Metabolic positron emission tomography/CT response after induction chemotherapy and chemo(re)irradiation is associated with higher negative resection margin rate in patients with locally recurrent rectal cancer

Received: 3 June 2021 | Revised: 19 September 2021 | Accepted: 27 September 2021

DOI: 10.1111/codi.15934

ORIGINAL ARTICLE

Metabolic positron emission tomography/CT response after induction chemotherapy and chemo(re)irradiation is associated with higher negative resection margin rate in patients with locally recurrent rectal cancer

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Abstract

Aim: Positron emission tomography (PET)/CT can be used to monitor the metabolic changes that occur after intensified treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer (LRRC). This study aimed to analyse the correlation between the PET/CT response and final histopathological outcomes.

Methods: All LRRC patients who underwent induction chemotherapy prior to surgery between January 2010 and July 2020 and were monitored with pretreatment and post-treatment PET/CT were included. Visual qualitative analysis was performed, and patients were scored as having achieved a complete metabolic response (CMR), partial metabolic response (PMR) or no response (NR). The histopathological response was assessed according to the Mandard tumour regression (TRG) score and categorized as major (TRG 1–2), partial (TRG 3) or poor (TRG 4–5). The PET/CT and TRG categories were compared, and possible confounders were analysed.

Results: A total of 106 patients were eligible for analysis; 24 (23%) had a CMR, 54 (51%) had a PMR and 28 (26%) had NR. PET/CT response was a significant predictor of the negative resection margin rate, achieving 96% for CMR, 69% for PMR and 50% for NR. The overall accuracy between PET score and pathological TRG was 45%, and the positive predictive value for CMR was 63%. A longer interval between post-treatment PET/CT and surgery negatively influenced the predictive value.

Conclusion: Metabolic PET/CT response evaluation after neoadjuvant treatment proves to be a complementary diagnostic tool to standard MRI in assessing tumour response, and may play a role for treatment planning in LRRC patients.

KEYWORDS
FDG-PET/CT, histopathological response, induction chemotherapy, locally recurrent rectal cancer

INTRODUCTION

The most important prognostic factor for oncological outcomes in the curative approach for locally recurrent rectal cancer (LRRC) is surgery with negative resection margins (R0 resection). Owing to the removal of the fascial resection planes during surgery for the primary tumour, LRRC is usually not well defined and often invades multiple planes and structures. In order to achieve R0 resection, major extended procedures are required, which are associated with high morbidity and loss of function. The rationale for intensified neoadjuvant strategies, including induction chemotherapy and chemo(re)irradiation, is to downsize and downstage the tumour to facilitate an R0 resection [1,2]. In locally advanced primary rectal cancer, a watch-and-wait policy is warranted in a subset of patients who achieve a clinical complete response [3,4]. Such an approach has not been developed for LRRC patients yet, due to difficulties in assessing a clinical complete response. In LRRC patients assessment relies heavily on imaging techniques as in most patients local recurrences cannot be assessed with endoscopy. However, pathological complete response (pCR) rates close to 20% have been described in LRRC [1,5].

The presence of postoperative changes and fibrosis mixed with tumour-bearing tissue complicates the assessment of the clinical response. After a complete response, the anatomy will not return to normal, and the remaining fibrosis can be challenging to differentiate from vital tumour tissue on MRI.

The gold standard for assessing the response to neoadjuvant treatment is histopathological analysis. However, this method only confirms the response postoperatively. An objective imaging tool that could accurately identify patients with a pCR would allow an R0 resection to be predicted and could help to develop research programmes in which surgery is postponed or avoided. Alternatively, a poor response might guide treatment intensification or deferral from curative strategies.

Traditionally, MRI and CT have been used to monitor the response to therapy and exclude distant metastases prior to surgery. MRI is particularly suitable for assessing anatomical changes in patients with primary rectal cancer [6]. However, in LRRC, anatomical changes might be more subtle and areas of the vital tumour may have been replaced by fibrotic tissue. In addition, PET/CT can be used to monitor the metabolic changes that occur following neoadjuvant therapy and to predict the histopathological response. A decrease in fluorodeoxyglucose (FDG) uptake after chemotherapy and/or radiotherapy has been correlated with the histopathological response in several tumour types [7-9]. The response on PET/CT can be scored visually, according to accepted guidelines, and/or quantitatively using full metabolic analysis [10,11]. The main objective of this retrospective study was to correlate the PET/CT response to the histopathological response in LRRC patients who underwent induction chemotherapy and chemo(re)irradiation prior to surgery. The role of induction chemotherapy on oncological outcome is being studied in two randomized studies, GRECCAR 15 and PELVEX 2, which have started recruiting patients [12,13].

Novel findings

Metabolic positron emission tomography/CT response evaluation in locally recurrent rectal cancer patients predicts histopathological outcomes and can be used as an additional tool for decision-making during multidisciplinary tumour board meetings. However, the validity of the response evaluation results is limited to a certain time frame, as the ongoing response or progression of the tumour reduces the predictive value.

METHODS

Patients

The data of consecutive LRRC patients treated at the Catharina Hospital (CZE), a national tertiary referral centre for LRRC in the Netherlands, were prospectively collected in a database and retrospectively reviewed. For this study, all LRRC patients who underwent induction chemotherapy and chemo(re)irradiation followed by resection with curative intent between January 2010 and July 2020 were selected. Induction chemotherapy consisted of four cycles of CAPOX (capecitabine and oxaliplatin) or FOLFOX (leucovorin, fluorouracil and oxaliplatin). Full course chemoradiation in radiotherapy naive patients ($n = 23$) consisted of 25 fractions of 2 Gy with concomitant capecitabine 825 mg/m^2 twice daily; chemo(re)irradiation in radiotherapy non-naive patients ($n = 83$) consisted of 15 fractions of 2 Gy with concomitant capecitabine 825 mg/m^2 twice daily. Full course chemoradiation and chemo(re)irradiation were delivered to 22 and 84 patients, respectively. All patients had at least a pretreatment PET/CT and a post-treatment PET/CT prior to surgery. Patients with PET/CT images that could not be revised were excluded, as were patients who underwent palliative treatment. Further details regarding the patient selection are shown in Figure 1.

This study was approved by the local medical ethics board (Medical Research Ethics Committees United—Nieuwegein, registration number W19.031); individual informed consent was not required.

PET/CT imaging

For non-referred patients, whole-body images from the skull base to the mid-thigh were obtained using PET/CT (Discovery 710, GE Healthcare) in accordance with accepted institutional procedures. Image acquisition was started approximately 60 min after the tracer injection. For referred patients, pretreatment whole-body PET/CT images were obtained from the referring hospital.

All patients underwent post-treatment PET/CT at our institution, once again in accordance with the accepted institutional procedures.

Qualitative visual analysis was performed using dedicated commercial software (Philips iPortal, Eindhoven, The Netherlands). Visual analysis was performed according to the accepted guidelines [11]. Complete metabolic response (CMR) was defined as no visible activiy at the initial tumour site, or activity at the initial tumour site not exceeding adjacent physiological bowel activity in the case of luminal recurrence. No response (NR) was defined as unchanged or increased activity, regarding intensity and/or extension. Partial metabolic response (PMR) was defined as any other response. A blinded nuclear medicine specialist re-evaluated all PET/CT images. To account for inter-reader variability, the PET/CT response categories from the re-evaluation were compared with those obtained from the report. If the report was written by the same dedicated specialist, a second dedicated nuclear medicine specialist re-evaluated these scans.

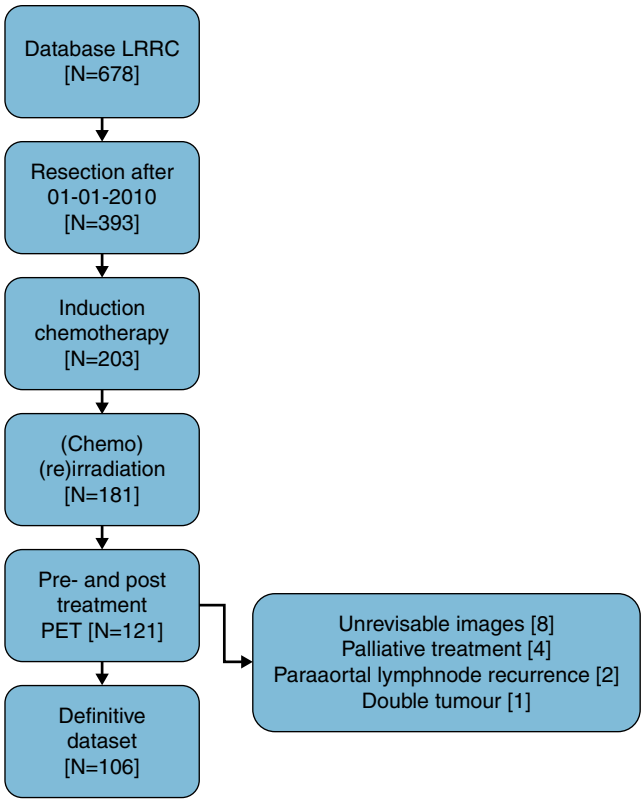

FIGURE 1 Flow chart on patient selection

Histopathological response analysis

The histopathological response was assessed according to the Mandard tumour regression (TRG) score. A major histopathological response was defined as TRG 1 or 2, a partial response as TRG 3, and a poor histopathological response as TRG 4 or 5 [14].

Statistical analysis

Continuous values were recorded in two categories according to the median. Categorical variables were analysed using the chi-squared test. Response prediction was deemed accurate when PET/CT showed a CMR, PMR or NR for a major, partial or poor histopathological response, respectively. The PET/CT response categories from the re-evaluation were compared with those obtained from the report using weighted kappa. Weighted kappa was also used to compare the PET/CT response categories to the magnetic resonance TRG categories, defined as complete response (TRG 1 or 2), partial response (TRG 3) and no response (TRG 4 or 5) [15].

Statistical analyses were performed using IBM SPSS® version 23 for Windows® (IBM, Armonk, New York, USA).

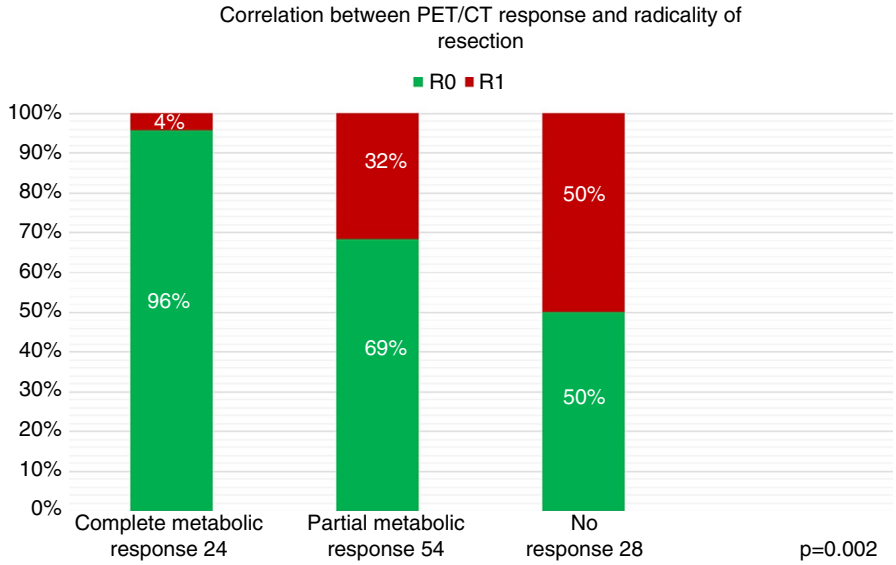

FIGURE 2 Correlation between PET/CT response and radicality of resection

RESULTS

Correlation with the radicality of resection

Figure 2 shows the correlation between PET/CT response and the radicality of the resection.

There was a significant correlation and linear relationship between the metabolic response and likelihood of R0 resection ($P = 0.002$). Patients with a PMR or NR had a smaller chance of R0 resection.

The numbers of radiotherapy naive patients were too small to calculate the correlation between PET/CT response and Mandard score for this group specifically. However, after induction chemotherapy and full course chemoradiation a significantly higher R0 resection rate and significantly better Mandard scores were noted (87% vs. 65%, $P = 0.046$, and 57% vs. 28%, $P = 0.010$, respectively).

Correlation with histopathological outcomes

Of the 106 patients who met the selection criteria, 24 (23%) had a CMR, 54 (51%) had a PMR and 28 (26%) had NR, based on visual analysis. Table 1 shows patient demographics. No differences in multifocal versus solitary recurrences, nor between central, single compartment and multiple compartment involvement, and no differences between patients with an anastomosis or abdominoperineal surgery for their primary tumour (patients with local treatment or watch and wait for their primary were excluded in this paper) could be demonstrated.

Figure 3 depicts the correlation between the PET/CT and histopathological responses. In 24 patients, PET/CT showed a CMR, which accurately predicted the major histopathological response in 15 patients (63%). However, 7/24 patients (29%) had a partial histopathological response and 2/24 patients (8%) had a poor histopathological response. In 54 patients, PET/CT showed a PMR, which accurately predicted a partial histopathological response in 23/54 patients (43%). However, 16/54 patients (30%) had a major histopathological response and 15/54 patients (28%) had a poor histopathological response. In 28 patients, PET/CT showed NR, which accurately predicted a poor histopathological response in 10 patients (36%). However, 5/28 patients (18%) had a major histopathological response and 13/28 patients (46%) had a partial histopathological response.

There was a significant correlation between the PET/CT response and histopathological outcomes ($P = 0.010$). The sensitivity to detect major histopathological response was 42%, and the positive predictive value was 63%. The sensitivity to detect a partial histopathological response was 53%, and the positive predictive value was 43%. The sensitivity to predict a poor histopathological response was 37%, and the positive predictive value was 36%.

Overall, PET/CT predicted the histopathological response correctly in 48 patients (45%). PET/CT underestimated the actual histopathological response in 34 patients (32%), and PET/CT overestimated the actual histopathological response in 24 patients (23%).

Table 1 shows potentially confounding clinical parameters that may affect the reliability of the PET/CT response category in predicting histopathological outcomes. The table shows that, for both male and female patients, a significant correlation persists. However, this significance was lost in several subsets. The presence of diabetes had a negative impact, as well as the presence of inflammation. The size of the largest post-treatment tumour diameter did not impact the predictability.

The assessment of the response by PET/CT is followed by a waiting period until surgery is performed. In this cohort, the median interval between post-treatment PET/CT and surgery was 51 days. Table 1 shows that an interval of fewer than 51 days significantly correlates with PET/CT predictability ($P = 0.009$), whereas an interval of 51 days or more did not ($P = 0.363$). Analyses were performed to compare patients with an interval of fewer than 51 days (short interval) to those with an interval of 51 days or more (long interval).

Figure 4 shows the correlation between the PET/CT outcomes and histopathological responses divided by long and short intervals.

The discrimination between patients with a major histopathological response and those who had a partial or poor histopathological response is better when surgery is performed within 51 days (positive predictive value for a major histopathological response is 86%, compared to 53% after a long interval).

Inter-reader variability

The level of agreement between the response assessment by the blinded dedicated nuclear medicine specialist and the response assessment by a second specialist was moderate. The weighted kappa value was 0.71 (95% CI 0.60–0.83, $P < 0.001$).

Correlation with MRI response assessment

The major histopathological response was correctly identified by PET/CT and MRI in 15 and 17 out of 36 cases, respectively. The evaluation overlapped in 11 cases. A partial histopathological response was correctly identified by PET/CT and MRI in 23 and 15 out of 43 cases, respectively. The evaluation overlapped in 10 cases. A poor histopathological response was correctly identified by PET/CT and MRI in 10 and 20 out of 26 cases, respectively. The evaluation overlapped in nine cases (Figure 5). The weighted kappa value for a correlation between the two tests was 0.38 (95% CI 0.23–0.52), $P < 0.001$. There was a significant correlation and linear relationship between the MRI response and the likelihood of R0 resection ($P = 0.041$).

DISCUSSION

The main finding of this study is that a CMR on PET/CT adequately predicts R0 resection in 96% of patients. In addition, this study

TABLE 1 Clinical parameters affecting response predictability

Clinical parameters		*N* = 106	CMR		PMR		NR		*P* value
			Sens	Spec	Sens	Spec	Sens	Spec	
			42%	87%	53%	51%	37%	77%	0.010
Gender	Male	77	39%	88%	65%	57%	44%	59%	0.030
	Female	29	50%	86%	25%	35%	22%	70%	0.018
Age at resection (years)	<65	56	37%	89%	50%	44%	38%	77%	0.070
	≥65	50	47%	85%	58%	58%	36%	78%	0.175
ASA	I–II	84	40%	87%	50%	48%	29%	73%	0.079
	III	22	57%	87%	67%	62%	67%	94%	0.016
Diabetes mellitus	No	95	42%	87%	51%	50%	36%	77%	0.012
	Yes	11	33%	88%	67%	60%	50%	78%	0.766
Number of recurrence	First	90	41%	88%	50%	50%	32%	75%	0.024
	Second/third	16	50%	86%	67%	57%	60%	91%	0.192
Number of lesions	Single	74	50%	88%	59%	51%	38%	83%	0.003
	Multifocal	32	25%	85%	43%	50%	33%	65%	0.725
Interval last radiotherapy – post-treatment PET/CT (days)	<32	48	29%	90%	68%	45%	42%	83%	0.214
	≥32	58	53%	85%	42%	56%	33%	72%	0.033
Inflammation on PET/CT[a]	No	48	57%	78%	33%	55%	25%	81%	0.033
	Yes	49	23%	92%	60%	50%	55%	74%	0.283
Size of tumour post-treatment (mm)[b]	<27	43	56%	74%	47%	62%	30%	74%	0.364
	≥27	50	31%	95%	57%	48%	50%	72%	0.086
Interval post-treatment PET/CT – surgery (days)	<51	52	40%	97%	64%	48%	42%	75%	0.009
	≥51	54	43%	76%	39%	53%	33%	79%	0.363

Abbreviations: ASA, American Society of Anesthesiologists; CMR, complete metabolic response; PET, positron emission tomography; NR, no response; PMR, partial metabolic response; Sens, sensitivity; Spec, specificity.

[a] Presence of inflammation on post-treatment PET/CT; nine missing values.

[b] Largest diameter measured on post-treatment MRI; 13 missing values.

established an association between the visual PET/CT response evaluation and the histopathological response. Although this connection is not strong enough to make definitive clinical decisions, it proves to be an alternative for the direct visualization of rectal cancer and is a complementary technique to aid decision-making in multidisciplinary tumour board meetings. A better response was noted in radiotherapy naive patients with regard to R0 resection rate and better Mandard scores, but this group was too small for further correlation analysis.

The study is the first to investigate the correlation between the PET/CT response evaluation and the histopathological outcomes in patients with LRRC. Although PET/CT is an accepted imaging technique to detect the suspected recurrence of colorectal disease, using PET/CT to monitor the metabolic response to neoadjuvant therapies in LRRC is more controversial [16,17]. To the best of our knowledge, no previous studies have described neoadjuvant therapy monitoring by PET/CT in LRRC. Neoadjuvant therapy monitoring by PET/CT has been explored to some depth in locally advanced primary rectal cancer, where studies showed an added benefit for PET/CT in addition to the current imaging modalities, MRI and CT [18,19]. Recent studies have assessed the relationship between the PET metabolic response and the histopathological response in patients with locally advanced rectal cancer. Maffione et al. reported both visual response assessment and quantitation (i.e., maximum standardized uptake value [SUVmax], delta metabolic tumour volume [deltaMTV] and delta total lesion glycolysis [deltaTLG]) predictive of the histopathological response [20]. Leccisotti et al. performed PET/CT both early and late in the course of neoadjuvant therapy [21]. They confirmed that the PET/CT predicted the deltaSUVmax for early response assessment at the end of the second week of chemoradiotherapy, but not for the late assessment prior to surgery. Avallone et al. found that the deltaTLG showed the best accuracy in predicting pCR [22]. In recent years, emphasis has been placed on 3D textural analyses of the primary tumour rather than its response to neoadjuvant therapy. In these studies, a relationship was found between the metabolic volume of the primary tumour, some of its textural features and the histopathological response as well as disease-free survival [23,24]. Unfortunately, a quantitative, full metabolic analysis was only possible in 23 patients in our study and therefore was not included.

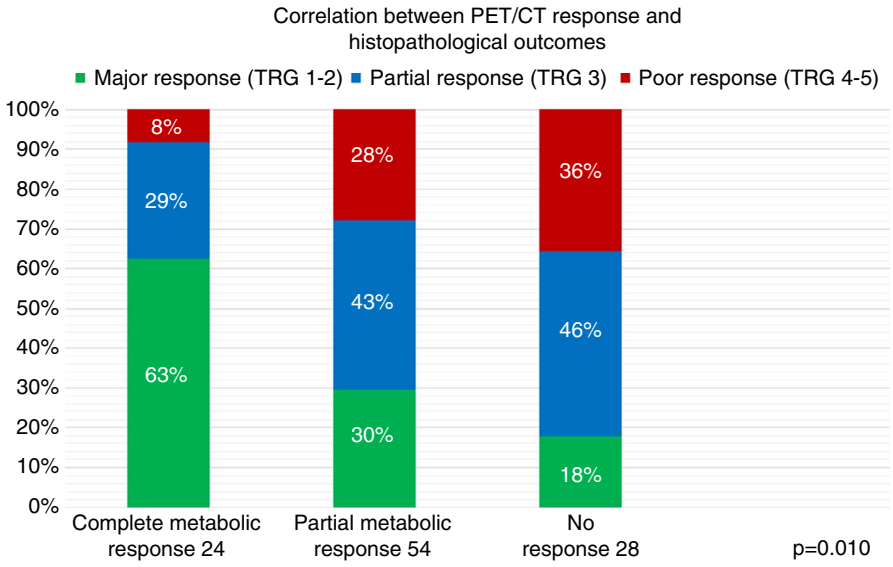

FIGURE 3 Correlation between PET/CT response and histopathological outcomes

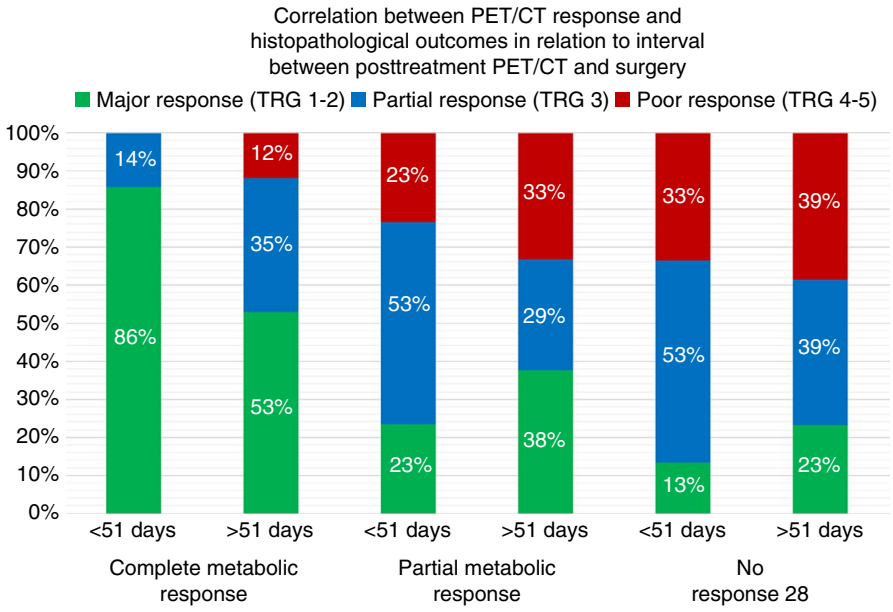

FIGURE 4 Correlation between PET/CT response and histopathological outcomes in relation to interval between post-treatment PET/CT and surgery

The issues that may be responsible for these discrepant findings need to be discussed. The most important factor impeding a good correlation between the PET/CT and histopathological responses is time. The metabolic processes in a tumour change over time and are influenced by different neoadjuvant treatment modalities. Even after the end of neoadjuvant treatment, tumour metabolism remains a dynamic process, and the tumour may either regress or progress. The timing of the post-treatment PET/CT and the interval to resection are important to predict the response. If the interval between the post-treatment PET/CT evaluation and resection is too long, local tumour regrowth might have occurred [25]. Alternatively, if the interval between the post-treatment PET/CT evaluation and resection is too short, there is no time for an ongoing response to develop. In this dataset, the median time between post-treatment PET/CT and surgery was 51 days. We found that the correlation between the PET/CT response and the histopathological outcome was significantly better at shorter intervals. The sensitivity to detect major histopathological response was as high as 86%, compared to only 53% for the longer interval. When the interval between post-treatment PET/CT and surgery exceeded 51 days, the PET/CT response did not reliably predict the histopathological response. If this prediction is pivotal for treatment planning, the PET/CT evaluation may need to be repeated.

Regardless of the fact that the PET/CT evaluation is a snapshot of a dynamic metabolic process, further factors can confound the correlation with the histopathological response. Mandard classification is a score based on tumour density, whereas the PET/CT response also accounts for the tumour volume, hindering a direct comparison of the scoring systems [10,14]. In some cases, the tumour volume may have decreased when the clinical response was recorded, but if the percentage of vital tumour cells in the residual tumour was above 50% the Mandard score would be 4 or 5, which is considered a poor response.

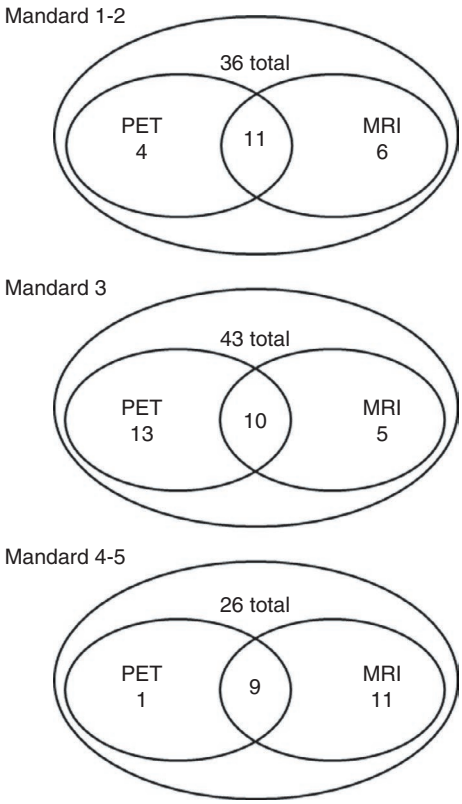

FIGURE 5 Correlation between PET/CT and MRI response assessment

It is also known that some histological types are less FDG-avid and persist after neoadjuvant therapy [26]. In this dataset, no patients with signet ring cell differentiation were included. Mucinous histopathology did not significantly impact the predictability of the response.

The tumour response can be underestimated by PET assessment when there is persistent inflammation at the time of PET/CT. Inflammation is known to occur after chemoradiotherapy. Usually, the inflammatory reaction is only temporary, but it can persist at recurrence locations such as the presacral area. For this area, the visual response assessment is probably advantageous over a quantitation because the visual assessment can appreciate the patterns of FDG uptake typical for inflammation (e.g., diffuse FDG uptake in the presacral area, FDG uptake of an even nature in the wall of a presacral cavity).

Another imaging modality often used to provide information about LRRC is MRI, which is also used to evaluate tumour regression. The correlation with R0 resection was a little worse than after PET/CT ($P = 0.042$ and $P = 0.002$, respectively). As the agreement between PET/CT and MRI is only fair [27], both imaging modalities seem complementary. PET/CT reflects the metabolic activity in vital tumour cells, whereas MRI focuses more on fibrosis surrounding the tumour cells. In selected patients there may be reasons to delay surgery after complete response. In these patients, PET/CT may be complementary to MRI to differentiate between good and poor responders and can therefore aid in treatment decision-making.

One of the major limitations of this study is that PET/CT evaluations were not performed according to a standard protocol. Regular PET/CT evaluations before, during and after neoadjvuant treatment were implemented during the entire inclusion period. This led to different time intervals, also caused by the fact that a substantial proportion of the included patients were referrals from other hospitals. The suboptimal timing of response assessment with PET/CT in some of the included patients negatively influenced the reliability of PET/CT. Another limitation is the relatively short interval of median 31 days between the end of radiotherapy and response evaluation PET/CT. The reason for this is that, after prolonging preoperative treatment with the implementation of induction chemotherapy, early re-evaluation was performed in order to avoid patients who were progressive and subsequently would forfeit the chance of resection as a consequence of this. However, no patients were identified as progressive and could not undergo surgery. It would be better to prolong the interval after radiotherapy and shorten the interval between PET/CT and surgery. Furthermore, in the early years of the inclusion period, PET/CT was performed only in highly complex cases. In addition, the number of patients with LRRC receiving induction chemotherapy is still low; therefore, the subset analysis is underpowered and should be considered with care.

CONCLUSION

Metabolic PET/CT response evaluation after neoadjuvant treatment proves to be a complementary diagnostic tool to standard MRI in assessing tumour response and may play a role in treatment planning in LRRC patients.

In order to be able to perform an R0 resection the anatomical and topographical information from an MRI remains the cornerstone of the preoperative imaging in LRRC. Comparable to primary rectal cancer, response evaluation in LRRC may become more important for decision-making.

MRI and PET/CT show different components of response—anatomical and metabolic changes respectively—and therefore are complementary. For both techniques correlation with final pathology is not optimal and is negatively influenced by longer intervals. However, the correlation with R0 resection is more useful. Future research is needed to establish for which patients response evaluation with PET/CT may be of added value before routine use can be advocated.

ETHICAL APPROVAL

This study was approved by the local ethics committee.

AUTHOR CONTRIBUTIONS

Conceptualization: HR, MR. Investigation: SL, MR. Formal analysis: DvZ, HR, MR. Writing - original draft: DvZ. Writing - review and editing: all authors. Final approval: all authors. Supervision: HR, MR.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: van Zoggel DMGI, Voogt ELK, van Lijnschoten IG, Cnossen JS, Creemers G-J, Nederend J, et al. Metabolic positron emission tomography/CT response after induction chemotherapy and chemo(re)irradiation is associated with higher negative resection margin rate in patients with locally recurrent rectal cancer. Colorectal Dis. 2022;24:59–67. https://doi.org/10.1111/codi.15934