The Efficiency of ^{18}F-FDG-PET/CT in Assessment of Tumor Response to Preoperative Chemoradiation Therapy for Locally Recurrent Rectal Cancer

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Research article

Keywords: Locally recurrent rectal cancer (LRRC), PET-CT, Chemoradiation, Response assessment, Pathologic response

Posted Date: March 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-318397/v1

Abstract

Background:

Locally recurrent rectal cancer (LRRC) remains a major problem after curative resection of primary rectal cancer. A noninvasive biomarker that accurately evaluates the disease status and assesses the treatment response with prognostic value is critically needed to optimize the treatment plan. This study assesses the effectiveness of PET/CT evaluation of preoperative chemoradiation therapy (CRT) in patients with LRRC.

Patients and Methods:

Since 2004, we have been performing preoperative CRT to improve local tumor control and survival. Between 2004 and 2013, 40 patients with LRRC underwent preoperative CRT (radiation; 50 Gy/25 fractions, chemotherapy; irinotecan plus UFT/leucovorin) and radical surgery, and underwent ^{18}F-FDG-PET/CT before and 3 weeks after the completion of CRT. The maximum standardized uptake value (SUVmax) of the pre-CRT scan (Pre-SUV) and the post-CRT scan (Post-SUV) were measured. The predictive ability of ^{18}F-FDG-PET and CT/MRI response assessment were evaluated.

Results:

The mean Pre-SUV was significantly higher than Post-SUV (8.2±6.1, vs 3.8±4.0; $P < 0.0001$). Following CRT, 17/40 patients (42.5%) were classified as responders according to Mandard tumor regression grade (TRG1-2). The mean Post-SUV was significantly lower in responders than in nonresponders (2.0±1.7 vs 5.1±3.9; $P = 0.0038$). Pathological response was not correlated with the response as evaluated by CT ($P > 0.9999$) or MRI ($P > 0.9999$). Multivariate regression analysis identified Post-SUV as an independent predictor of local re-recurrence-free survival ($P = 0.0383$) and for overall survival ($P = 0.0195$).

Conclusions:

PET/CT is useful in assessing tumor response to preoperative CRT for LRRC and predicting prognosis after surgery.

Introduction

Locally recurrent rectal cancer (LRRC) remains a major problem after curative resection of primary advanced rectal cancer [1]. The reported incidence of LRRC ranges between 5% and 30% after curative resection [2, 3]. Since 20% to 50% of these patients have local recurrence in the absence of distant metastasis, surgical intervention is one of the best curative treatment choices [3, 4]. Local control and long-term survival are possible for patients with isolated pelvic recurrence after extended radical operations, such as total pelvic exenteration. However, local re-recurrence and distant metastasis after resection of LRRC are relatively frequent [5]. We have been performing preoperative chemoradiation therapy (CRT) aiming to achieve local control and survival benefit [6]. Assessment of the tumor response is clinically important, but evaluation of the extent of LRRC by abdomino-pelvic computed tomography (CT) and pelvic magnetic resonance imaging (MRI) is sometimes difficult due to the main characteristics of LRRC, such as infiltrating growth, tissue scarring, and fibrosis [5].

^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-PDG-PET) is a powerful, noninvasive tool for imaging tumor metabolic activity [7] particularly suitable to assessment of changes in tumor glucose metabolism after

neoadjuvant treatment. The semiquantitative assessment of glucose metabolism by evaluation of the standardized uptake value (SUV) has been shown to have clinical relevance in evaluation of the response to CRT in several tumor types, including esophageal and advanced rectal cancer [8-10].

The objective of this study is to assesses the effectiveness of ^{18}F-FDG-PET/CT (PET-CT) evaluation of preoperative chemoradiation therapy (CRT) in patients with LRRC.

Materials And Methods

Patients

Between 2004 and 2013, a total of 82 patients underwent resection for LRRC at the Department of Surgery, Gastroenterological Surgery, Osaka University Hospital. All patients had undergone a previous curative intent resection for primary rectal cancer without pre or post operative radiation therapy. Of these, 40 patients (26 male and 14 female) underwent preoperative CRT and radical surgery with pre- and postoperative PET-CT evaluation at the Department of Surgery, Gastroenterological Surgery, Osaka University Hospital. The extent of the recurrent tumor was evaluated by abdomino-pelvic CT, MRI, and colonoscopy. All patients underwent surgery between 3 and 6 weeks after completion of CRT. Resection was performed with curative intent on all patients. Patients were excluded from extensive pelvic surgery for posterior invasive LRRC when they exhibited distant metastasis or cancerous ascites. Sacral resections were performed only in the caudal regions (below S2) to preserve S1 sacral nerve function and to prevent walking disorders. Patients with apparent invasion to bone parenchyma of side pelvic wall were also excluded from radical surgery. The median follow-up period after surgery was 53 (range 5.3–172) months.

PET/CT

Patients fasted at least 6 hours before PET-CT scanning to minimize the blood insulin level and ensure standardized metabolism across patients. Blood glucose levels were determined just before FDG injection. All patients were normoglycemic (blood glucose < 150 mg/dL). Whole-body images were obtained 1 hour after FDG injection (transmission source 68Ge-68Ga line source). Imaging was subsequently performed with a dedicated PET scanner (HEADTOME/SET 2400W; Shimadzu Co, Kyoto, Japan). All patients received an PET/CT scan before CRT and another scan 3 weeks after completion of CRT. In a pilot phase of the study, 12 patients received an additional PET scan 2 weeks after the beginning of CRT as an interim assessment.

The maximum standardized uptake value (SUVmax) was calculated according to the following formula: PET count at most intense point ×calibration factor (MBq/kg)/injection dose (MBq)/body weight (kg). The SUVmax values of the pre-CRT scan (Pre-SUV), interim scan (Mid-SUV), and the post-CRT scan (Post-SUV) were measured. ⊿SUV was defined by calculating the Pre-SUV−Post-SUV difference, and the percentage decrease between the Pre-SUV and the Post-SUV was presented as the decreasing rate (DR) = (⊿SUV/Pre-SUV) × 100. Correlations between each of the SUV parameters (Pre-SUV, Post-SUV, ⊿SUV, and DR) and pathologic tumor responses were analyzed.

Preoperative chemo-radiotherapy

Preoperative radiation therapy of 50 Gy/25 fractions was delivered to the pelvis over 5 weeks (2 Gy/day for 5 days per week). Chemotherapy consisting of irinotecan (given biweekly at 30-60 mg/m^2) plus UFT/leucovorin (given as a daily dose; 300 mg/m^2/day and 75 mg/body/day, respectively) was administered concomitantly.

Pathological assessment of response to preoperative CRT

Tumor response was assessed based on tumor viability and the extent of fibrosis and inflammation. Tumor regression grade (TRG), as described by Mandard et al. [11] in patients treated for esophageal cancer, was used to assess the pathologic tumor response after preoperative therapy. TRG score induced by the neoadjuvant CRT was defined as follows: TRG1, complete regression with absence of residual cancer and fibrosis extending through the wall; TRG2, presence of rare residual cancer cells scattered through fibrotic tissue; TRG3, increase in the number of residual cancer cells, with fibrosis predominant; TRG4, residual cancer outgrowing fibrosis; and TRG5, absence of regressive changes. We categorized responders as patients with TRG1 and TRG2 scores, while nonresponders had scores of TRG3 to TRG5. Resection was considered complete (R0) if a complete microscopic resection was confirmed, and R1 resection was defined in cases where resection was macroscopically complete but microscopically incomplete.

Response evaluation by CT and MRI

Tumor response after preoperative CRT was evaluated by CT and MRI after the completion of preoperative CRT, according to assessment using RECIST criteria [12]. We defined responders as those patients obtaining a complete (CR) or partial (PR) response.

Statistical Analysis

Continuous data were expressed as median and range. Statistical analysis was performed using the c^2 test or Fisher's exact test for categorical data and Mann-Whitney U test for nonparametric data. The Kaplan–Meier method was used to examine disease-free survival, and the log-rank test was used to examine statistical significance. Prognostic factors were evaluated by univariate and multivariate analyses (Cox proportional hazard regression model). A value of $P < 0.05$ was considered significant. Statistical analysis was performed using JMP software (SAS Institute Inc., Cary, NC, USA).

Results

Patients and treatment for LRRC

A total of 26 males and 14 females were enrolled, with a median age of 68.5 years (36-81). All patients received radical resection with curative intent after pre-operative CRT. Among the 40 patients, 22 underwent total pelvic exenteration, while 10 patients underwent abdominoperineal resection, and 6 underwent low anterior resection. Sacral bone resection was concomitantly performed in 21 patients (52.5%) to secure a negative surgical margin. Resection was considered to be curative (R0 resection) in 36 patients and microscopically incomplete (R1) in 4 patients. According to Mandard's criteria [11], 17 of the 40 patients were classified as responders (TRG1-TRG2) and 23 patients were classified as nonresponders (TRG3-TRG5). Clinical characteristics of the patients are described in Table 1-a.

Response assessment by PET-CT

Pre-SUVs ranged from 1.0 to 26.3 (8.2±6.1, median 5.9). Post-SUVs ranged from 0.0 to 18.7 (3.81±4.0, median 3.0), and Post-SUVs were found to be significantly lower than the pre-SUVs ($P < 0.0001$). The mean ⊿SUV was 4.4±4.8 (range, -1.3–22.5, median 2.8). The mean DR was 48.1±30.3% (range, -30.2–100, median 44.7%) (Table 1-b).

Twelve patients underwent PET-CT after the initial 2 weeks of CRT. In this pilot phase study, Post-SUVs were significantly lower than Pre-SUVs (P = 0.0442). However, Mid-SUVs were not significantly different from Pre-SUVs and Post-SUVs (P = 0.215 and 0.4068, respectively) (Supplementary Figure 1)**.** Subsequent to the pilot phase, Mid-SUVs were no longer examined because this time point appeared to be too soon to assess the effect of CRT.

Post-SUVs in the responder (TRG1-2, n = 17) group were significantly lower than those in the nonresponder (TGR3-4, n = 23) group (2.0±1.7 vs. 5.1±3.9, P = 0.0038). DR (%) was significantly higher in the responder group than in the nonresponders (65.3±32.3 vs. 35.4±21.7, P = 0.0012). Pre-SUVs and ⊿SUV were not significantly different between the responder and the nonresponder groups (P = 0.5103 and 0.2502, respectively) (Table 2).

Response assessment by CT and MRI

Table 3 shows the relationship between the CT/MRI response evaluation and pathological response grade. Most of the patients were classified in the nonresponder group by CT or MRI evaluation (26/40: 65.0% and 28/40: 70.0%, respectively), though almost half of these nonresponders were classified as responders using the pathological criteria (11/26: 42.3% and 11/28: 39.2%, respectively). There was no significant correlation between histological response classification and CT/MRI response classification (P > 0.9999 and P > 0.9999, respectively). One other observation of note is that CT or MRI could not evaluate LRRC lesion in some cases (9/40: 22.5%, 3/40: 7.5%).

Local re-recurrence free survival

Patients' age, gender, primary lesion-related factors, and locally recurrent lesion-related factors were analyzed by univariate analysis. The extent of resection and post-SUV were significant prognostic factors for local re-recurrence-free survival (P = 0.0299 and 0.0102, respectively) (Figure 1-A). When analyzed with these statistically significant parameters by univariate analysis, multivariate Cox regression analysis revealed that post-SUV was a significant prognostic factor (P = 0.0383) (Table 4).

Overall survival

In univariate analysis, extent of resection, pathologic tumor response, and post-SUV were significantly associated with prognostic factors for overall survival (P = 0.0035, 0.0411, and 0.0009, respectively) (Figure 1-B). Multivariate Cox regression analysis demonstrated that Post-SUV was a significant prognostic factor for overall survival (P = 0.0195) (Table 5).

Discussion

In this study, a significant decrease in SUVmax was found after CRT, and we observe that Post-SUV is especially useful in assessment of LRRC survival, whereas CT and MRI less accurately reflect the pathological tumor response. Our data indicate that PET-CT is a useful imaging modality for the detection and evaluation of LRRC, and that it recommended over CT and MRI. PET-CT can distinguish cancer recurrence from postoperative scarring tissues or fibrosis [13-15] because it evaluates the metabolic activity of the region of interest, and consequently [1] PET-CT is an ideally suited imaging modality for LRRC, considering its characteristic features of infiltrating growth, tissue scarring, and fibrosis [5].

In the current study, the Post-SUV was statistically lower in histopathologic responders than nonresponders, suggesting that the effect of CRT can be predicted by the SUVmax. Moreover, the Post-SUV was a significant independent prognostic factor with respect to both local re-recurrence-free survival and overall survival of LRRC (P =

0.0383 and 0.0195, respectively). According to several previous reports, a highly significant correlation was observed between a decreased FDG uptake rate after CRT and survival in patients with cancer of the esophagus [8, 16]. In these studies, multivariate regression analysis identified Post-SUV as an independent predictor of local re-recurrence-free survival and overall survival. These findings conclude that low Post-SUV results from a decrease in the number of viable esophageal tumor cells, which may lead to better prognosis. Likewise, we find that low Post-SUV in the treatment of LRRC is a sign of therapeutic response and that it is indicative of better prognosis.

There is no current consensus regarding the best time to perform PET-CT to achieve optimal assessment of LRRC tumor response. Several reports have suggested the utility of early PET-CT assessment during treatment, due to the potential for modification of the subsequent treatment strategy [17-19]. However, our preliminary pilot study (n = 12) evaluating early PET-CT assessment during CRT (2 weeks after beginning of CRT) failed to show positive results with respect to clinical utility in LRRC treatment. A possible explanation for this discrepancy is that LRRC cancer cells are exposed to a hypoxic environment in scar tissue, and consequently might be more resistant to CRT than those in primary rectal cancers or esophageal cancers [5, 20]. We performed resection after 3 to 6 weeks following initiation of CRT, so we could not measure SUV at later time points and decided to carry out the PET evaluation 3 weeks after completion of CRT, as was previously described for primary cancers [16, 21, 22].

The major reason for the introduction of CRT into the course of treatment was to prevent local re-recurrence, which was previously found in 57.1% (12/21) of patients who received resection with curative intent and without preoperative CRT at our institution (detailed data not shown). After initiation of preoperative CRT for patients with LRRC, the local re-recurrence rate was still high (42.3%: 22/52, detailed data not shown). To improve the surgical outcome, it is important to be able to identify the patients with a high risk of local re-recurrence. We do not routinely perform adjuvant chemotherapy after the resection of LRRC, because patients' conditions after surgery are widely variable, including postoperative complications such as pelvic abscess [6]. In this study, we find that patients with higher Post-SUV are highly recommended as candidates to receive adjuvant chemotherapy after resection of LRRC.

This study had some limitations. First, this study is a single center study. Second, the cohort was relatively small, though this is the first report discussing the usefulness of PET-CT for patients with LRRC.

In conclusion, PET-CT is useful in assessment of tumor response to preoperative CRT for patients with LRRC. Post-SUV and DR were significantly associated with a pathological treatment response. Post-SUV is especially valuable as an independent prognostic indicator for patients with LRRC.

Declarations

Ethics approval The study protocol was approved by the Ethics Committee of Osaka University Hospital.

Consent to participate

All study participants provided written informed consent.

Availability of data and materials Not applicable

Competing interest The authors declare that they have no conflict of interest.

Funding Not applicable

Author contributions:

Conception and design of the study: Uemura, Ikeda

Analysis and interpretation of data: Uemura, Handa, Danno

Acquisition of data: Uemura, Mizushima,

Drafting of manuscript: Uemura

Critical revision of manuscript: Uemura, Ikeda, Sekimoto, Doki, Eguchi

Final approval of the article: Eguchi

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Tables

TABLE 1-a. Patient Characteristics	
Characteristic	total (n=40)
Gender	
Male	26
Female	14
Median age (years)	68.5 (36-81)
Median tumor size (mm)	33.5 (8.3-76.0)
Median CEA level pre-CRT (ng/ml)	9.0 (1.0-1022.0)
Median CEA level post-CRT (ng/ml)	3.0 (1.0-108.0)
Operation	
Tumorectomy*	2
Low anterior resection	6
Abdominoperineal resection	10
Total pelvic exenteration	22
Concomitant sacrectomy	
Done	21
Not done	19
Curability of resection	
R0	36
R1	4
Tumor Regression Grade (TRG)	
TRG1-2	17
TRG3-4	23

*tumor resection without adjacent organs

TABLE 1-b. FDG uptake (all patients, n = 40)			
	Mean±SD	Median	Range
Pre-SUV	8.2±6.1	5.9	1.0~26.3
Post-SUV	3.8±4.0	3.0	0.0~18.7
⊿SUV	4.4±4.8	2.8	-1.3~22.5
DR(%)	48.1±30.3	44.7	-30.2~100.0
Abbreviations: FDG,^{18}F-fluorodeoxyglucose			
SUV, standardized uptake value			
Pre-SUV, SUVmax values on the initial scan			
Post-SUV, SUVmax values on the post-CRT scan			
⊿SUV, Pre-SUV- Post-SUV			
DR, decreasing rate, ⊿SUV/Pre-SUV×100(%)			
CRT, chemoradiation therapy			

TABLE 2. FDG-PET measurements and pathological classification			
	Pathological responder (N=17)	Pathological nonresponder (N=23)	*P-value*
Pre-SUV	7.5±5.2	8.8±6.8	0.5103
Post-SUV	2.0±1.7	5.1±3.9	0.0038
⊿SUV	5.4±5.8	3.7±3.8	0.2502
DR(%)	65.3±32.3	35.4±21.7	0.0012
Abbreviations: FDG-PET, ^{18}F-fluorodeoxyglucose positron emission tomography			
SUV, standardized uptake value			
Pre-SUV, SUVmax values on the initial scan			
Post-SUV, SUVmax values on the post-CRT scan			
⊿SUV, Pre-SUV- Post-SUV			
DR, decreasing rate, ⊿SUV/ Pre SUV×100(%)			
CRT, chemoradiation therapy			

TABLE 3. CT and MRI evaluation of pathological grade

Response evaluation by CT				Response evaluation by MRI			
		Pathological responder (N=17)	Pathological nonresponder (N=23)			Pathological responder (N=17)	Pathological nonresponder (N=23)
CR	(CT responder)	0	0	CR	(MRI responder)	1	1
PR		2	3	PR		1	3
SD	(CT nonresponder)	11	15	SD	(MRI nonresponder)	11	17
PD		0	0	PD		0	0
NE		4	5	NE		1	2

Abbreviations:

CR, complete response

PR, partial response

SD, stable disease

PD, progressive disease

NE, not determined

TABLE 4-A. Univariate and multivariate analysis of prognostic factors for local recurrence free survival				
Variables	No. of patients	Univariate analysis	Multivariate analysis	
			Relative risk (CI)	*P* value
Age				
≧62	20	0.2070		
62	20			
Gender				
Male	26	0.7584		
Female	14			
Primary lesion-related factors				
Tumor differentiation				
Well	18	0.2617		
Others	17			
Tumor depth				
-MP	9	0.6736		
SS(A)-	31			
TNM stage				
/	21	0.4869		
/ IV	18			
Venous invasion				
(-)	13	0.3436		
(+)	21			
Lymph node metastasis				
(-)	26	0.4522		
(+)	13			
Lymphatic invasion				
(-)	7	0.5315		
(+)	27			
Locally recurrent lesion-related factors				

Tumor size (maximal diameter)				
<34 mm	19	0.1067		
≧34 mm	19			
CEA Pre-CRT				
<5 ng/ml	15	0.7853		
≧5 (ng/ml)	25			
CEA Post-CRT				
<5 (ng/ml)	26	0.8175		
≧5 (ng/ml)	14			
Extent of resection				
R0	36	0.0299	0.433 (0.108-10729)	0.2359
R1	4			
Pathologic tumor response				
Responders (TRG1-TRG2)	17	0.0601		
Nonresponders (TRG3-TRG5)	23			
Pre-SUV				
Low	20	0.5475		
High	20			
Post-SUV				
Low	20	0.0102	0.383 (0.104-0.940)	0.0383
High	20			
⊿SUV				
Low	20	0.9160		
High	20			
DR				
Low	20	0.0488		
High	20			

Table 4-B. Univariate and multivariate analysis of prognostic factors for overall survival				
Variables	No. of patients	Univariate analysis	Multivariate analysis	
			Relative risk(CI)	*P* value
Age				
≧62	20	0.0893		
62	20			
Gender				
Male	26	0.5103		
Female	14			
Primary lesion-related factors				
Tumor differentiation				
Well	18	0.5670		
Others	17			
Tumor depth				
-MP	9	0.7037		
SS(A)-	31			
TNM stage				
/	21	0.8033		
/ IV	18			
Venous invasion				
(-)	13	0.0560		
(+)	21			
Lymph node metastasis				
(-)	26	0.7551		
(+)	13			
Lymphatic invasion				
(-)	7	0.2828		
(+)	27			
Locally recurrent lesion-related factors				

Tumor size (maximal diameter)				
<34 (mm)	19	0.6026		
≧34 (mm)	19			
CEA (Pre-CRT)				
<5 (ng/ml)	15	0.9454		
≧5 (ng/ml)	25			
CEA (Post-CRT)				
<5 (ng/ml)	26	0.6716		
≧5 (ng/ml)	14			
Extent of resection				
R0	36	0.0035	0.355 (0.084-1.501)	0.1590
R1	4			
Pathologic tumor response				
Responders (TRG1-TRG 2)	17	0.0411	0.576 (0.169-1.960)	0.3769
Nonresponders (TRG3-TRG 5)	23			
Pre-SUV				
Low	20	0.2012		
High	20			
Post-SUV				
Low	20	0.0009	0.203 (0.053-0.774)	0.0195
High	20			
⊿SUV				
Low	20	0.6765		
High	20			
DR				
Low	20	0.1127		
High	20			

Figures

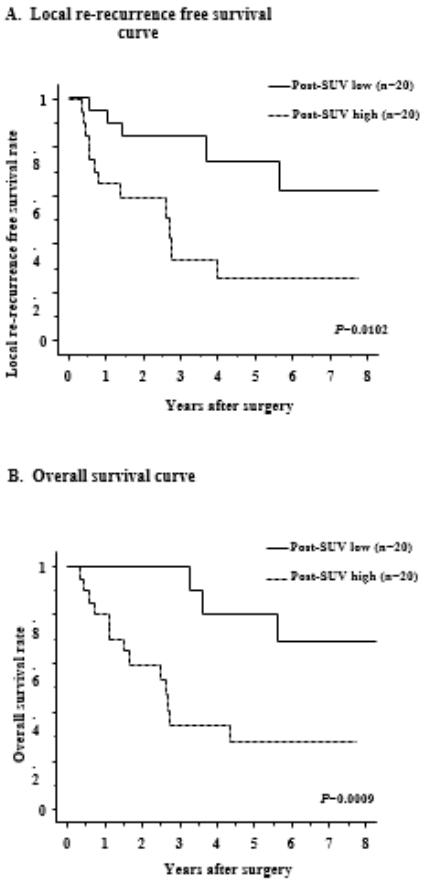

Figure 1

Kaplan-Meier local re-recurrence-free survival curve (A) and overall survival curve (B) for patients with LRRC, separated according to high and low Post-SUV.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuppleFig1.xlsx