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FDG-PET/MRI in patients with pelvic recurrence of rectal cancer: first clinical experiences

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Abstract

Objectives To determine the value of ^{18}F-FDG-PET/MRI in the diagnosis and management of patients with pelvic recurrence of rectal cancer.

Methods Forty-four patients (16 women, 28 men) with a history of rectal cancer who received FDG-PET/MRI between June 2011 and February 2017 at our institution were retrospectively enrolled. Three patients received two FDG-PET/MRIs; thus a total of 47 examinations were included. Pelvic recurrence was confirmed either with histology ($n = 27$) or imaging follow-up ($n = 17$) (> 4 months). Two readers (one radiologist, one nuclear medicine physician) interpreted the images in consensus. Pelvic lesions were assessed regarding FDG uptake and morphology. Sensitivity, specificity, positive and negative predictive values as well as accuracy of PET/MRI in detecting recurrence were determined.

Results In 47 FDG-PET/MRIs 30 suspicious pelvic lesions were identified, 29 of which were malignant. Two patients underwent resection and had histologically proven pelvic recurrence without showing suspicious findings on FDG-PET/MRI. Changes in management due to FDG-PET/MRI findings had been implemented in eight patients. Eighty per cent (16/20) of resected patients had histologically negative resection margins (R0), one patient had uncertain resection margins. Sensitivity of FDG-PET/MRI in detecting recurrence was 94%, specificity 94%, positive/negative predictive value and accuracy were 97%, 90% and 94%, respectively.

Conclusions FDG-PET/MRI is a valuable tool in the diagnosis and staging of pelvic recurrence in patients with rectal cancer.

Key Points

- *Metabolic information obtained from PET coupled with excellent soft tissue contrast from MRI could facilitate detection of rectal cancer recurrence and assist in treatment planning.*
- *PET/MRI demonstrates high sensitivity and specificity for the diagnosis of local recurrence of rectal cancer*
- *PET/MRI led to alterations in management in 18.2% of patients.*

Keywords Positron-emission tomography · Magnetic resonance imaging · Rectal cancer · Neoplasm · Recurrence, local

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Introduction

Colorectal cancer is the third most common cancer worldwide with an estimated 1.2 million new cases per year, ultimately responsible for 8% of all cancer deaths [1]. The majority of patients present with localised disease which is amenable to surgical resection. However, up to 40% of patients with rectal cancer develop local or distant recurrence, with the risk of local recurrence between 4% and 10% [2–4]. Complete resection of local recurrence, which has been demonstrated to improve survival rates [5–9], is the only curative treatment. As a result of the potential extent of surgery and its associated morbidity [10–12], adequate selection of patients for surgery is based, to great extent, on preoperative imaging, which can be challenging because of previous surgery and radiation therapy. Some patients also develop anastomotic leaks or chronic fistulas, rendering the diagnosis of local recurrence difficult because of extensive post-inflammatory/therapeutic changes and scarring in the pelvic region [2, 13–16].

Whereas for the primary staging of rectal cancer there are specific guidelines and recommendations and MRI is well established in this setting [17], different imaging modalities have been used in the follow-up of rectal cancer, including CT, MRI and ^{18}F-FDG-PET/CT. Since there is frequently extensive scarring and reactive changes after radiotherapy and resection, the diagnosis of local recurrence can be challenging. CT is the most commonly used modality in this setting, with sensitivity for diagnosing pelvic recurrence around 80% and specificity ranging from 50% to 97% [3]. MRI provides superior soft tissue contrast compared to CT, thus facilitating the distinction of presacral scarring from recurrent tumour. In a study by Titu et al., the sensitivity, specificity, positive and negative predictive value of MRI in the detection of local recurrence were 87%, 86%, 48% and 98%, respectively [18]. Several studies have investigated the use of FDG-PET for the detection of local recurrence in rectal cancer, with accuracy ranging from 74% to 96% [3]. In a retrospective study Moore et al. found a sensitivity of 84%, specificity of 88%, overall accuracy of 87%, PPV of 76% and NPV of 92% for FDG-PET in the diagnosis of pelvic recurrence [19]. FDG-PET/CT was shown to help differentiate benign from malignant presacral lesions with a sensitivity of 100% and a specificity of 96% [2].

PET/CT has been demonstrated to improve sensitivity and specificity in the diagnosis of local recurrence [2, 3], but soft tissue contrast is inferior to PET/MRI. When planning surgical resection, exact knowledge regarding the invasion of adjacent structures such as piriform muscles, sacral bone or lumbosacral nerves is vital and should therefore be determined accurately. PET/MRI as a hybrid imaging technique provides functional imaging with good sensitivity and specificity in detecting recurrence and has the added benefit of excellent soft tissue contrast, which helps in determining the local extent of recurrence.

Thus, the aim of our study was to assess the value of FDG-PET/MRI in the diagnosis and management of patients with pelvic recurrence of rectal cancer.

Material and methods

Patients

The study was approved by the local ethics committee. All patients had given written informed consent to PET/MRI as well as retrospective review of their records, files and imaging studies.

Imaging and clinical data of 72 patients (29 women, 43 men) with a history of rectal cancer who received PET/MRI at our institution between June 2011 and February 2017 were retrospectively reviewed. Twenty-eight patients were excluded because they were lost to follow-up. The remaining 44 patients were included in the study (for patient characteristics, see Table 1). Three patients received two PET/MRIs; thus a total of 47 examinations were included. To avoid bias, repeat PET/MRIs of the same patient were only included if there was either follow-up using a different imaging modality or separate histology for each PET/MRI available. Indications for PET/MRI are summarised in Table 2.

FDG-PET/MRI imaging

Patients underwent routine preparation for FDG-PET/MRI at our institution. They were instructed to fast for at least 6 h prior to FDG injection and asked to empty the urinary bladder before the examination. Blood glucose levels were taken prior to FDG injection and ranged from 4.8 to 11.6 mmol/l.

4.5 MBq ^{18}F-FDG/kg body weight was administered intravenously (241–350 MBq, mean 308 MBq; GlucoRos®, Helmholtz-Zentrum Dresden Rossendorf, Germany). PET/MRI was performed using a 3-T PET/MRI scanner (Ingenuity Time-of-Flight PET/MRI scanner; Philips Medical Systems). The PET component features time-of-flight technology, an axial field of view of 18 cm, 9 cm overlap between bed positions and a reconstructed isotropic spatial resolution of about 5.5 mm. Patients were examined in supine position, arms positioned by the sides. PET/MRI comprised a low-resolution attenuation MRI scan (T1-weighted fast field echo, head to distal femur, integrated quadrature body coil). An MR-based attenuation map for attenuation correction is created via segmentation of the MR image volume into three tissue classes (air, lung, soft tissue), followed by an assignment of respective attenuation values [20]. PET was performed immediately after the attenuation scan. To achieve optimal co-registration of PET and MRI data, the patient's position remained unchanged during the examination. The average time between ^{18}F-FDG injection and PET/MRI was

Table 1 Patient characteristics

Age	33-80 years (mean 60 years)
Gender	
Male	28
Female	16
Primary tumour stage	
Stage I	9
Stage IIa	9
Stage IIb	1
Stage IIIa	6
Stage IIIb	13
Stage IIIc	3
Stage IV	2
Unknown	1
Primary tumour histology	
Adenocarcinoma	29
Mucinous adenocarcinoma	2
Squamoid cell carcinoma	1
Unknown	12
Previous therapy	
Abdominoperineal resection	20
Neoadjuvant radiochemotherapy	9
Neoadjuvant radiotherapy	2
Neoadjuvant chemotherapy	2
No neoadjuvant therapy	6
Unknown	1
Anterior resection	19
Neoadjuvant chemoradiation	7
Neoadjuvant radiotherapy	1
No neoadjuvant therapy	11
Restorative coloproctectomy	1
Full thickness local excision	1
Sigmoid resection	1
Curative chemoradiation	2

80 min (60–181 min). If excreted tracer in the urinary bladder was thought to disguise local recurrence, a second PET scan covering the urinary bladder was performed after voiding. Depending on the indication for PET/MRI further MR sequences were performed. Thirty-seven of 47 examinations included diagnostic axial T2-weighted sequences of the pelvis (Sense-XL-Torso coil, axial T2-weighted turbo spin echo sequence). Fused PET/MRI images including multiplanar reconstructions were created using the Philips Fusion Viewer software.

Table 2 Indications for PET/MRI[a]

Suspicious findings on previous imaging	36
Treatment monitoring and follow-up	8
Elevated serum carcinoembryonic antigen (CEA) levels	1
Suspicious clinical findings	2

[a] Note: Of 44 patients, three had two PET/MRIs each

Image interpretation

PET/MRI images were reviewed at a PACS workstation (MDCC-4130, Barco GmbH). Two readers (one radiologist, one nuclear medicine physician), each with more than 5 years of experience in hybrid imaging, jointly reviewed all cases for pelvic recurrence, metastases and other relevant findings (consensus reading). Each PET/MRI finding was scored 0 or 1 (0 = no recurrence/metastases, 1 = suggestive of recurrence/metastases). The readers were blinded to medical history, prior imaging and referral diagnoses. Patients' names were removed to avoid bias when reviewing repeat imaging.

Sites of FDG uptake were reviewed taking into account shape, location and intensity. Since no threshold standardised uptake value (SUV) has been established in this setting or in other malignancies, diagnosis of possible malignancy was based on visual assessment, regarding increased uptake compared to liver background as suspicious [21]. Typical uptake in the urinary tract or along bowel loops was considered physiological. Low FDG uptake (defined as lower than liver background) in anatomical structures like ovaries or rectal stump and areas after recent radiation or surgery (up to 12 months) was considered benign [2, 22]. MR images were assessed regarding soft tissue masses, considering morphology on T2-weighted sequences. Nodular or irregularly shaped soft tissue masses with inhomogeneous structure and with a signal equivalent or higher compared to muscle were considered suggestive of malignancy. Infiltration of adjacent organs was also considered a malignant feature. Lesions on PET were considered fluid retentions when they showed photopenic areas without any FDG uptake and just slight uptake in the margins of the lesion. Less FDG uptake without focal character compared to background and overall context of the tracer distribution was also considered to be due to inflammation. If this corresponded to the MRI findings, an inflammatory lesion was diagnosed. Lesions were considered malignant if they showed intense focal FDG uptake as well as suspicious MR findings as described.

Data analysis

Patient files were reviewed to determine clinical and imaging follow-up as well as histology of suspicious lesions. Follow-up ranged between 4 and 60 months (mean 21 months) and included CT and MRI as well as clinical findings. The mean time between PET/MRI and surgical resection was 8 weeks.

PET/MRI was considered true negative if no tumour recurrence was found at histopathology or if the lesion remained unchanged or reduced in size without treatment on follow-up. PET/MRI was considered true positive if a suspicious lesion was either confirmed on histopathology or showed progression on follow-up or improvement under treatment.

Statistical analysis

The sensitivity, specificity, PPV, NPV and accuracy of PET/MRI in diagnosing pelvic recurrence was determined using lesion-based analyses and a 2 × 2 table (SPSS package for Windows, SPSS Statistics 23, IBM, https://www.medcalc.org/calc/diagnostic_test.php).

Results

In 47 PET/MRIs 30 suspicious pelvic lesions were identified. Twenty-seven lesions were found in the presacral region, one in the penile root, one in a sacral nerve root and one at the pelvic wall. Average SUV of suspicious lesions was 10.5 (range 3.8–26.0). Lesion sizes ranged from 1.0 to 13.3 cm (average 5.2 cm). These 30 suspicious lesions were found on 28 PET/MRIs, since two PET/MRIs showed two suspicious lesions each. Twenty-nine of the 30 lesions were proven to be recurrence (surgery = 22, biopsy = 7). The remaining suspicious lesion was small (12 × 8 mm) and located at the rectal stump. It was treated with neoadjuvant chemotherapy followed by surgery 5 weeks after PET/MRI without repeat imaging. At histopathology, no residual tumour was found. This case was regarded as false positive.

The remaining 19 PET/MRIs showed no suspicious findings. Of these, 17 showed no signs of recurrence on imaging and clinical follow-up. Two patients underwent resection and had proven recurrence on histopathology without showing suspicious findings on PET/MRI. Of the two surgical patients with false negative imaging findings, one patient had a metastasis adherent to the ileum, which was interpreted as physiological bowel activity on PET and not detected on MRI. The patient had received neoadjuvant radiochemotherapy until 4 months prior to PET/MRI, and surgical resection was performed 5 weeks after PET/MRI. Histology showed mucinous adenocarcinoma. The second patient had received neoadjuvant chemotherapy for local recurrence until 1 week prior to PET/MRI, and surgical resection was performed 5 weeks after PET/MRI. In this case, metabolic activity of the residual tumour was indistinguishable from background (PET) and no lesion was detectable on MRI.

Sensitivity of FDG-PET/MRI in detecting recurrence was 94%, specificity 94%, positive predictive value 97%, negative predictive value 90% and accuracy was 94% (Table 3).

Table 3 Detection of pelvic recurrence using PET/MRI (lesion-based analysis)

	PET/MRI	
	positive[a]	negative[b]
Histology/Follow-up		
Positive	29	2
Negative	1	17

[a] Note: 30 lesions detected on 28 PET/MRIs

[b] Note: 19 PET/MRIs without suspicious lesions

Clinical relevance

Changes in management due to PET/MRI, based on the primary PET/MRI report in keeping with the results of our evaluation, were implemented in eight patients (Table 4). Five patients with histologically proven recurrence had previous imaging without malignant findings or equivocal findings. One patient demonstrated bone metastases on FDG-PET/MRI not visible on a CT scan 1 month prior to hybrid imaging, and resection of the local recurrence was therefore not deemed feasible. In another patient FDG-PET/MRI showed a previously unknown metastasis of the penile root (Fig. 1). The eighth patient demonstrated an also previously unknown metastasis of a sacral nerve (Fig. 2). All patients with suspicious findings were discussed in a multidisciplinary meeting. Ultimately, 80% (16/20) of resected patients had histologically negative resection margins (R0), and one patient was deemed as having uncertain resection margins.

Discussion

Our study demonstrates that PET/MRI shows promising accuracy in the diagnosis of local recurrence of rectal cancer, with a sensitivity and specificity of 94% in this setting. Of the two false negative cases in our study, both applied to patients

Table 4 Patients with changes in management after PET/MRI

	Finding	Previous imaging
Patient 1	Bone metastases	CT
Patient 2	Metastasis penile root	CT
Patient 3	Metastasis sacral nerve root	CT
Patient 4	Local recurrence	CT
Patient 5	Local recurrence	CT
Patient 6	Local recurrence	CT
Patient 7	Local recurrence	CT
Patient 8	Local recurrence	CT

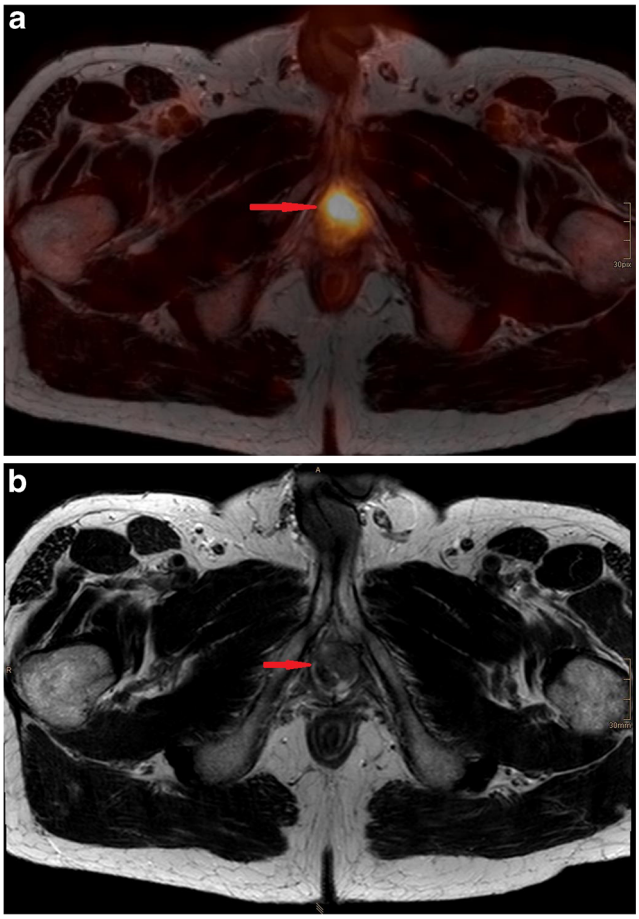

Fig. 1 **a** Axial PET/MRI fusion image demonstrating a lesion with intense FDG uptake in the penile root. **b** Axial T2-weighted MRI image demonstrating an inhomogeneous lesion in the penile root

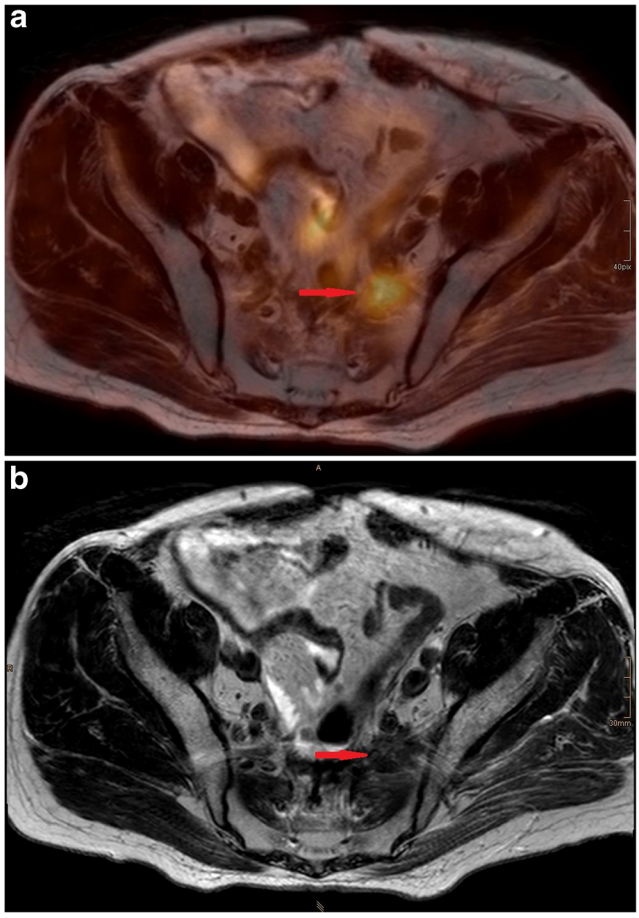

Fig. 2 **a** Axial PET/MRI fusion image demonstrating a lesion with FDG uptake in the course of a sacral nerve. **b** Axial T2-weighted image showing diffuse hypointense changes in the left presacral region

who had received neoadjuvant chemotherapy prior to PET/MRI. As reported in the literature, FDG-PET can demonstrate false negative results after chemotherapy [19]. In the first case, the preoperative PET/MRI after chemotherapy showed no suspicious FDG uptake in the tumour region. MRI demonstrated diffuse hypointense changes on T2, with no soft tissue masses or contrast enhancement, leading to a diagnosis of avital residual tumour. The second patient had mucinous adenocarcinoma adherent to bowel loops on histology. PET imaging has been shown to be of limited value in the diagnosis of mucinous adenocarcinoma [23]. Another explanation for the false negative result could be the misinterpretation of FDG uptake as physiological uptake in the bowel wall. One patient was classified as false positive, according to the gold standard. PET/MRI in this case demonstrated a small area of increased FDG uptake at the rectal stump; MRI, however, showed only a very small correlating soft tissue lesion. As a result of the increased FDG uptake, the lesion was diagnosed as recurrence. After chemotherapy, no residual tumour tissue was found at histopathology 5 weeks later. The false positive result in this case could be due to inflammatory changes of the rectal stump, since histopathology showed signs of proctitis after prior radiation. Another possible explanation could be complete response after chemotherapy. Further studies with larger patient numbers are necessary to determine the effect of (radio)chemotherapy on the accuracy of PET/MRI in this setting.

Various studies have postulated the usefulness of PET and PET/CT in the detection and staging of recurrent rectal cancer, with MRI including diffusion-weighted imaging proving to be useful in the detection of local tumour regrowth after organ-preserving treatment [2, 19, 24–30]. A study by Ito et al. suggested a complementary role of PET and MRI in differentiating recurrent rectal cancer from scar tissue [31]. However, hybrid imaging with FDG-PET/MRI has not been widely used in this clinical setting.

There are several limitations to our study. Firstly, the number of patients included is relatively low and data was analysed retrospectively. Consequently, the results of our study have to be confirmed in a larger cohort of patients. Secondly, the enrolled patients had a high risk of recurrence due to prior clinical and imaging findings creating a

preselection bias. This issue, however, is difficult to tackle in a clinical setting as referrals for the limited resources of PET/MRI are confined to patients with a high level of suspicion of recurrence. Thirdly, images were read in consensus and by only two readers. To calculate parameters such as interobserver variability three to five independent readers should be involved. Regarding changes in management based on PET/MRI results, another limitation is that prior imaging was inconsistent and included CT as well as MRI and multiple scans performed at other institutions using a variety of protocols. Finally, not all patients received diagnostic MRI sequences as part of PET/MRI, rendering the patient cohort somewhat inhomogeneous. On the basis of our first experience, the protocol was changed in that diagnostic MRI became an integral part of PET/MRI.

In conclusion, our study suggests that FDG-PET/MRI is a valuable diagnostic tool in selected patients with pelvic recurrence of rectal cancer, particularly in the preoperative setting, aiding in assessing the feasibility and adequately planning the extent of surgical resection. Prospective studies are necessary to compare the performance of PET/MRI in comparison to established methods, especially MRI and PET/CT.

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained from all subjects (patients) in this study.

Ethical approval Institutional review board approval was obtained.

Study subjects or cohorts overlap Some study subjects or cohorts have been previously reported at the RSNA 2017.

Methodology
- retrospective
- diagnostic or prognostic study
- performed at one institution

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