

Restaging of rectal cancer with hybrid positron emission tomography magnetic resonance imaging after preoperative chemoradiotherapy

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ABSTRACT

Introduction: This study determines the sensitivity and specificity of positron emission tomography/magnetic resonance imaging (PET/MRI) parameters in predicting treatment response in patients with localised rectal cancer who have undergone preoperative chemoradiotherapy (CRT).

Method: Patients with stage I–III adenocarcinoma of the rectum planned for preoperative CRT followed by surgery were recruited. Patients had PET/MRI scans at baseline and 6–8 weeks post-CRT. Functional MRI and PET parameters were assessed for their diagnostic accuracy for tumour regression grade (TRG). Nonparametric receiver operating characteristic analysis was employed to determine the area under the ROC curve (AUC), and the sensitivity and specificity of each quantile cut-off.

Results: A total of 31 patients were recruited, of whom 20 completed study protocol. All patients included had mid or lower rectal tumours. There were 16 patients (80%) with node-positive disease at presentation. The median time to surgery was 75.5 days (range 52–106 days). Histopathological assessment revealed 20% good responders (TRG 1/2), and the remaining 80% of patients had a poor response (TRG 3/4). When predicting good responders, the AUC values for percent maximum thickness reduction and percent apparent diffusion coefficient (ADC) change were 0.82 and 0.73, respectively. A maximum thickness reduction cut-off of $\geq 47\%$ and a percent ADC change of $\geq 20\%$ yielded a sensitivity and specificity of 75%/95% and 75%/73%, respectively.

Conclusion: Parameters such as percent maximum thickness reduction and percent ADC change may be useful for predicting good responders in patients undergoing preoperative CRT for rectal cancer. Larger studies are warranted to establish the utility of PET/MRI in rectal cancer staging.

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INTRODUCTION

Neoadjuvant chemoradiotherapy (CRT) followed by surgery is the current standard of care for locally advanced rectal cancers. Randomised trials have shown that a neoadjuvant approach results in improved tumour downstaging, improved R0 resections, improved local control and increased sphincter preservation rates.¹ Reliable response assessment and restaging post-CRT add invaluable information for making optimal surgical and subsequent management decisions.

Current imaging modalities for response assessment and local restaging of rectal cancer patients post-CRT

are inaccurate in this regard, particularly for T staging prediction and nodal status prediction.^{2,3} This is due to an overlap in the appearance of the underlying residual tumour and post-treatment changes after CRT. A non-invasive and accurate way of assessing the treatment effect of CRT will guide surgical planning and allow for optimal selection of patients who need less extensive surgery, thereby reducing surgical morbidity.

One forerunner in the evaluation of rectal cancer burden pre- and post-CRT is hybrid positron emission tomography/magnetic resonance imaging (PET/MRI).^{4,5} PET/MRI is a new imaging technology that can

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CLINICAL IMPACT

What is New

- This study evaluated the role of PET/MRI in rectal cancer restaging after chemoradiotherapy (CRT), with clearly defined and standardised protocols for MRI and PET acquisition.
- Using a percent maximum thickness reduction cut-off of $\geq 47\%$ and a percent apparent diffusion coefficient (ADC) change of $\geq 20\%$, there was a sensitivity and specificity of 75%/95% and 75%/73%, respectively.
- The presence of mucinous rectal lesions can limit the role of PET/MRI due to their low fluorodeoxyglucose activity.

Clinical Implications

- MRI parameters, such as percent maximum thickness reduction and percent ADC change, may be useful for predicting good responders in patients undergoing preoperative CRT for rectal cancer.
- Future studies evaluating the role of PET/MRI in rectal cancer staging should also aim to specifically evaluate its utility in rectal cancers with a mucinous component.

overcome the shortfalls of existing imaging techniques. The MRI data acquired provide a detailed high-resolution anatomical map that can be correlated to the metabolic information from the PET scan, which has been shown to be highly sensitive for residual tumour detection. However, the diagnostic accuracy of PET/MRI in identifying good responders to preoperative CRT treatment remains unclear.

Thus, this prospective study aims to determine the diagnostic accuracy of various PET/MRI parameters in determining the treatment response of rectal cancer patients to preoperative CRT.

METHOD

Patients

This prospective study was approved by the National Healthcare Group Domain Specific Review Board B- 2014/00626 and 2015/01172. Eligible patients must be ≥ 18 years of age, diagnosed with cT2–4, N0–2 and M0 biopsy-proven adenocarcinoma of the rectum ≤ 12 cm from the anal verge. Patients must have adequate renal, liver and haematological function and

medically operable, with ECOG performance status 0–2. Exclusion criteria included patients with contraindications to MRI. Informed consent was obtained from all trial participants. The planned accrual was 30 patients over 2 years. The study workflow is shown in Fig. 1. All patients underwent a computed tomography (CT) of thorax/abdomen/pelvis and MRI rectum as standard workup for distant and local staging, respectively.

Radiotherapy

All patients received preoperative CRT followed by surgery. The radiotherapy regimen utilised 50.4 Gy in 28 daily fractions delivered using conventional 3-dimensional conformal radiation therapy. The clinical target volume (CTV) included primary tumour and gross nodes. Elective nodal irradiation included the presacral, mesorectal, obturator and internal iliac lymph nodes. The planning target volume included the CTV with a 5 mm margin.

Chemotherapy

The chemotherapy regimen was either concurrent capecitabine (at a dose of 825 mg/m²) or concurrent infusional 5 fluorouracil (at a dose of 425 mg/m²).

PET/MRI

The PET/MRI was acquired on a single machine. The MRI sequences were (1) multiplanar T2-weighted images of the pelvis; (2) diffusion-weighted images of the pelvis, including b values for intravoxel-incoherent motion analysis; (3) dynamic contrast-enhanced MRI of the pelvis; (4) magnetic resonance spectroscopy; and (5) T1-weighted (Dixon technique) and T2-weighted images of the whole body for PET data anatomic correlation and attenuation correction. PET data were acquired simultaneously with MRI, obtained 60 minutes after the injection of 18F-fluorodeoxyglucose (FDG) (300–385 MBq).

Pathological assessments

Tumour response post-CRT and surgery was graded according to the tumour regression grade (TRG). TRG 1 is defined as no viable tumour cells, TRG 2 is defined as single or small groups of cancer cells, TRG 3 is defined as residual cancer outgrown by fibrosis, TRG 4 is defined as significant fibrosis outgrown by cancer, and TRG 5 is defined as no regressive changes in tumour.

Endpoints

Patients underwent PET/MRI scans at baseline and 6–8 weeks post-CRT. The scan findings were compared

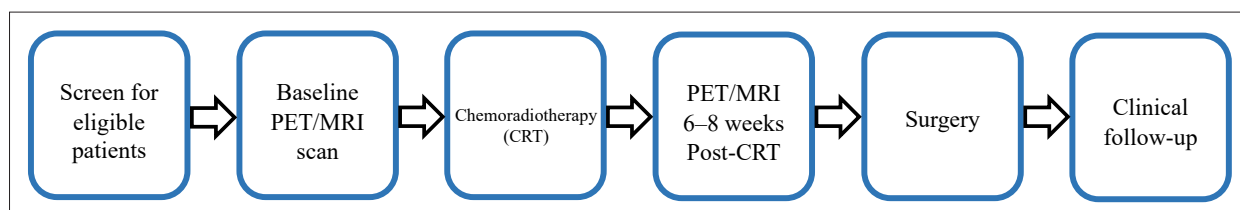


Fig. 1. Study workflow.

CRT: chemoradiotherapy; PET/MRI: positron emission tomography/magnetic resonance imaging

against the TRG on the histopathological specimen. The diagnostic accuracy of functional MRI and PET parameters was assessed based on TRG 1/2 (good responders). These parameters include percent volume reduction, percent standard uptake volume (SUV) reduction, percent SUV volume reduction, percent glycolysis reduction, percent maximum thickness reduction, percent apparent diffusion coefficient (ADC) change, post-treatment (PTx) volume, PTx SUV max, PTx SUV volume, PTx glycolysis, PTx maximum thickness and PTx ADC values. Each parameter is divided equally into 5 quantiles. Nonparametric receiver operating characteristic analysis was employed to determine the sensitivity and specificity of each quantile cut-off. An AUC value of ≥ 0.8 was taken to be clinically useful in predicting for response to preoperative CRT. Statistical analysis was performed with STATA version 14 (Stata Corp, College Station, TX, US).

RESULTS

Patients

From April 2015 to August 2019, 31 patients were recruited. Twenty patients completed the study protocol. Eleven did not, including one who withdrew voluntary consent, and one lost to follow-up. Nine patients did not complete their scheduled scans.

Patient and tumour characteristics are highlighted in Table 1. Eighty percent (16/20) of patients were male. Majority of patients were aged 50 years or older. Patients had mid or lower rectal tumours. Eighty percent (16/20) of patients had node-positive disease.

Surgery

The median time to surgery was 75.5 days (range 52–106 days). All patients underwent surgery post-CRT. Eighty percent (16/20) of patients had anterior resection. R0 resection was obtained in 95% (19/20) of patients. Lymphovascular invasion was present in 75% (17/20) of patients, and no patients had perineural invasion. Twenty percent of patients had a good response (TRG 1/2) to preoperative CRT. Surgical

Table 1. Patient characteristics and tumour staging.

Patient characteristics	N=20	%
Sex		
Male	16	80.0
Female	4	20.0
Age, years		
≤ 50	1	5.0
≥ 50	19	95.0
Location of tumour (cm from the anal verge)		
High (9–12cm)	0	0
Mid (5–8cm)	7	35.0
Lower (0–4cm)	13	65.0
cT		
T2	3	15.0
T3	15	75.0
T4	2	10.0
cN		
N0	4	20.0
N1	2	10.0
N1a	1	5.0
N1b	3	15.0
N2a	5	25.0
N2b	5	25.0
Combined clinical stage		
T2N0	2	10.0
T2N2	1	5.0
T3N0	1	5.0
T3N1	6	30.0
T3N2	8	40.0
T4N0	1	5.0
T4N2	1	5.0

procedures performed and pathological findings are detailed in Table 2.

Pathological response

Ten percent (2/20) of patients had a complete pathological response (TRG1). Tumour was successfully downstaged

Table 2. Surgical procedures and pathological findings.

	N=20	%
Surgical procedure		
Abdominoperineal resection	4	20.0
Anterior resection	15	75.0
Low anterior resection	1	5.0
Lymphovascular invasion		
Yes	3	15.0
No	17	85.0
Perineural invasion		
Yes	0	0.0
No	20	100.0
Margin		
Positive	1	5.0
Negative	19	95.0
ypT		
T0	2	10.0
T1	2	10.0
T2	5	25.0
T3	11	55.0
T4	0	0.0
ypN		
N0	13	65.0
N1	6	30.0
N2	1	5.0
TRG		
0	2	10.0
1	2	10.0
2	13	65.0
3	3	15.0

in the remaining 18 patients (2 TRG 2 and 13 TRG 3), 95% (19/20) of patients had clear margins after surgery, whereas 5% (1/20) had a positive surgical margin after surgery.

PET/MRI in predicting tumour response

Figs. 1 and 2 illustrate how PET/MRI can help accurately predict tumour response during surgery. Fig. 1A displays the PET/MRI images of a patient with poorly differentiated low rectal carcinoma. Pretreatment sagittal T2 and fused PET/MRI images show primary tumour (SUV max=11.2) with pathological enlarged and hypermetabolic presacral node (short arrow). Fig. 1B depicts post-CRT images, showing marked tumour volume reduction with residual tumour of MRI and marked remnant metabolic uptake in the primary tumour (SUVmax=9.6) and presacral node. Preoperative clinical stage was cT3N1. Final stage was ypT3N2a. Histological response was a poor response TRG 3.

By contrast, Fig. 2A shows another patient's PET/MRI images. Pretreatment axial T2 images and fused PET/MRI images show primary tumour (SUVmax=13.4) with no suspicious nodes in the mesorectum. Fig. 2B depicts post-CRT images, showing marked tumour volume reduction with residual wall thickening posteriorly that was indeterminate for remnant tumour. However, there was no significant corresponding metabolic update (SUVmax=2.5) in the area of wall thickening. Preoperative clinical tumour state was cT3N1. Postoperative tumour stage was ypT0N0. Histological response assessment was a complete response (TRG 1).

Correlation of PET/MRI parameters with tumour response

Table 3 shows the AUC for PET and MRI parameters for the prediction of pathological response. The correlation of these parameters with TRG 3/4/5 (reference) versus 1/2 is presented in Supplementary Table S1. When predicting good responders, the AUC values for percent maximum thickness reduction and percent ADC change were 0.82 and 0.73, respectively. The AUC values for all other parameters were less than 0.6. A maximum thickness cut-off of $\geq 47\%$ and a percent ADC change of $\geq 20\%$ yielded a sensitivity and specificity of 75%/95% and 75%/73%, respectively.

DISCUSSION

PET/CT has conventionally been used for the staging and assessment of treatment response for rectal cancer patients treated with CRT.^{6,7} However, the limited soft tissue contrast and lower anatomic detail afforded by the CT component render it less useful for providing accurate local staging information in rectal cancer. Similarly, the use of MRI for restaging post-CRT is also not ideal as changes in tumour or lymph node size on MRI have not been shown to correlate with tumour response.^{5,8}

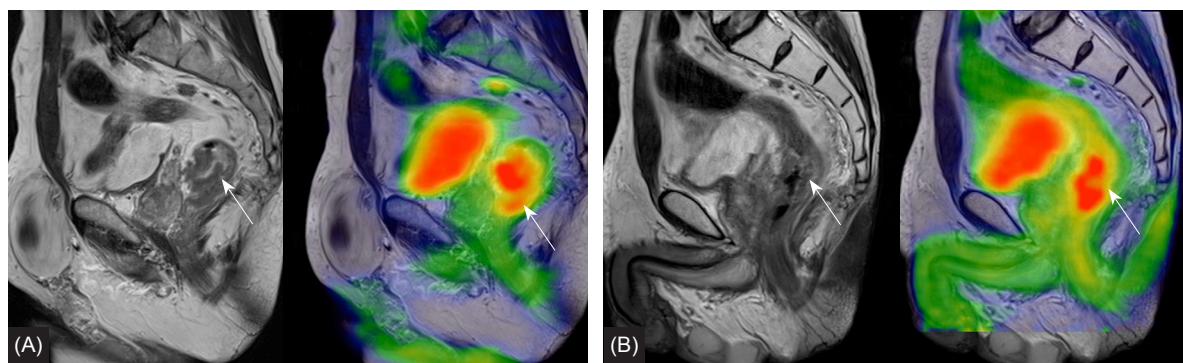


Fig. 2. Poor response to preoperative chemoradiotherapy (CRT). (A) Preoperative positron emission tomography/magnetic resonance imaging (PET/MRI). (B) Post-CRT PET/MRI. Arrows indicate the rectal tumour.

Table 3. AUC values for PET/MRI parameters with TRG 3/4/5 (ref) vs. 1/2.

	AUC
Volume reduction	0.31
SUV reduction	0.50
SUV volume reduction	0.38
Glycolysis reduction	0.44
Maximum thickness reduction	0.82
ADC change	0.73

ADC: apparent diffusion coefficient; PET/MRI: positron emission tomography/magnetic resonance imaging; SUV: standard uptake volume; TRG: tumour regression grade

In addition, the interpretation of MRI in the post-CRT setting can be more challenging due to difficulties in discriminating residual tumour from areas of radiation-induced fibrosis. A meta-analysis performed to evaluate MRI accuracy in the post-CRT setting revealed a mean overall sensitivity of only 40.3% for tumour response.^{9,10} The hybrid PET/MRI approach potentially overcomes the aforementioned limitations seen in MRI and PET/CT. It also offers the added advantage of reducing ionising radiation exposure to patients.

Several studies have attempted to elucidate the utility of PET/MRI in the staging of rectal cancer patients.⁵ In terms of local staging, PET/MRI has been shown in some reports to be superior to MRI alone and comparable to PET/CT.^{11,12} Although the use of PET/MRI also confers an advantage in characterising distant metastasis to abdominal solid organs, such as the liver, it is known to be a poorer modality in identifying pulmonary lesions than CT.^{8,11,13,14} Specific to restaging after CRT, Crimi et al. investigated the role of PET/MRI in 22 patients with locally advanced mid/low rectal cancer treated with preoperative CRT by correlating ADC maps, FDG images and histogram analysis

with pathological response.⁵ They found a significant correlation between the post-treatment SUV mean values and tumour regression grading. However, the interpretation of the results was limited by the relatively small sample size.

The advent of total neoadjuvant therapy for patients with locally advanced rectal cancer has led to improved pathological responses.^{15,16} Patients who achieve a complete clinical response to preoperative chemotherapy and radiotherapy may be suitable candidates for the watch and wait approach, thereby allowing for organ preservation through the omission of surgery.¹⁷ As one of the first few studies evaluating the role of PET/MRI in rectal cancer restaging, the current study demonstrates that hybrid PET/MRI data acquisition provides complementary information, which allows for more accurate evaluation of residual disease post-CRT, as shown in Figs. 2 and 3. In such cases, the combination of morphological, functional and metabolic data using PET/MRI is particularly important to enhance differentiation between viable tumour tissue that has been replaced by fibrosis. This is further demonstrated in various studies that have reported alterations made to patient treatment strategies after the analysis of PET/MRI findings.^{5,11,14}

Nonetheless, only MRI parameters, such as ADC change and maximum thickness reduction, predicted for good tumour response to preoperative CRT in the current study. Using a percent maximum thickness reduction cut-off of $\geq 47\%$ and a percent ADC change of $\geq 20\%$, there was a sensitivity and specificity of 75%/95% and 75%/73%, respectively. Other parameters, such as percent volume reduction, percent SUV reduction, percent SUV volume reduction, percent glycolysis reduction, PTx volume, PTx SUV max, PTx SUV volume, PTx glycolysis, PTx maximum thickness and PTx ADC values, were not useful in predicting tumour responses to preoperative CRT. These findings can be explained by the presence of mucinous rectal

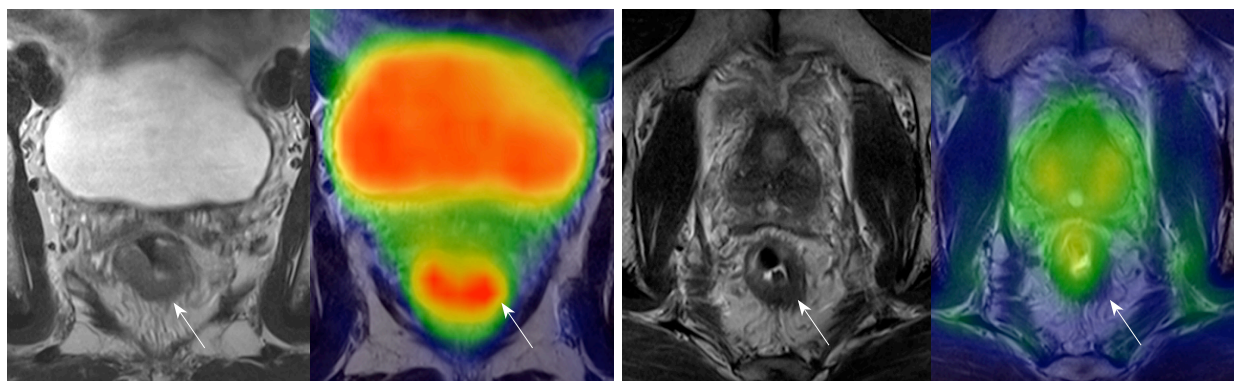


Fig 3. Good response to preoperative chemoradiotherapy (CRT). (A) Preoperative positron emission tomography/magnetic resonance imaging (PET/MRI). (B) Post-CRT PET/MRI. Arrows indicate the rectal tumour.

lesions, which can limit the role of PET/MRI due to their low FDG activity. Future studies evaluating the role of PET/MRI in rectal cancer staging should also aim to specifically evaluate its utility in rectal cancers with a mucinous component.

Although limited by the small sample size, this study is one of the first few works evaluating the role of PET/MRI in rectal cancer restaging after CRT. It is also conducted in a prospective manner with clearly defined and standardised protocols for MRI and PET acquisition. Notably, 11 of the 31 patients did not complete the study protocol, and this was likely due to the long acquisition time required for PET/MRI. Future studies should also evaluate the length of the acquisition time and the impact it has on patients undergoing PET/MRI, including the cost effectiveness of PET/MRI in rectal cancer staging.

CONCLUSION

Parameters such as percent maximum thickness reduction and percent ADC change may be useful for predicting good responders in patients undergoing preoperative CRT for rectal cancer. Larger studies are warranted to establish the utility of PET/MRI in rectal cancer staging.

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