Accurate Prediction of Pathological Rectal Tumor Response after Two Weeks of Preoperative Radiochemotherapy Using 18F-Fluorodeoxyglucose-Positron Emission Tomography-Computed Tomography Imaging

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CLINICAL INVESTIGATION **Rectum**

ACCURATE PREDICTION OF PATHOLOGICAL RECTAL TUMOR RESPONSE AFTER TWO WEEKS OF PREOPERATIVE RADIOCHEMOTHERAPY USING ^{18}F-FLUORODEOXYGLUCOSE-POSITRON EMISSION TOMOGRAPHY-COMPUTED TOMOGRAPHY IMAGING

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Purpose: To determine the optimal time point for repeated ^{18}F-fluorodeoxyglucose-positron emission tomography (PET)-CT imaging during preoperative radiochemotherapy (RCT) and the best predictive factor for the prediction of pathological treatment response in patients with locally advanced rectal cancer.

Methods and Materials: A total of 30 patients referred for preoperative RCT treatment were included in this prospective study. All patients underwent sequential PET-CT imaging at four time points: prior to therapy, at day 8 and 15 during RCT, and shortly before surgery. Tumor metabolic treatment responses were correlated with the pathological responses by evaluation of the tumor regression grade (TRG) and the pathological TN (ypT) stage of the resected specimen.

Results: Based on their TRG evaluations, 13 patients were classified as pathological responders, whereas 17 patients were classified as pathological nonresponders. The response index (RI) for the maximum standardized uptake value (SUV_{max}) on day 15 of RCT was found to be the best predictive factor for the pathological response (area under the curve [AUC] = 0.87) compared to the RI on day 8 (AUC = 0.78) or the RI of presurgical PET imaging (AUC = 0.66). A cutoff value of 43% for the reduction of SUV_{max} resulted in a sensitivity of 77% and a specificity of 93%.

Conclusions: The SUV_{max}-based RI calculated after the first 2 weeks of RCT provided the best predictor of pathological treatment response, reaching AUCs of 0.87 and 0.84 for the TRG and the ypT stage, respectively. However, a few patients presented with peritumoral inflammatory reactions, which led to mispredictions. Exclusion of these patients further enhanced the predictive accuracy of PET imaging to AUCs of 0.97 and 0.89 for TRG and ypT, respectively. © 2010 Elsevier Inc.

Rectal cancer, Preoperative radiochemotherapy, Repeated PET-CT imaging, Pathological response prediction, TRG.

INTRODUCTION

For patients diagnosed with locally advanced rectal cancer (LARC), preoperative radiochemotherapy (RCT) has become a standard procedure (1–3). Importantly, however, preoperative RCT has been shown to not only reduce the risk for local recurrence but also to induce a significant tumor downsizing and downstaging (4–6). Consequently, in 15 to 30% of these patients, even a pathologically complete tumor regression has been observed (4–7). Interestingly, correlations between the reduction of the uptake of ^{18}F-fluorodeoxyglucose (FDG) within the tumor and the pathological tumor response after RCT have been reported by some groups (5–14). Most of these studies performed positron emission tomography (PET)-CT scans before the start and after the finish of preoperative RCT, correlating semiquantitative measurements of FDG uptake with the tumor regression grade (TRG) (5–12). For the clinical practice, however, an earlier prediction of

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the pathological tumor response would be even more attractive because it could enable response-guided modifications of the treatment protocol based on changes in FDG uptake, possibly strengthened by clinical or biological factors (13–15). Until now, only two studies have reported an early prediction of the pathological tumor response based on PET-CT imaging during preoperative RCT (13, 14). Cascini *et al*. showed that early changes in the metabolic activity of the tumor, measured 12 days after the start of preoperative treatment with RCT, were predictive for the pathological treatment response in rectal cancer (13). Rosenberg *et al*. presented a correlation of both the early metabolic response evaluation and the late metabolic response evaluation with the histopathological tumor response, of which the accuracy of the late metabolic response was marginally superior (14). Both studies used a protocol in which the second PET-CT scan was performed at the end of the second week during RCT (13, 14). However, no studies have yet examined other time points of PET imaging during preoperative RCT in order to define the best prediction of pathological tumor response as advised by Hindie *et al*. (15). Thus, we initiated this study, in which we performed PET-CT scans at two different time points during preoperative RCT and a presurgical PET-CT scan, in order to determine the optimal time point of PET imaging during preoperative RCT and to define the PET criteria that would result in the best prediction of pathological tumor response.

METHODS AND MATERIALS

Patient characteristics

A cohort of 30 patients diagnosed with nonmetastasized LARC were included in this study, for whom clinical TN staging was evaluated with a pretreatment magnetic resonance (MR) scan (Table 1). All patients were preoperatively treated with radiotherapy (28 fractions of 1.8 Gy, 5 fractions/week) and concomitant chemotherapy (capecitabine, 825 mg/m^2, twice daily), followed by a total mesorectal excision. As a part of the study, all patients underwent sequential FDG-PET-CT imaging at four different time points: once prior to therapy, on days 8 and 15 of RCT, and once shortly before surgery. Due to technical problems or patient incompliance, not all PET-CTs could be performed as planned. Three patients refused PET-CT imaging on day 15, and for one patient, no FDG could be injected on the second PET-CT scan. For 7 patients, no PET-CT scan could be performed prior to surgery. According to Dutch law, the medical ethics committee approved the trial. All patients gave written informed consent before entering the study.

Table 1. Comparison of predictive factors during the first 15 days of preoperative RCT*

Patient	cTNM	ypTN	TRG	RI of SUV_{max} 0–15
1	T3N1M0	T3N0	3	
2	T2N1M0	T0N0	1	51.9
3	T3N2M0	T3N1	3	41.7
4	T3N2M0	T2N0	2	69.4
5	T3N1M0	T3N0	3	
6	T4N2M0	T3N0	2	38.9
7	T3N1M0	T2N0	2	64.8
8	T3N2M0	T2N0	2	−2.4
9	T3N2M0	T2N0	3	31.5
10	T3N2M0	T4N0	3	−11.8
11	T3N2M0	T3N0	3	47.6
12	T3N2M0	T3N1	4	14.4
13	T3N1M0	T0N0	1	70.4
14	T3N2M0	T3N0	4	28.8
15	T3N1M0	T2N0	3	39.7
16	T3N0M0	T2N0	3	5.1
17	T3N2M0	T3N1	3	35.9
18	T3N1M0	T1N0	2	9.7
19	T3N2M0	T3N2	3	33.4
20	T3N2M0	T3N2	4	28.6
21	T3N2M0	T0N0	1	54.6
22	T3N2M0	T3N1	2	45.5
23	T3N0M0	T3N1	4	5.2
24	T3N1M0	T3N2	3	−8.2
25	T4N1M0	T4N0	4	−15.7
26	T3N1M0	T2N0	2	48.6
27	T3N0M0	T0N0	1	68.4
28	T3N2M0	T2N2	2	45.6
29	T3N2M0	T2N0	2	46.7
30	T3N1M0	T3N1	4	−7.1

* Overview of the clinical (c) and pathological (yp) staging (TN(M)), the tumor-regression-grade (TRG) and the reduction of SUV_{max} during the first 15 days of pre-operative radiochemotherapy.

PET-CT imaging and processing

All PET-CT scans were performed by use of a dedicated Siemens Biograph 40 TruePoint PET-CT simulator (Siemens Medical, Erlangen, Germany) with an axial field of view of 16.2 cm, a slice thickness of 3 mm, and a pixel spacing of 5.3456 mm in both directions. The scanner is equipped with ultrafast detector electronics (Pico3D) and has a spatial resolution of approximately 6 mm at full-width-at-half-maximum. PET imaging was done in three dimensions, requiring a proper scatter correction. CT-based attenuation and decay correction were performed. PET images were reconstructed from the acquired list mode data, using Fourier rebinning and ordered subset expectation maximization reconstruction (two dimensional) with four iterations and eight subsets. After a fasting period of at least 6 hours prior to FDG injection, patients received an intravenous injection of FDG, with the activity normalized for the weight of the patient (where weight [kg] · 4 + 20) [MBq]), followed by an injection of physiologic saline (10 ml). After an uptake period of 60 minutes, the patient was positioned on a flat tabletop, using a movable laser alignment system in a ''head-first supine'' position with the arms crossed above the chest. A PET-CT scan of the abdominal region was performed using an acquisition time of 5 minutes per bed position. Additionally, all PET data were normalized for the blood glucose level measured shortly before FDG administration (16).

PET analysis

For each of the PET scans, a tumor contour was generated using automated standardized uptake values (SUV) that reached threshold levels in which the threshold value (percentage of SUV_{max} within the tumor) was dependent on the tumor-to-background signal ratio, with the gluteus muscle selected as the relevant background (17, 18). Dedicated software (TrueD; Siemens Medical, Erlangen, Germany) was used to calculate the SUV_{mean} and SUV_{max} within the tumor. Subsequently, the response indices (RIs), indicating the percent reduction relative to the pretreatment measured value, were calculated and correlated to the pathological tumor response. If no residual metabolic activity was present on the presurgical PET-CT scan, the patient's tumor was classified as a metabolic complete responder

(mCR) (Fig. 1A), and the SUV was defined as zero, and the RI was set as 100% for the presurgical PET scan.

Pathological tumor response

For each patient, the pathological tumor response was evaluated by determining the TRG, as proposed by Mandard *et al.* (19). All tumors were retrospectively classified by an experienced pathologist (RR) who was blinded to the PET data, as follows: TRG 1, complete tumor response; TRG2, residual cancer cells scattered through fibrosis; TRG 3, an increased number of residual cancer cells, with predominant fibrosis; TRG 4, residual cancer outgrowing fibrosis; and TRG 5, no regressive changes within the tumor. Based on the TRG, the tumors were grouped into responders (TRG 1 and 2) and nonresponders (TRG 3–5). Furthermore, the pathological TN (ypTN) classification was collected from the patients' pathology reports. Subsequently, patients were subdivided into a group with ypT0, ypT1, and ypT2 stages and a group with a ypT3 or a ypT4 stage.

Statistical analysis

Statistical analyses were performed using SPSS software (version 15.0; SPSS Inc., Chicago, IL). All quantitative values were expressed as means ± standard deviations (SD) and ranges (minimum to maximum). Comparisons of related measurements were performed using a Wilcoxon signed rank test, whereas a Mann-Whitney U test was used in cases of independent samples. Receiver operating characteristics (ROC) analysis was performed to evaluate the optimal cutoff value used for the prediction of the pathologic treatment response.

RESULTS

Metabolic response evaluation

In general, the highest FDG uptake value was detected on the pretreatment PET-CT scan, followed by a statistically significant reduction of the FDG uptake during preoperative RCT ($p < 0.001$) (Fig. 2A). Six of the patients (20%) were classified as mCR (Fig. 1A), whereas 4 patients (13%) presented with an increased FDG uptake during RCT in peritumoral tissues, indicating an inflammatory reaction (Fig. 1C). For these 4 patients, the histopathological reports also described a fibroinflammatory reaction within the resected tumor specimen. Overall, an average SUV_{mean} of 8.3 ± 2.8 (range, 4.3 to 15.5) was calculated for the pretreatment PET scan. During preoperative RCT, the SUV_{mean} within the tumor decreased to average values of 7.1 ± 2.3 (range, 4.2 to 12.7) on day 8 ($p = 0.002$) to 5.7 ± 1.7 (range, 3.5 to 9.9) on day 15 ($p < 0.001$) to 2.6 ± 1.8 (range, 0.0 tot 5.1) on the presurgical scan ($p = 0.001$) (Fig. 2A). The SUV_{max} showed a time trend comparable to that of SUV_{mean}, with average values starting at 16.3 ± 5.9 (range, 7.4 to 28.1) on day 0, decreasing to 13.4 ± 4.7 (range, 8.1 to 27.4) on day 8 ($p < 0.001$) and to 10.4 ± 3.5 (range, 6.0 to 18.9) on day 15 ($p < 0.001$) to 5.4 ± 3.8 (range 0 to 12.1) on the presurgical PET scan ($p < 0.001$) (Fig. 2A).

Pathologic response evaluation

Thirteen of the patients (43%) were classified as pathological responders (4 TRG 1, 9 TRG 2), and seventeen patients (57%) were classified as pathological nonresponders (11 TRG 3, 6 TRG 4) (Table 1). Based on the pathological reports, three specimens were classified as ypT0, one as ypT1, six as ypT2, twelve as ypT3, and two as ypT4 (Table 1).

Correlation between the metabolic and pathological treatment response

The RIs of SUV_{mean} 0 to 8, SUV_{max} 0 to 8, SUV_{mean} 0 to 15, and SUV_{max} 0 to 15 were found to be significantly different with respect to the pathological treatment responses (Table 2). ROC curve analyses for the RIs of both the SUV_{mean} and the SUV_{max} at day 8 of RCT revealed no cutoff value for the differentiation between pathological responders and nonresponders due to a substantial overlap of the RIs relative to the TRG. However, the RIs of the SUV_{max} based on the PET scan performed on day 15 of RCT were found to accurately differentiate between histopathological responders and nonresponders because less overlap was observed between the RIs relative to the TRG (Fig. 3). Using ROC curve analysis, a cutoff value of 43% SUV_{max} reduction on day 15 resulted in a sensitivity of 77%, a specificity of 93%, a negative predictive value (NPV) of 82%, and a positive predictive value (PPV) of 91%. Correlating the PET criteria and RIs with the ypT stage revealed significantly different values for RIs of SUV_{max} 0 to 8, SUV_{mean} 0 to 15, and SUV_{max} 0 to 15 (Table 2). Based on ROC curve analysis for RIs of SUV_{max} on day 15, an optimal cutoff value of 43% was defined, resulting in a sensitivity of 57%, a specificity of 85%, a NPV of 65%, and a PPV of 80% (Fig. 4). By excluding those patients with a perceived peritumoral inflammatory response from further analysis, the models used for the prediction of both the TRG and the ypT classifications improved from an area under the curve (AUC) of, respectively, 0.87 ± 0.07 and 0.84 ± 0.08 to AUCs of 0.97 ± 0.04 and 0.89 ± 0.08 (Fig. 3A and 4A). The prediction of TRG improved to a sensitivity of 90%, a specificity of 93%, a NPV of 93%, and a PPV of 90%, whereas the prediction of the ypT classification improved to a sensitivity of 80%, a specificity of 85%, a NPV of 80%, and a PPV of 85%.

Tumors classified as mCR after RCT did not all correlate with a pathologically complete response. Only 1 out of 6 patients who demonstrated an mCR tumor on the presurgical PET-CT scan responded completely on pathology (TRG 1). The other five tumors turned out to be pathologically partial responding malignancies (one was TRG 2, and four were TRG 3).

DISCUSSION

This prospective study revealed a significant correlation between the metabolic tumor response, assessed with repeated FDG-PET-CT-imaging during RCT, and the pathological tumor response.

The best predictor of pathological tumor response turned out to be the RI of the SUV_{max} calculated on day 15 of preoperative RCT. Presurgical PET imaging, however, did not reveal significantly different values for the PET criteria evaluated by comparison of pathologically responding and

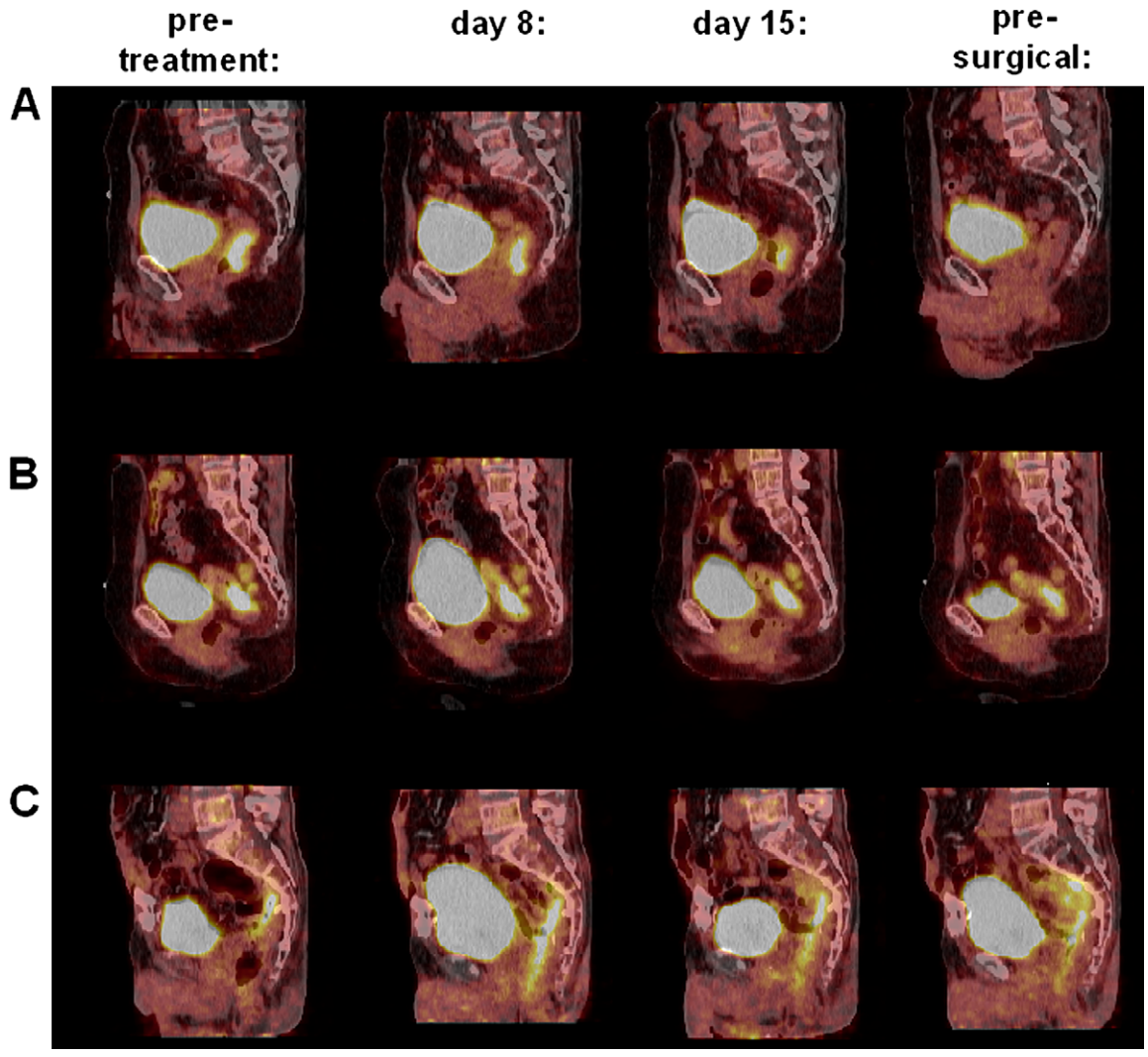

Fig. 1. Representative FDG-PET-CT images at all four time points from a complete metabolic responder (A) a non-complete metabolic responder (B) and a patient with a pathological reported peritumoral inflammatory reaction (C).

nonresponding malignancies. Interestingly, four of the patients included presented with a (histopathologically reported) peritumoral inflammatory response which could be visually observed on the repeated PET images. The increased FDG uptake associated with these inflammatory reactions resulted in mispredictions. Exclusion of those patients with a visually perceived peritumoral inflammatory response already apparent during early RCT from further analysis improved the accuracy of the models used for prediction of both the TRG and the ypT classification.

Previous reports of sequential PET-CT imaging during preoperative RCT for rectal cancer suggested further investigations to determine the best time point for the sequentially performed PET-CT image in order to find the best predictive model for the pathological tumor response (13, 15). This study presents the first prospective study of LARC in which multiple PET-CT scans were performed during preoperative RCT in order to define the optimal time point for PET imaging during therapy. In line with our findings, Cascini *et al.* also reported that early pathological response predictions assessed from PET imaging 12 days after the start of therapy were superior to presurgical PET-based response predictions (13). Interestingly, Wieder *et al.* showed comparable results for esophageal squamous cell carcinomas in two studies, also demonstrating that presurgical PET measurements were less predictive for the pathological response than mid-treatment measurements (20, 21). In contrast to our findings, however, Rosenberg *et al.* presented a study showing that presurgical PET data were slightly superior to those of PET imaging on day 14 of RCT for the prediction of the pathological treatment response in cases of rectal cancer (14).

Presurgical PET images obtained after a long course of RCT treatment, however, reveal mostly smaller malignancies due to significant tumor downsizing, which can result in an underestimation of the FDG uptake within the malignancy due to the partial volume effect (PVE) (22).

Most of the patients included in our study demonstrated only a small residual PET-positive tumor volume on the presurgical PET-CT scan due to a significant downsizing of the tumor, which was not the case during early RCT. Thus, for LARC patients, PET images performed early during RCT are less influenced by the effects of PVE than

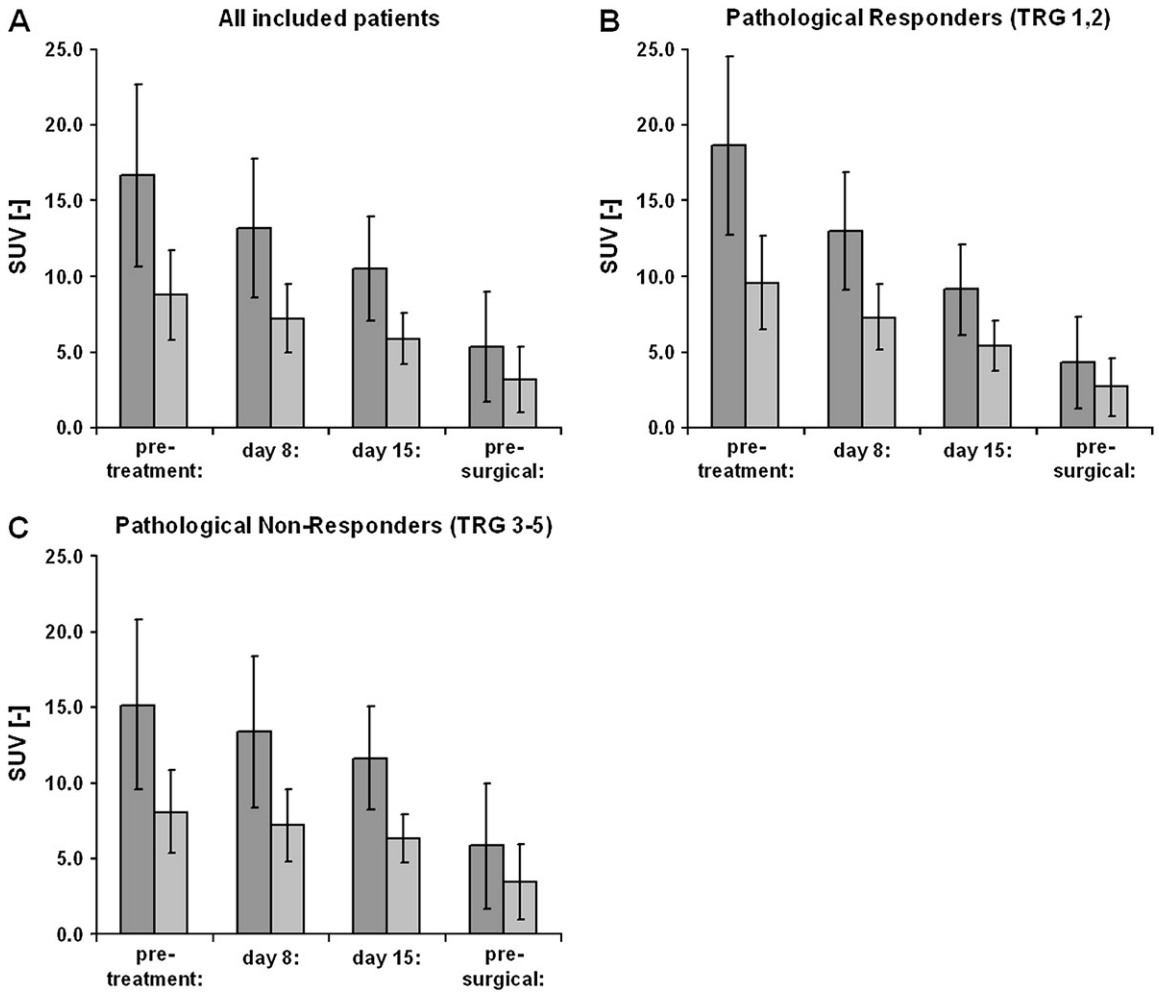

Fig. 2. Overview of the SUV_{max} (dark gray bars) and SUV_{mean} (light gray bars) time trends during preoperative RCT. (A) Average time trends are shown for all patients included in this study; (B) average time trends are shown for the pathologically responding patients, indicating a strong reduction of FDG uptake during the first 2 weeks of preoperative treatment; (C) average time trends are shown for the pathologically nonresponding patients, showing less reduction of FDG uptake during RCT compared to the pathologically responding patients.

presurgical PET images. The underestimation of the residual presurgical FDG uptake within the tumor due to the PVE might also explain the lack of correlation between the mCR and the pathological complete response found in our study.

Another important finding of this study and the study by Rosenberg *et al*. was the increased number of patients whose false negative PET-results classified them as pathological nonresponders due to the accumulation of inflammatory cells in areas where tumor cells underwent necrosis (14). Thus, an important confounder in the use of PET imaging as a response predictor is the presence of peritumoral inflammatory reaction. Inflammatory cells

Table 2. Statistically significant RIs for pathological responders and nonresponders*

	% Pathologic responders ± SD		% Pathologic nonresponders ± SD			
Uptake value	TRG 1 and 2	ypT stages 0 to 2	TRG 3 to 5	ypT stages 3 and 4	*p* value	ROC AUC ± SE
SUV_{mean} 0–8	23.3 ± 16.1		9.0 ± 16.4		0.026	0.75 ± 0.10
SUV_{max} 0–8	29.5 ± 17.7		9.4 ± 18.0		0.013	0.78 ± 0.09
SUV_{mean} 0–15	40.3 ± 19.2		17.4 ± 19.4		0.005	0.82 ± 0.08
SUV_{max} 0–15	47.2 ± 22.0		17.9 ± 21.6		0.001	0.87 ± 0.07
SUV_{max} 0–8		26.8 ± 21.9		11.7 ± 17.7	0.037	0.73 ± 0.10
SUVmean 0–15		39.7 ± 19.2		21.4 ± 18.9	0.007	0.81 ± 0.09
SUVmax 0–15		46.8 ± 21.1		21.9 ± 22.6	0.003	0.84 ± 0.08

Abbreviations: SD = standard deviation; SE = standard error.

* Data show average response indices for both pathological responders and nonresponders, statistical significance, and ROC curve analysis for all PET criteria revealing statistically significant different response indices for the two groups.

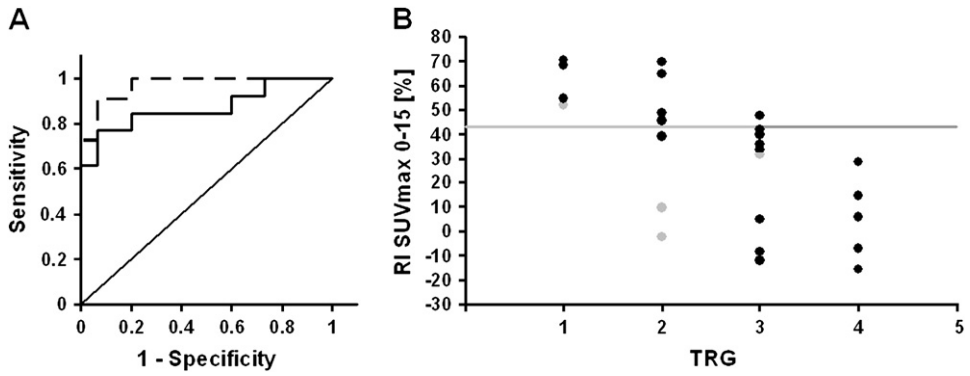

Fig. 3. (A) ROC curves of the SUV_{max} RI on day 15 of the RCT relative to the TRG stage before (solid line indicates AUC of 0.87) and after (dashed line indicates AUC of 0.97) exclusion of the patients with a reported peritumoral inflammatory response. (B) RIs of the SUV_{max} on day 15 relative to the TRG stage. The gray horizontal line indicates the ROC curve analysis based on the cutoff value of 43%, differentiating pathological responders from nonresponders. The grey dots highlight the four patients with a reported peritumoral inflammatory response.

are known to avidly consume FDG (23). An increased FDG uptake by inflammatory cells in the direct neighborhood of the tumor can lead to an underestimation of the decrease of FDG uptake within pathologically responding malignancies, which could result in false-negative classifications (14). When sequential PET imaging for the prediction of the pathological treatment response is applied, tumors presenting with an increased peritumoral FDG uptake should be handled with care or even excluded from further response predictions. It would thus be helpful to be able to distinguish malignant lesions from inflammatory responses, which might help to further increase the accuracy of response predictions based on sequential PET imaging. From static PET images such as those performed in this study, no further differentiation was feasible. Dynamic- and dual-time point PET imaging, however, might well be able to distinguish malignant from inflammatory tissue (24, 25).

Reliable FDG uptake quantification should be ensured when sequential PET-CT imaging is used for the prediction of the treatment response (15). Hindie *et al*. discussed the absolute necessity of imaging a malignancy at exactly the same time interval after FDG injection, when sequential PET imaging is used, because of the continuous FDG uptake during the first hours after FDG injection (15). In contrast, however, most studies involving the prediction of pathological treatment response with sequential PET imaging in rectal cancer based their analyses on FDG uptake times varying between 40 and 60 minutes (5, 6, 8, 13, 14). Furthermore, strong fluctuations of the patient's serum glucose level exist at the time of PET imaging and might further influence the time trend of the FDG uptake on sequential PET images of the same patient (15, 16, 26–28). None of the studies using sequential PET imaging of patients with rectal cancer to date performed a normalization of the PET data for the measured serum glucose level. In our study, however, all PET data were normalized for the serum glucose level measured shortly before the FDG injection in order to minimize the possible influence of the fluctuating serum glucose level on the time trend of FDG uptake. Also, strict time management with an exact time

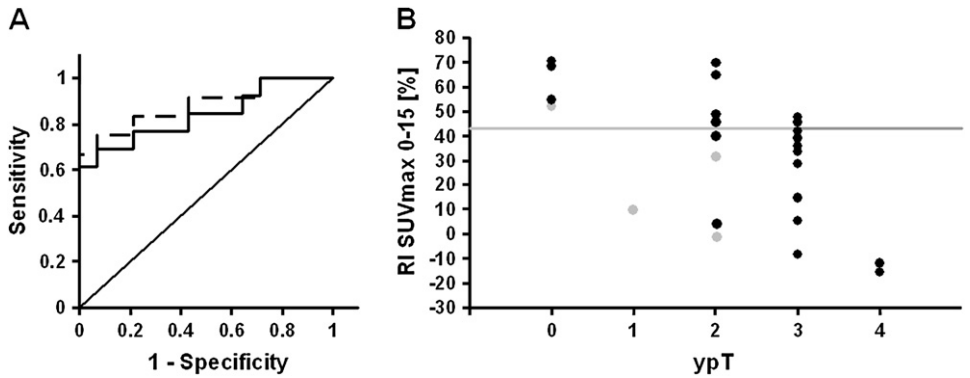

Fig. 4. (A) ROC curves for the SUV_{max} RI on day 15 of RCT relative to the ypT stage before (solid line indicates AUC of 0.84) and after (dashed line indicates AUC of 0.89) exclusion of the patients with a peritumoral inflammatory response. (B) RIs of the SUV_{max} on day 15 relative to the ypT stage. The grey horizontal line indicates the ROC curve analysis based on the cutoff value of 43%, differentiating pathological responders from nonresponders. The grey dots highlight the four patients with a peritumoral inflammatory response.

interval of 60 minutes between FDG administration and PET imaging was followed.

An accurate prediction of the pathological tumor response early during preoperative treatment would enable more individualized treatment regimens with the goal of further improving the tumor response or a modified surgical approach. A reliable prediction of the final T stage at the time of surgery with the help of the day 15 PET-CT would allow the surgeon to adapt the surgical approach to a less invasive technique, sparing the sphincter or even allowing a TEM surgery with a laparotomy, which would significantly reduce morbidity, provided that other imaging modalities like MRI could assure an accurate prediction of a ypN0 stage. In general, in attempts to define the right cutoff value for the FDG uptake decrease as a predictor of pathological response, a high PPV and a high specificity of the resulting prediction model are preferred over a high NPV and a high sensitivity in order to avoid at least the possibility of undertreatment rather than overtreatment. However, the findings presented need to be validated in an independent dataset before final conclusions can be drawn for the clinic.

CONCLUSIONS

In conclusion, reduction of the SUV_{max} after 2 weeks of preoperative RCT was found to be the best predictor for both the TRG response and the ypT stage. Thus, our data suggest that an accurate prediction of the TRG and the ypT stage is feasible early during RCT with AUC values of 0.87 and 0.84, respectively.

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