherapy accumulated less ^{18}F-FDG than therapy with radiotherapy [14].

A cut-off value for the RI has not previously been reported for pre-operative chemotherapy in colorectal cancer. In this study, we set a high specificity for predicting therapeutic effect.

Our study is limited by the classification of responders (grade 1b, 2, 3) and non-responders (grade 0, 1a). There may be obvious differences between grade 1a and grade 2/3, but it may be difficult to classify between grade 1a and 1b. If the RI was compared to an alternative barometer, such as ki-67, there may be a more positive correlation. In terms of picking out non-responders, we set the RI cut-off as 0.32. This value may change with more cases. In addition, we employed only SUV_{max} to evaluate the therapeutic effect. We may be able to evaluate the therapeutic effect more exactly if assessments, such as RECIST classification, were added.

Conclusion

This retrospective study showed that the ratio of SUV_{max} in the primary tumor before and after chemotherapy for advanced colorectal cancer significantly correlated with the therapeutic effect on pathology. If the RI is < 0.32, the colorectal cancer patient may be a responder.

Compliance with ethical standards

Conflict of interest All authors had no commercial interest in the study subject.

Ethical standards This report is a retrospective cohort study.

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