Cancer Chemother Pharmacol (2013) 71:1201–1207
DOI 10.1007/s00280-013-2114-0

ORIGINAL ARTICLE

Clinical implications of initial FDG-PET/CT in locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy

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Received: 14 February 2012 / Accepted: 5 February 2013 / Published online: 19 February 2013

Abstract
Purpose The present study evaluated the predictive and prognostic impact of initial fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) in patients with locally advanced rectal cancer treated with neoadjuvant concurrent chemoradiotherapy (CCRT).
Methods Eighty-one consecutive patients with locally advanced rectal cancer (cT3-T4 N−/N+) treated with neoadjuvant CCRT were enrolled. The FDG-PET/CT parameters, including the SUVmax, metabolic tumor volume (MTV, 50 % of SUVmax), and multiplication of the SUVmean and MTV (total lesion glycolysis, TLG), were analyzed in relation to the pathologic response and disease recurrence.
Results Five patients (6.2 %) achieved a pathologic complete response (pCR) after CCRT followed by surgery. None of the FDG-PET/CT parameters was identified as a predictive factor for pCR. After a median follow-up period of 26.7 (range 10.9–63.3) months, 19 patients (23.5 %) presented a local and/or distant recurrence. In a multivariate analysis including the clinicopathologic parameters, the TLG of the primary tumor was associated with a worse disease-free survival after neoadjuvant CCRT (HR 20.035, 95 % CI 1.726–232.559; $P = 00.017$).
Conclusions The TLG of the primary tumor in the initial FDG-PET/CT can be considered as a prognostic factor for patients with locally advanced rectal cancer treated with neoadjuvant CCRT.

Keywords Total lesion glycolysis · Positron emission tomography · Rectal cancer · Chemoradiotherapy · Prognosis

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Introduction

Neoadjuvant concurrent chemoradiotherapy (CCRT) followed by an optimal surgical technique is considered the standard of care for patients with locally advanced adenocarcinoma of the middle/low rectum, as it provides the opportunity to downstage tumors, increases sphincter preservation, and decreases the risk of locoregional recurrence when compared with postoperative treatment, even though no improvement in overall survival has been observed [1, 2]. However, the tumor response to neoadjuvant CCRT varies considerably among patients, ranging from the complete disappearance of the tumor in about 15–20 % of cases to a

lack of any pathological change or even tumor progression during the treatment. It is also well known that rectal cancer patients who achieve pCR after neoadjuvant CCRT have a lower local recurrence rate and improved overall survival when compared to patients with residual cancer cells [3, 4]. Thus, to facilitate a better individualized multidisciplinary therapeutic approach, including preoperative treatment, surgery, and adjuvant treatment, for each patient, additional predictive and prognostic markers for pCR and early relapse have been actively sought in clinical research.

Standard imaging modalities, such as endoscopic transrectal ultrasound (ERUS), computed tomography (CT), and pelvic magnetic resonance imaging (MRI), allow a valid morphological assessment of the tumor extent at the initial diagnosis, yet their accuracy for restaging after neoadjuvant CCRT is very low as regards predicting pCR [5, 6].

Fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), which evaluates the tissue metabolic activity using the glucose metabolism, is useful not only for staging but also for assessing the tumor response to treatment. Several previous studies have observed that FDG-PET/CT could be an indicator of treatment response, and in a neoadjuvant setting, it could have a predictive and/or prognostic value for many tumors, such as esophagogastric cancer [7], non-small-cell lung cancer [8], and breast cancer [9]. For rectal cancer, Dencke et al. [10, 11] reported that FDG-PET was superior to CT and MRI in predicting the response to the preoperative multimodal treatment of locally advanced rectal cancer. Moreover, Calvo et al. [12] found FDG-PET to be useful in assessing the chemoradiation response of locally advanced rectal cancer and suggested that the initial SUVmax may be of prognostic value as regards the long-term patient outcome. However, since the sample size of these studies was very small (fewer than 30 patients), it is difficult to draw a conclusion on the prognostic value of FDG-PET in the case of rectal cancer.

The metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are the tumor metabolic activity measures determined by FDG-PET/CT [13], and these functional parameters could have clinical value as regards treatment evaluation and disease prognostication.

Accordingly, this study evaluated the predictive and prognostic impact of the initial FDG-PET/CT in patients with locally advanced rectal cancer treated with neoadjuvant CCRT.

Patients and methods

Patient characteristics

The study population included consecutive patients with clinical T3/4, N−/+ rectal cancer suitable for neoadjuvant CCRT observed between December 2005 and July 2010. The diagnosis and staging of the rectal cancer were assessed according to the WHO classifications [14, 15]. The initial imaging TNM status was obtained from pretreatment MRI imaging, while the M stage was obtained from structural imaging and FDG-PET/CT; any discordance was resolved by confirmation at surgery, a biopsy, or subsequent follow-up imaging. All the patients underwent FDG-PET/CT before CCRT. The pathologic analysis of the surgical specimens was performed by the local pathologist department according to the ypTNM system [16].

Chemoradiotherapy

The chemoradiotherapy consisted of radiotherapy, delivered at a total dose of 4,500 cGy in 25 daily fractions of 1.8 Gy in combination with a concurrent chemotherapy regimen of a 5-fluorouracil plus leucovorin bolus infusion (‘Mayo’ regimen). All the patients underwent rectal surgery (total mesorectal excision) with curative intent 6 weeks after the end of the neoadjuvant treatment. Adjuvant chemotherapy using the ‘Mayo’ regimen was also delivered for 4 months.

PET protocol and measurement of tumor volume

All the patients fasted for at least 6 h before the administration of F-18 FDG, and the blood glucose concentration was confirmed to be less than 150 mg/dL. Approximately 8.1 MBq of F-18 FDG per kg of body weight was injected intravenously, and the patients were advised to rest for an hour before the acquisition of the FDG-PET/CT image. The PET/CT scans were performed using a Reveal HiRez (Siemens-CTI, Knoxville, TN, USA, 6-slice CT) and Discovery STE (GE Healthcare, Milwaukee, WI, USA, 16-slice CT). A low-dose CT scan was initially obtained for attenuation correction, followed by the PET scan at 3 min per bed position. The PET data were reconstructed iteratively based on an ordered-subset expectation maximization algorithm using the low-dose CT datasets for the attenuation correction. A standardized uptake value (SUV) was measured for all primary rectal cancer lesions and presented as the SUVmax. The PET/CT images were interpreted by two experienced nuclear medicine physicians, and a final consensus reached for all the patients. Regions of interest (ROIs) were placed manually over all the rectal tumors in the attenuation-corrected images, and the SUVmax within the ROIs was recorded.

The maximum and average standardized uptake values (SUVmax and SUVmean) were quantitatively used to determine the FDG-PET activity. The measured variables included the MTV, SUVmax, and SUVmean in the pretreatment scans, and the threshold intensity value used in

this study was a SUV of 50 %. After segmenting all the hypermetabolic tumor foci, the software calculated the MTV, defined as the total volume of the primary tumor in the body, along with the maximum and average SUV within the MTV. The TLG was also calculated by multiplying the SUVmean of the primary tumor by the MTV. The quartile value of the TLG was used in all the analyses (range 13.09–763.32, Q1 < 43, Q2 43–85, Q3 85–145, and Q4 > 145). This study only analyzed the pretreatment FDG-PET/CT and does not address any changes in the SUV parameters following CCRT.

Clinical follow-up

The postoperative program included follow-up visits every 3 months for the first 2 years, then every 6 months for the following 3 years, and once annually thereafter. At each visit, clinical examinations were performed and the serum level of the carcinoembryonic antigen (CEA) was monitored. Chest X-rays and abdominal computed tomography scans were obtained every 6 months, plus a full colonoscopy was performed 6 months after surgery and then once every 3–5 years. FDG-PET/CT was ordered selectively in the case of any abnormalities during the examination.

Statistical analyses

The chi-square test or t test was used to analyze the correlation between the FDG-PET and clinicopathologic parameters. The prognostic significance of the primary tumor SUVmax, SUVmean, MTV, and TLG relative to disease-free survival (DFS) or overall survival (OS) was also analyzed. DFS was calculated from the date of diagnosis to the date of any events, including all local, regional, or distant recurrences. Kaplan–Meier curves were used to calculate the DFS and OS values. A multivariate analysis was performed according to the Cox proportional hazards model with the backward elimination of factors found to be statistically significant in the univariate analyses. All the tests were two sided and performed at a 5 % level of significance using SPSS (version 15.0; SPSS Inc., Chicago, IL).

Results

Patient characteristics

Eighty-one consecutive patients with locally advanced rectal cancer were enrolled at Kyungpook National University Hospital (Daegu, Korea) between December 2005 and July 2010. The clinicopathologic characteristics of these 81 patients are shown in Table 1. All the patients were operated on 6 weeks after the end of their CCRT: Complete resection (R0) was achieved in 78 (96.3 %) patients, whereas positive margins (R1) were found in two (2.5 %) patients, and one patient showed liver metastasis (R2) at surgery. Low anterior resection was performed on 67 (86.4 %) patients, while the others received an abdominoperineal resection. Laparoscopy surgery was performed on 57 (70.4 %) patients. Seventy-two patients (88.9 %) received postsurgical adjuvant chemotherapy.

Table 1 Patient characteristics

	No. ($N = 81$)	%
Age, years (median)	59	36–79[a]
Sex (M/F)	54/27	66.7/33.3
cT		
2/3/4	7/65/9	8.6/80.2/11.1
cN		
0/1/2	3/23/55	3.7/28.4/67.9
Clinical stage		
IIA	3	3.7
IIIA/B/C	6/17/55	7.4/21.0/67.9
ypT		
T pCR	5	6.2
1/2/3	3/15/58	3.7/18.5/71.6
ypN		
N pCR	48	59.3
1/2	21/12	25.9/14.8
Pathologic stage		
pCR	5	6.2
I	11	13.6
IIA/B	30/2	37.0/2.5
IIIA/B/C	5/14/11	6.2/17.3/13.6
IV[b]	3	3.7
Histologic differentiation		
G1/G2/G3	5/60/16	6.2/74.1/19.8
Lymphatic invasion	17	21.0
Venous invasion	2	2.5
Neural invasion	14	17.3
CEA, elevated	23	28.4
CA19-9, elevated	20	24.7
Surgery		
LAR	67	86.4
APR	14	13.6
Relapse	20	24.7
Death	11	13.6

LAR low anterior resection, *APR* abdominoperineal resection

[a] Range

[b] Pathologic stage IV: 2 para-aortic LN, 1 liver

Post-CCRT pathologic evaluation and FDG-PET/CT

Table 1 shows the post-CCRT pathologic staging in the surgical specimen. Five patients (6.2 %) demonstrated a pathologic complete response (pCR, ypT0N0), and 48 patients (59.3 %) experienced ypN0. When compared with the clinical baseline stage, primary tumor downstaging was documented in 33 patients (40.7 %) and locoregional nodal involvement downstaging found in 57 patients (70.4 %). At the baseline, all the patients presented abnormal ^{18}F-FDG avidity at the site of the primary tumor. The mean baseline SUVmax was 10 (range 4.1–30.0), the mean MTV (threshold 50 %) was 12 mL (range 2.35–15.64 mL), and the mean TLG was 85 (range 13.09–763.32). Among the clinicopathologic factors, the differences in the TLG were not all significant in this study (Table 2), and none of the investigated parameters, including the tumor volume parameters (SUVmax, SUVmean, MTV, and TLG), was shown to be an independent predictive factor for pCR (Table 3).

Disease recurrence and FDG-PET/CT

After a median follow-up of 26.7 (range 10.9–63.3) months, 19 patients (23.5 %) presented a recurrent disease (2 local, 15 distant, and 2 local + distant) and 12 (14.8 %) had died of a recurrent disease. Eighteen (94.7 %) of the patients with a recurrent disease had achieved less than pCR after CCRT. In the univariate analysis, the TLG of the primary tumor was found to be significantly associated with DFS and OS (Table 4). Moreover, the multivariate analysis demonstrated that the TLG of the primary tumor was an independent prognostic factor for DFS for locally advanced rectal cancer treated with neoadjuvant CCRT (HR 20.035, 95 % CI 1.726-232.559; $P = 0.017$), whereas the SUVmax and MTV were not significant prognostic factors (Table 5, Fig. 1).

Table 2 FDG-PET/CT parameters (TLG) related to clinicopathological factors

	¶*P* value
Age, ≥60	0.649
Sex, male	0.951
cT stage	0.084
cN stage	0.109
ypT stage	0.204
ypN stage	0.508
Differentiation, G3	0.087
CEA, elevated	0.244
CA19-9, elevated	0.749
Lymphatic invasion	0.207
Venous invasion	0.685
Neural invasion	0.795

¶ *P* value, χ^2 -test, comparison of patient characteristics according to TLG

Table 3 PET/CT parameters and the histopathologic response to chemoradiotherapy

	pCR	Non-pCR	*P* value
SUVmax	10.52 ± 3.01	11.36 ± 5.09	0.675
SUVmean	6.84 ± 2.08	7.49 ± 3.42	0.675
MTV	13.92 ± 13.32	15.92 ± 10.86	0.887
TLG	91.44 ± 91.40	121.85 ± 115.43	0.201

t test two-sample t test)

Discussion

The current study found that the pretreatment TLG, a volumetric parameter of FDG-PET/CT, was an important prognostic factor for DFS in patients with locally advanced rectal cancer treated with neoadjuvant CCRT.

The use of FDG-PET/CT for staging and predicting tumor response is now one of the most rapidly expanding areas in diagnostic imaging. Rectal cancer is a disease model of particular interest, because an accurate and non-invasive method for evaluating the response to preoperative CCRT could lead to patient selection for minimally invasive surgical approaches or even the selection of candidates for additional chemotherapy [17, 18]. A systematic review of monitoring and predicting the response to therapy using FDG-PET/CT in the case of rectal cancer was recently carried out by de Geus-Oei et al. [19]. They identified and analyzed a series of 19 studies, although almost all the studies were very small and heterogeneous as regards the methods applied for PET quantification (visual FDG-PET response, SUVmax, SUVmean, and TLG), the timing of the examination, metabolic response evaluation criteria, and clinical end points. Yet, despite such strong limitations for drawing consistent conclusions, the authors consider that most of the studies showed that FDG-PET was 'a significant predictor of therapy outcome' [19]. Notwithstanding, in the present study, none of the investigated parameters, including the SUVmax, SUVmean, MTV, and TLG, was identified as an independent predictive factor for pCR, even though the patients who achieved pCR had a lower initial SUV value than the non-pCR patients. Possible explanations for these results are that the sample size of the current study was relatively small and only 6.2 % of the patients achieved pCR after neoadjuvant CCRT due to the relatively low dose of radiation (4500 cGy) and intermittent infusion of 5-fluorouracil in

Table 4 Univariate analysis of prognostic factors for survival

	Disease-free survival			Overall survival		
	HR	95 % CI	*P* value	HR	95 % CI	*P* value
SUVmax, >10	1.599	0.653–3.913	0.304	2.047	0.591–7.091	0.258
MTV, >12.0 mL	1.416	1.586–3.422	0.044	2.815	0.744–10.643	0.127
TLG, >85	3.663	1.329–10.098	0.012	4.860	1.046–22.575	0.044

HR hazard ratio, *CI* confidence interval, *SUVmax* maximum standardized uptake value, *MTV* metabolic tumor volume, *TLG* total lesion glycolysis

Table 5 Multivariate analysis of prognostic factors for DFS

Characteristics	Disease-free survival		
	HR	95 % CI	*P* value
Age, ≥60	3.012	1.055–8.759	0.039
cT			
T2-3 vs. T4	16.364	2.935–91.224	0.001
cN			
N0-1 vs. N2	0.576	0.092–3.623	0.557
CEA, Elevated	7.975	2.272–27.986	0.001
ypT			
TpCR vs. T1/2/3	5.512	0.415–73.198	0.196
ypN			
NpCR vs. N1/2	0.646	0.160–2.612	0.540
Differentiation, G3	1.808	0.421–7.758	0.425
Lymphatic invasion	3.106	0.940–10.264	0.063
Venous invasion	6.116	0.480–77.871	0.163
Neural invasion	7.939	1.986–31.732	0.003
SUVmax, >10[a]	1.426	0.403–5.044	0.582
MTV50 %, >12.0 mL[a]	0.672	0.175–2.581	0.563
TLG			
1st quartile (<43)	1		0.115
2nd quartile (43–85)	1.191	0.978–14.624	0.891
3rd and 4th quartiles (>85)	20.035	1.726–232.559	0.017

[a] Mean

the current study. Martoni et al. [20] also reported that while the baseline PET expressed as SUV-1 was correlated with the pathologic response, this correlation was lost in a multivariate analysis. Thus, they concluded that FDG-PET/CT as a baseline did not appear to have any relevance in the standard staging workup as a predictor of the pathologic response.

The use of a semiquantitative index for the tumor FDG uptake, such as the SUV, is one possible source of metabolic information, and several studies have already shown that the SUVmax of the primary tumor is useful for determining the prognosis in patients with rectal cancer [12, 20]. However, in the current study, the SUVmax of the primary tumor was not identified as a significant prognostic factor for DFS or OS. While the SUVmax is a robust and convenient quantitative measure, it has been argued that since it is only the measurement of a single pixel with the highest radiotracer concentration within the ROI, it may not reflect the heterogeneous nature of the tumor. Thus, the TLG has been proposed as a more accurate parameter, which takes account of both the metabolic activity (SUV-mean or SUVmax) and the tumor volume [21]. In the present study, the DFS for the patients with a high TLG for the primary tumor was worse than that for the patients with a low TLG ($P = 0.017$). These findings are consistent with the prior study by Gulec et al. [22], who found a statistically significant association between the functional tumor parameters (TLG) and the clinical outcomes in patients with colorectal cancer with liver metastasis. In their study, the median survival for patients with pretreatment TLG values above and below 600 g was 11.2 and 26.9 months, respectively ($P < 0.05$). Thus, they concluded that the pretreatment TLG could be a useful predictive marker for survival. Recent studies have also reported similar TLG-related outcomes with other solid tumors, including malignant pleural mesothelioma [23], non-small-cell lung cancer [24], and nasopharyngeal carcinoma [25, 26]. The prognostic benefits of pCR have already been proven in patients with locally advanced rectal cancer treated with neoadjuvant CCRT. Plus, since PET can illustrate changes in the tumor biology and provide an earlier assessment of the cancer response following CCRT, sequential PET has been shown to provide a more accurate prediction of the pathological response of locally advanced rectal cancer than other anatomic staging systems. Several studies have also showed that, irrespective of the pretreatment T stage, a poorer metabolic response obtained by FDG-PET/CT can be an independent predictor of recurrence [20, 27, 28]. Accordingly, the metabolic response assessed by FDG-PET/CT may be an alternative approach of pathologic staging to stratify the management of patients with locally advanced rectal cancer.

In conclusion, the TLG of the primary tumor in the initial FDG-PET/CT can be considered as a prognostic factor for neoadjuvant CCRT in patients with rectal cancer. As such, this value can be a useful quantitative criterion for patient selection and disease prognostication, leading to

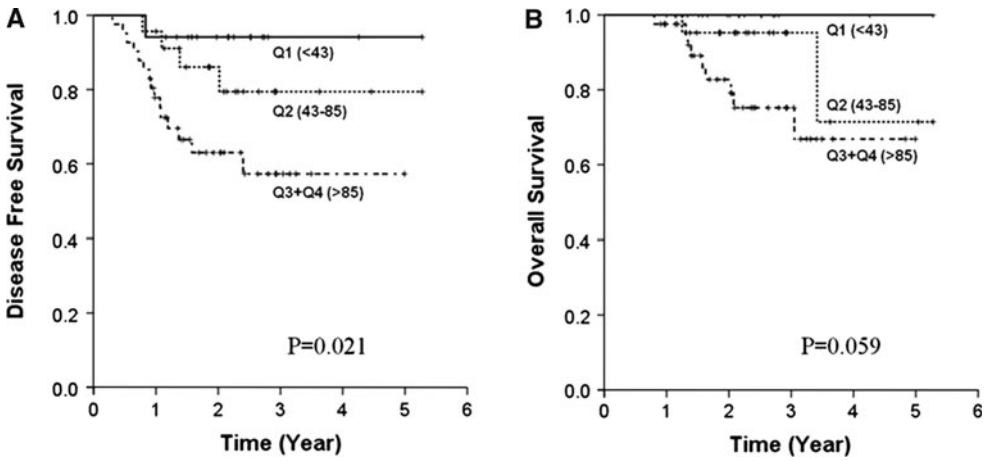

Fig. 1 Kaplan–Meier curve of DFS and OS from initial FDG-PET/CT by TLG

more appropriate and efficient clinical treatment with improved long-term outcomes. Additional prospective studies with larger numbers of patients are needed to validate the prognostic utility of this promising functional biomarker derived from FDG-PET/CT.

Acknowledgments This study was supported by a grant from the Korea Health Technology R and D Project, Ministry of Health and Welfare, Republic of Korea (A111345).

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