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^{18}F-FDG PET/MRI for restaging esophageal cancer after neoadjuvant chemoradiotherapy

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Purpose **The purpose of this study was to investigate whether 18F-fluorodeoxyglucose (^{18}F-FDG) PET/MRI may potentially improve tumor detection after neoadjuvant chemoradiotherapy (nCRT) for esophageal cancer.**

Methods **This was a prospective, single-center feasibility study. At 6–12 weeks after nCRT, patients underwent standard ^{18}F-FDG PET/computed tomography (CT) followed by PET/MRI, and completed a questionnaire to evaluate burden. Two teams of readers either assessed the ^{18}F-FDG PET/CT or the ^{18}F-FDG PET/MRI first; the other scan was assessed 1 month later. Maximum standardized uptake value corrected for lean body mass (SUL_{max}) and mean apparent diffusion coefficient (ADC_{mean}) were measured at the primary tumor location. Histopathology of the surgical resection specimen served as the reference standard for diagnostic accuracy calculations. When patients had a clinically complete response and continued active surveillance, response evaluations until 9 months after nCRT served as a proxy for ypT and ypN (i.e. 'ycT' and 'ycN').**

Results **In the 21 included patients [median age 70 (IQR 62–75), 16 males], disease recurrence was found in the primary tumor in 14 (67%) patients (of whom one ypM+, detected on both scans) and in locoregional lymph nodes in six patients (29%). Accuracy (team 1/team 2) to detect yp/ycT+ with ^{18}F-FDG PET/MRI vs. ^{18}F-FDG PET/CT was 38/57% vs. 76/61%. For ypN+, accuracy was 63/53% vs. 63/42%, resp. Neither SUL_{max} (both scans) nor ADC_{mean} were discriminatory for yp/ycT+ . Fourteen of 21 (67%) patients were willing to undergo a similar ^{18}F-FDG PET/MRI examination in the future.**

Conclusion **^{18}F-FDG PET/MRI currently performs comparably to ^{18}F-FDG PET/CT. Improvements in the scanning protocol, increasing reader experience and performing serial scans might contribute to enhancing the accuracy of tumor detection after nCRT using ^{18}F-FDG PET/MRI.**

Trial registration **Netherlands Trial Register NL9352.**

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Introduction

Neoadjuvant chemoradiotherapy (nCRT) followed by esophagectomy is a standard treatment for locally advanced esophageal cancer. After nCRT, one-third of patients have a pathologically complete response, opening the way for active surveillance [1]. The safety and efficacy of active surveillance are currently investigated in two clinical trials [2,3]. Patients in active surveillance undergo clinical response evaluations (CREs) [2]. Surgery is performed only when locoregional residual disease is detected in the absence of distant metastases.

18F-fluorodeoxyglucose (^{18}F-FDG) PET/computed tomography (CT) has been shown to detect distant metastases before esophagectomy in approximately 10% of patients [4]. Within CREs during active surveillance, ^{18}F-FDG PET/CT also guides the detection of suspected lymph nodes using endoscopic ultrasound with targeted fine-needle aspiration. For the detection of local residual tumors in the esophagus, however, ^{18}F-FDG PET/CT has been shown inaccurate [4]. A high rate of false

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positives was observed because ^{18}F-FDG cannot reliably discriminate residual tumors from postradiotherapy esophagitis.

MRI is hypothesized to enhance primary tumor detection after nCRT. This is primarily due to higher soft tissue contrast compared to CT and also to the potential to differentiate postradiation inflammation from tumor using the apparent diffusion coefficient (ADC) on diffusion-weighted imaging (DWI) [5,6]. Integrated PET/MRI is a relatively new imaging technique that has the advantage of perfect alignment of PET and MR images. Earlier studies have shown no significant difference between ^{18}F-FDG PET/MRI and ^{18}F-FDG PET/CT in the pretreatment staging of esophageal cancer [7–9]. The feasibility of ^{18}F-FDG PET/MRI after nCRT has not yet been studied. We hypothesize that in the setting after nCRT, ^{18}F-FDG PET/MRI might be helpful to distinguish residual tumor from inflammation as well as to detect and characterize new (small) metastatic lesions [8]. In the current study, the aim was to evaluate whether ^{18}F-FDG PET/MRI is feasible to detect residual tumor after nCRT.

Materials and methods

Study design

This was a single-center, prospective observational feasibility study. The study was registered on the International Clinical Trials Registry Platform (NL9352) and approved by the Medical Ethical Committee of the Erasmus MC (MEC-2020-0784). All patients provided written informed consent.

Patients

Eligible patients were diagnosed with an adenocarcinoma or squamous cell carcinoma of the esophagus or esophagogastric junction, located at or below the carina. This region was chosen to obtain a homogenous cohort for which the scanning protocol was optimized. All patients underwent five weekly cycles of carboplatin/paclitaxel with concurrent 41.1 Gy of radiotherapy [1]. Patients were consecutively identified between February 2021 and May 2022 from the Surgery As Needed for Oesophageal Cancer (SANO)-2 study, an extension study of the SANO trial [10]. Exclusion criteria were contra-indications for MRI and an ^{18}F-FDG nonavid tumor at diagnosis.

Active surveillance

As part of the SANO-2 study, patients underwent the first CRE-1 at 4–6 weeks after nCRT [2]. When a residual tumor was detected or highly suspected using endoscopy with bite-on-bite biopsies, patients underwent ^{18}F-FDG PET/CT to exclude distant metastases. If residual tumor was not identified at CRE-1, CRE-2 was scheduled after 4–6 weeks. CRE-2 included ^{18}F-FDG PET/CT, endoscopy with bite-on-bite biopsies, and endoscopic ultrasound with fine-needle aspiration. In patients with clinically complete response, subsequent CREs were scheduled every 3 months in the first year, with intervals becoming longer until 5 years after nCRT [2].

Study procedures

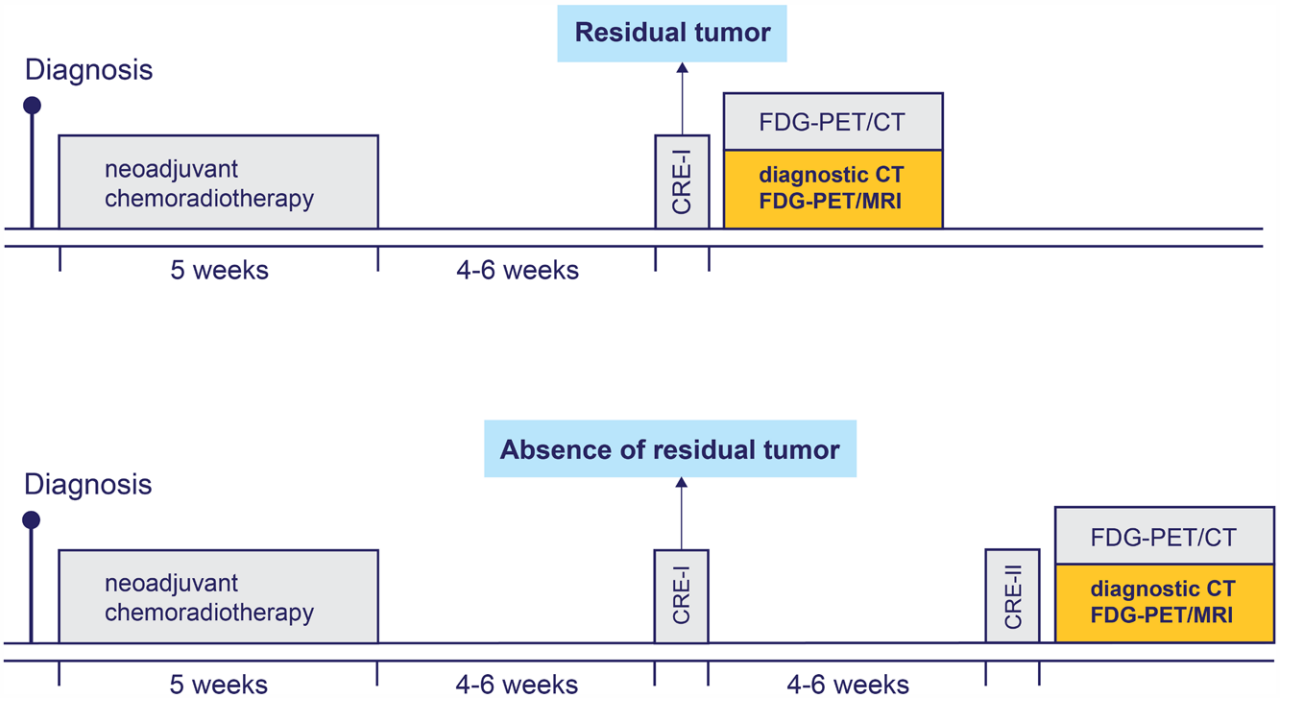
The ^{18}F-FDG PET/CT at CRE-1/-2 was complemented with a contrast-enhanced CT scan (to have the highest-quality ^{18}F-FDG PET/CT available for study assessments) and a PET/MRI acquisition (Fig. 1). Before PET/MRI was performed, patients had a short break to eat and drink. During this break and directly after the ^{18}F-FDG PET/MRI, patients completed a self-constructed questionnaire to evaluate the burden of undergoing these scans, based on a similar study in esophageal cancer patients [11].

Scanning protocols

Patients underwent a whole-body PET/low dose CT scan 60 ± 5 min after injection of ^{18}F-FDG [median 2.7 MBq/kg; interquartile range (IQR) 2.2–2.9 MBq/kg], according to the guidelines of the European Association of Nuclear Medicine v.2.0 [12], as implemented in the institutional protocols. Scans were performed on a 40- or 128-slice Siemens BioGraph PET/CT system (Siemens Medical Systems, Erlangen, Germany). After PET/low dose CT acquisition at 3 min/bed, a contrast-enhanced CT of the neck, chest and abdomen was acquired on the same scanner without repositioning the patient, according to standard clinical protocol.

Directly following the ^{18}F-FDG PET/CT scan, a non-enhanced PET/MRI was performed on an integrated 3.0 Tesla PET/MRI whole-body system (Signa PET/MR, GE Healthcare, Waukesha, Wisconsin, USA). MRI sequences were acquired simultaneously with the PET bed positions and comprised sequences for whole-body, dedicated esophagus and dedicated liver imaging. Full protocol details are listed in Supplementary Table 1, Supplemental digital content 1, *http://links.lww.com/NMC/A270*. Briefly, the whole-body MRI sequences comprised axial T1-weighted (T1w) liver acquisition with volume acceleration Flex, axial T2w fast recovery fast spin echo Flex, and axial DWI single-shot echo planar imaging (b-values: 50, 800 s/mm^2) sequence. For the primary tumor location, additionally, an axial T2w periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER) and an axial field-of-view optimized and constrained undistorted single-shot (FOCUS) DWI (b-values: 50, 200, 800 s/mm^2) sequences were obtained. For each of the 6–7 bed positions, a default zero echo time- (head-only) and Dixon-based sequence was performed to calculate attenuation correction maps for PET image reconstruction. ADC maps were calculated on the scanner console using the acquired b-values and a mono-exponential fit.

Fig. 1



Time points at which the study scans (listed in the yellow box) were performed. When patients had residual tumor as detected with bite-on-bite biopsies during CRE-1, then the standard ^{18}F-FDG PET/CT was combined with a diagnostic CT and ^{18}F-FDG PET/MRI. When patients had absence of residual tumor at this time point, CRE-2 was scheduled 4–6 weeks later. At this time point, the first ^{18}F-FDG PET/CT with diagnostic CT and ^{18}F-FDG PET/MRI was performed, followed by endoscopy with bite-on-bite biopsies, and endoscopic ultrasound with fine-needle aspiration of suspected lymph nodes. CRE, clinical response evaluations.

Study endpoints

The following criteria were defined to determine the feasibility of ^{18}F-FDG PET/MRI in the restaging of esophageal cancer after nCRT:

1. the concordance between ^{18}F-FDG PET/MRI and the reference standard (see below);
2. the possibility to perform quantitative measurements, including the interobserver variability and the concordance with the reference standard;
3. the burden for the patient of undergoing ^{18}F-FDG PET/MRI.

Reference standard

Histology of the resection specimen served as the reference standard in patients who underwent surgery. Resection specimens were assessed using the tumor regression grade (TRG): TRG 1, 0% residual tumor cells; TRG 2, 1–10%; TRG 3, 11–50%; TRG 4 > 50% [13]. In patients without surgery, subsequent CREs during active surveillance until 9 months after nCRT served as a proxy for ypT and ypN. For example, when patients had a persistent clinically complete response until 9 months after nCRT, the reference standard at the time of scanning was considered 'ycT0N0' (i.e. postneoadjuvant clinical staging) [14]. The cutoff of 9 month was chosen since we expected that in patients with a residual tumor at the time of the study scan, while undetected at that moment, this would become apparent after two subsequent CREs (i.e. timed at 6 and 9 months after nCRT).

Sample size

A formal sample size calculation was not performed because this was a feasibility study. A sample of at least 20 patients was considered sufficient for an indication of parameters for diagnostic accuracy.

Qualitative assessments

Two teams of readers assessed the scans qualitatively and quantitatively using VUE Carestream (Carestream Health, Rochester, New York, USA). Each team included two members: one radiologist with expertise in MRI and one nuclear medicine physician with expertise in PET (all with >10 years of experience). A random sequence was generated to determine whether the ^{18}F-FDG PET/CT or the ^{18}F-FDG PET/MRI was assessed first. The other scan was assessed 1 month later, to prevent recall bias as much as possible. The evaluation of pretreatment imaging was allowed during scoring, but readers were blinded from all other clinical and outcome data. Qualitative assessments were performed using European Association of Nuclear

Medicine Research Ltd (EARL)-1 reconstruction of the PET/CT and the Q. Clear 300 or 150 of the PET/MRI.

First, team members independently assessed the scans, allowing them to study the scans before the subsequent consensus meeting per team. Independent assessments included confidence scores (CS) for the presence of residual tumor, tumor-involved lymph nodes and distant metastases [4,6]: 1 = benign; 2 = probably benign; 3 = equivocal; 4 = probably malignant; 5 = malignant. During team consensus, the two members assessed the scan together. They reconsidered and discussed their independent scores to generate an integrated conclusion regarding the presence of residual tumor in the esophagus, lymph nodes, and distant metastases: 'benign' (CS1–2); 'equivocal' (CS3); 'malignant' (CS4–5). Furthermore, the quality of the CT of the ^{18}F-FDG PET/CT and MRI of the ^{18}F-FDG PET/MRI was scored per team as either 'good', 'artifacts, but sufficient', or 'poor'.

Quantitative measurements

EARL-1 PET reconstructions were used for both scans to measure the maximum standardized uptake value corrected for lean body mass (SUL_{max}) at the primary tumor bed [4]. During team consensus meetings, the mean apparent diffusion coefficient (ADC_{mean}) was measured on the ADC map corresponding to the DWI FOCUS $b = 800\,s/mm^2$. An oval or free-form shape was delineated in the axial plane, covering at least all hyperintense parts. In the absence of such a signal, an area representative of the primary tumor location was delineated, using the pretreatment ^{18}F-FDG PET/CT scan for reference.

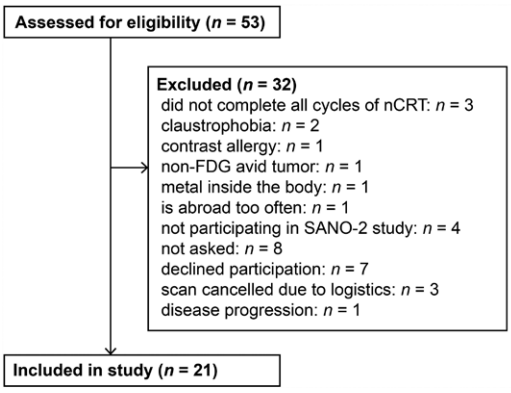
Statistical analysis

Per team, the integrated scores were dichotomized as 'benign' (CS 1–2) vs. 'malignant' (CS 3–5) [4]. Residual tumor in the esophagus was defined as yp/ycT+ (i.e. TRG 2-3-4 or highly suspected or proven during CREs); a residual tumor in locoregional lymph nodes was defined as yp/ycN+ (i.e. ypN1-3 or highly suspected or proven during CREs). Sensitivity, specificity, positive predictive value, negative predictive value and accuracy were described with 95% confidence intervals.

Five-point Likert-scale items of the questionnaire were described with mean and SD, using the Wilcoxon signed-ranks test for pair-wise comparisons. Other items were described with numbers and percentages. The burden was predefined in the study protocol as acceptable when ≥60% of patients were neutral or willing to undergo another ^{18}F-FDG PET/MRI scan.

The interobserver agreement between teams for qualitative assessments was reported using the percentage exact

Fig. 2



Study flowchart.

Table 1 Patient and tumor characteristics

	n = 21
Age	70 (62–75)
Sex, male	16 (76.2)
Histology	
Adenocarcinoma	19 (90.5)
Squamous cell carcinoma	1 (4.8)
High-grade dysplasia	1 (4.8)
Pretreatment tumor differentiation	
Good-moderate	5 (61.9)
Poor	3 (14.3)
Unknown	5 (23.8)
cT	
cTis	1 (4.8)
cT2	4 (19.0)
cT3	13 (61.9)
cT4a	1 (4.8)
cTx	2 (9.5)
cN	
cN0	13 (61.9)
cN1	6 (28.6)
cN2	1 (4.8)
cN3	1 (4.8)
Resection	
Yes	13 (61.9)
No, refused surgery	1 (4.8)
No, distant metastasis	1 (4.8)
No, continued active surveillance	6 (28.6)
Weeks between end nCRT and detection of ypT+/ypN+/ypM+	26 (13–33)
Weeks between positive CRE and surgery[a]	4 (3–5)
Weeks between study scan and surgery[a]	17 (6–29)
ypT[a]	
ypT0	1 (8.0)
ypT1a-1b	4 (30.8)
ypT2	2 (15.3)
ypT3	6 (46.2)
TRG[a]	
TRG 1, ypN1	1 (8.0)
TRG 2	2 (15.3)
TRG 3	5 (38.5)
TRG 4	5 (38.5)
ypN[a]	
ypN0	7 (53.8)
ypN1	3 (23.0)
ypN2	3 (23.0)
R0[a]	13 (100)

Continuous data are median (interquartile range). Categorical data are numbers (percentages).
Staging was performed according to the AJCC cancer staging manual, 8th edition [14]
[a]Only for patients undergoing resection

agreement and Cohen's kappa: <0: no agreement; 0–0.20 slight; 0.21–0.40 fair; 0.41–0.60 moderate; 0.61–0.80 substantial and 0.81–1.0 almost perfect.

Quantitative measurements were compared using a Student's *t*-test for normally distributed data and otherwise a Mann–Whitney *U* test. Bland–Altman analysis was performed to compare measurements of the same patients on ^{18}F-FDG PET/CT vs. ^{18}F-FDG PET/MRI.

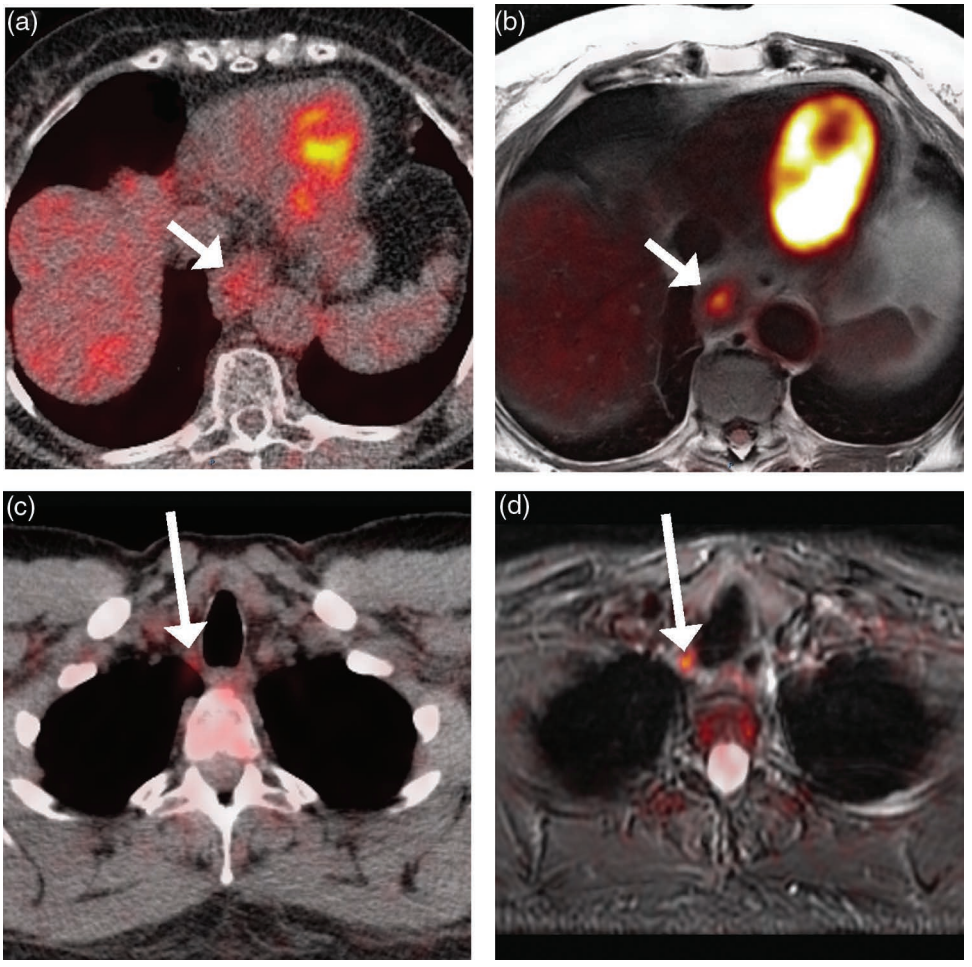
Statistical analysis was performed using R version 4.0.4 (www.r-project.org). The code can be accessed via github.com/mjvalkema/PRIMERO.

Results

Patients

Twenty-one patients were included (Fig. 2). Clinicopathological characteristics are presented in Table 1. Fourteen of 21 patients (67%) had yp/ycT+. Twelve of 14 underwent surgery. The other two patients had highly suspected disease (i.e. ycT+), but did not undergo surgery; one had an interval bone metastasis, and one refused surgery. In seven of 21 patients (33%), no residual cancer was detected during CREs until 9 months after nCRT (ycT0). One of these seven patients nevertheless underwent surgery, because a solitary lymph node metastasis (Fig. 3) and high-grade

Fig. 3



To demonstrate the image quality between the two techniques within the same patients, two cases are shown. (a,b) Case 1. The distal esophagus region on the ^{18}F-FDG PET/low dose CT vs. ^{18}F-FDG PET/ T2w PROPELLER in the same patient with residual tumor (ypT3N2; 11–50% residual tumor). Both scans were considered of good quality. (c,d) Case 2. The cervical region in another patient is shown on ^{18}F-FDG PET/low dose CT vs. ^{18}F-FDG PET/T2w FrFSE Flex. The ^{18}F-FDG uptake in the lymph node at level 2R is more pronounced on the ^{18}F-FDG PET/MRI than on the ^{18}F-FDG PET/CT since it is acquired at a prolonged interval after ^{18}F-FDG injection. Subtle characterization of the lymph node on the MRI was however, hindered by lung motion artifacts. Three months later, a further increase in ^{18}F-FDG uptake was seen in this node and the patient underwent surgery, which confirmed this lymph node metastasis (ypT0N1). FrFSE, fast recovery fast spin echo; PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction.

dysplasia were detected at 6 months after nCRT. The resection specimen confirmed the lymph node metastasis, but high-grade dysplasia or residual tumor was absent (TRG 1, ypT0N1).

Six of 21 (29%) patients had ypN+. Thirteen of 21 (62%) had ypN0 (n = 7) or ycN0 (n = 6). For the other two of 21 patients, the ypN stage remained unknown since these patients did not undergo surgery because of resp. distant metastasis and refusal. These two patients were left out of the analysis for yp/ycN+ detection.

Scanning parameters

Twenty patients completed both ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MRI. One patient decided to quit during the ^{18}F-FDG PET/MRI scan, and a DWI was missing from the esophagus region. Because a sufficient-quality T2-weighted PROPELLER was acquired, the patient was included in the analysis.

Median glucose levels were 5.7 (IQR 5.4–6.4). Scans were performed at a median of 11.9 weeks after nCRT (IQR 11.6–12.1). Median scan duration was 32 min (IQR 30–35) for ^{18}F-FDG PET/CT and 61 min (IQR 56–64) for ^{18}F-FDG PET/MRI. The interval between ^{18}F-FDG injection and scanning was 61 min (IQR 56–63) for ^{18}F-FDG PET/CT and 124 min (IQR 121–130) for ^{18}F-FDG PET/MRI. No adverse events occurred.

Qualitative assessments

The image quality of the scans was scored at least sufficient for all ^{18}F-FDG PET/CT scans and for 18 of 21 (86%) ^{18}F-FDG PET/MRI scans (Supplementary Table 2, Supplemental digital content 1, *http://links.lww.com/NMC/A270*). Some examples of the image quality of the two techniques are shown in Fig. 3.

For teams 1 and 2 resp., a sensitivity for yp/ycT+ detection with ^{18}F-FDG PET/MRI was achieved of 36% and 78%, and the specificity of 43% and 14%, respectively. The sensitivity for ypN+ was 17% and 33%, and the specificity was 85% and 62%, respectively. The one-interval bone metastasis was detected on both scans. All diagnostic accuracy parameters of ^{18}F-FDG PET/MRI and ^{18}F-FDG PET/CT are presented in Tables 2 and 3. Examples of patients correctly and incorrectly assessed by both teams are shown in Figs. 4–7.

The interobserver agreement regarding yp/ycT+ was 86% for ^{18}F-FDG PET/CT (Cohen's kappa 0.59, i.e., moderate agreement) and 62% for ^{18}F-FDG PET/MRI (Cohen's kappa 0.30, i.e., fair agreement). The interobserver agreement regarding ypN+ was 71% for ^{18}F-FDG PET/CT (Cohen's kappa 0.41, i.e., moderate agreement) and 62% for ^{18}F-FDG PET/MRI (Cohen's kappa 0.48, i.e., moderate agreement).

Quantitative measurements

SUL_{max} measurements on both ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MRI were not discriminative for locoregional tumor; neither was ADC_{mean} (Table 4). Bland–Altman analysis showed good agreement between ^{18}F-FDG PET/CT and ^{18}F-FDG PET/MRI regarding SUL_{max} (Supplementary Figure 1, Supplemental digital content 1, http://links.lww.com/NMC/A270). The intraclass coefficient for ADC_{mean} between the two teams was 0.27, indicating poor agreement.

Patient burden

All patients completed questionnaires (Supplementary Table 3, Supplemental digital content 1, *http://links.lww.com/NMC/A270*). Fourteen of 21 patients (67%) were neutral or willing to undergo a similar ^{18}F-FDG PET/MRI examination in the future. ^{18}F-FDG PET/MRI was less comfortable, and patients had more anxiety. The most stressful aspects of ^{18}F-FDG PET/MRI were scan duration (7 of 21, 33%) and the noise of the scanner (6 of 21, 29%). Sixteen of 21 patients (76%) experienced the additional ^{18}F-FDG PET/MRI as not (so) unpleasant.

Discussion

This feasibility study shows that the diagnostic performance of ^{18}F-FDG PET/MRI at 12 weeks after nCRT appears comparable to ^{18}F-FDG PET/CT for the detection of locoregional residual tumor. Therefore, an added value to improve clinical response evaluations was not yet demonstrated in this first exploration of ^{18}F-FDG PET/MRI in the post-treatment setting.

Table 2 Qualitative assessments vs. reference standard for detecting primary tumor in the esophagus

	Team 1		Team 2	
	^{18}F-FDG PET/CT	^{18}F-FDG PET/MRI	^{18}F-FDG PET/CT	^{18}F-FDG PET/MRI
Sensitivity	86 (57–98)	36 (13–82)	86 (57–98)	78 (49–95)
Specificity	57 (18–90)	43 (10–82)	14 (0.4–58)	14 (0.4–58)
PPV	80 (62–90)	56 (33–76)	67 (58–74)	65 (55–73)
NPV	67 (32–89)	25 (12–46)	33 (5–82)	25 (4–73)
Accuracy	76 (53–89)	38 (18–62)	61 (38–82)	57 (34–78)

Data are median (95% confidence interval).
NPV, negative predictive value; PPV, positive predictive value.

Table 3 Qualitative assessments vs. reference standard for detecting locoregional lymph node metastases

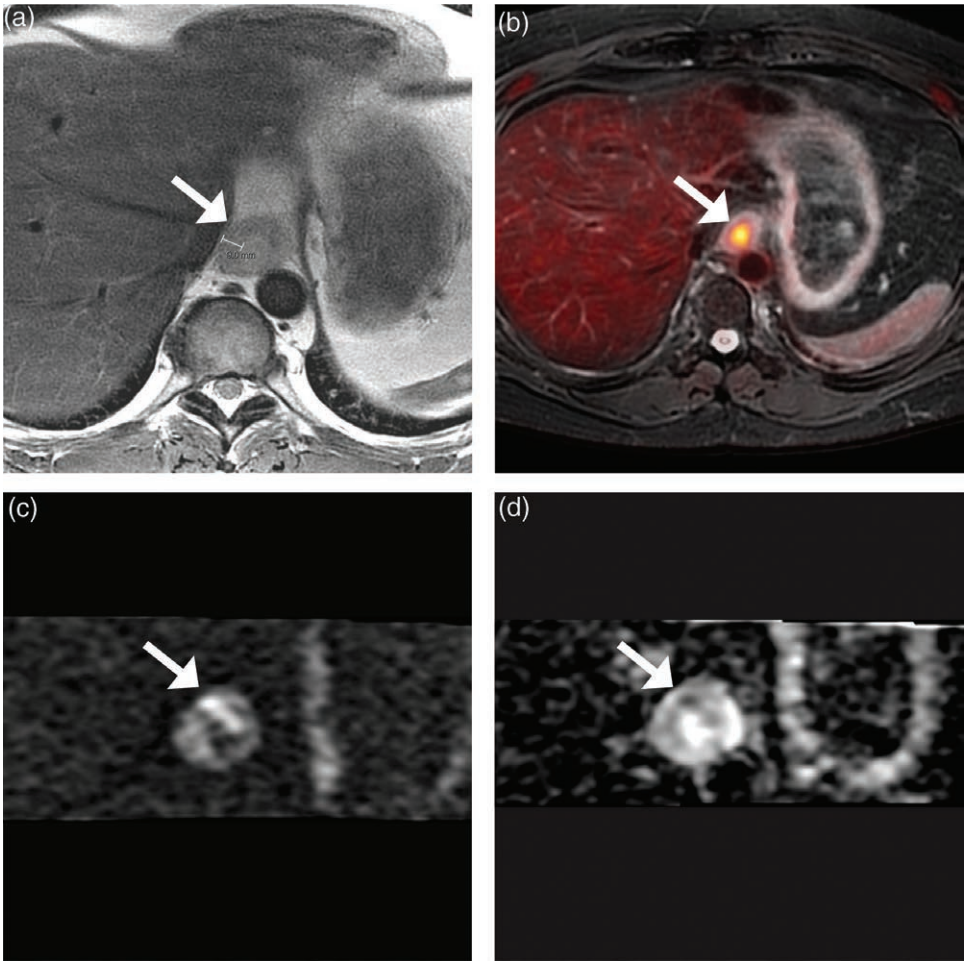
	Team 1		Team 2	
	^{18}F-FDG PET/CT	^{18}F-FDG PET/MRI	^{18}F-FDG PET/CT	^{18}F-FDG PET/MRI
Sensitivity	17 (0.4–64)	17 (0.4–64)	33 (4–78)	33 (4–78)
Specificity	85 (55–98)	85 (55–98)	46 (19–75)	62 (32–86)
PPV	33 (5–82)	33 (5–82)	22 (8–50)	29 (10–60)
NPV	69 (59–77)	69 (59–77)	60 (40–77)	67 (50–80)
Accuracy	63 (38–84)	63 (38–84)	42 (20–67)	53 (29–76)

Data are median (95% confidence interval).
NPV, negative predictive value; PPV, positive predictive value.

To our best knowledge, this is the first study that prospectively investigated the value of ^{18}F-FDG PET/MRI for esophageal cancer response evaluation after nCRT. The DWI did not appear to provide complementary value regarding the discrimination of residual tumor vs. inflammation in the present study cohort. Although DWI may show diffusion restriction in substantial tumor masses, diffusion restriction may be less clearly observed in small residual tumor volumes or in post-treatment necrotic tumor masses [15]. As illustrated in Figs. 6–7, a single ^{18}F-FDG PET/MRI scan will not always provide clear guidance regarding the response after nCRT and, as such, the decision to proceed to surgery or continue active surveillance. ^{18}F-FDG PET/MRI might be more suitable for assessing larger tumor volumes, for example, in the pretreatment staging and delineation of gross tumor volumes [7–9].

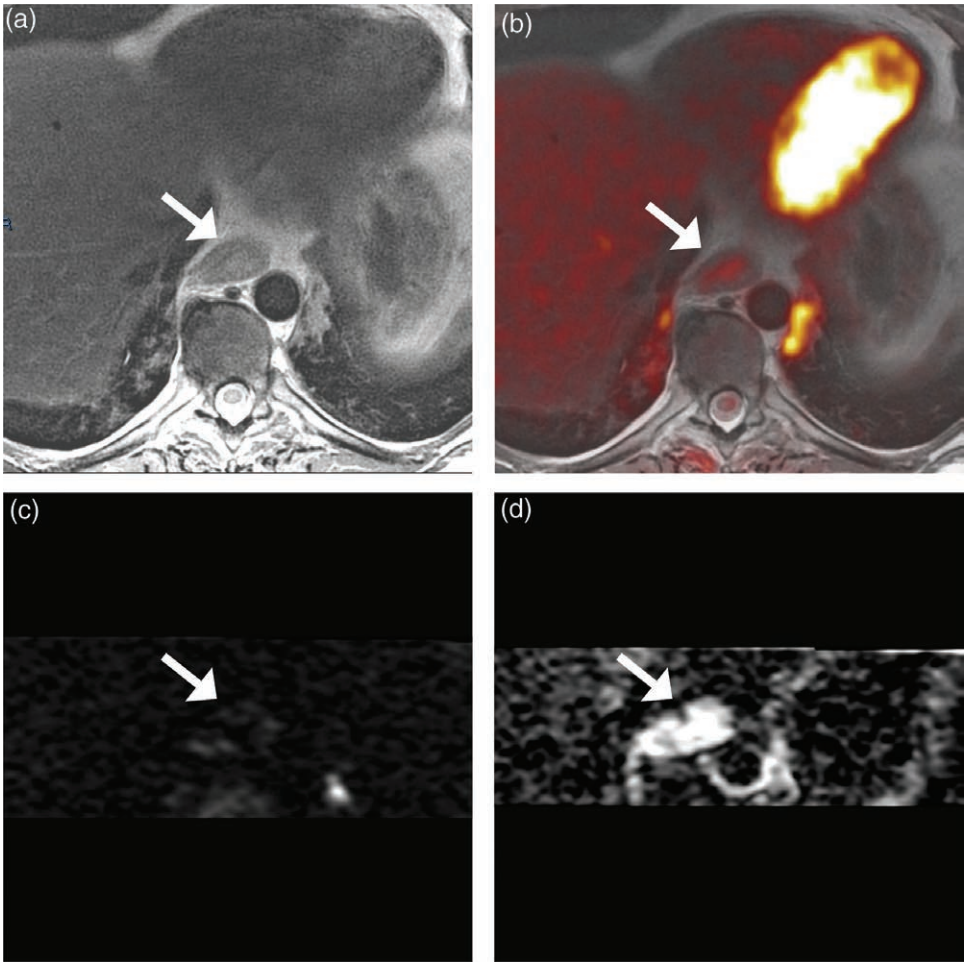
A striking finding was that the performance of the two teams of readers was relatively similar regarding the detection of ypN+ using ^{18}F-FDG PET/MRI. The assessment of yp/ycT+ only reached a fair agreement. In retrospect, team 1 seems to have considered the MRI component as a leading factor in their integrated conclusion (data not shown): when ^{18}F-FDG uptake was considered probably malignant or equivocal, but diffusion restriction was visually absent, postradiotherapy inflammation was considered more likely than the presence of a residual tumor. On the contrary, team 2 applied the DWI more in support of their integrated conclusion rather than considering it as leading. This phenomenon was not the case for ypN+ detection because diffusion restriction is not indicative of lymph node metastases and was not used as such by both teams. With the application of a new technique in esophageal cancer restaging,

Fig. 4



Patient with cT2N0M0 adenocarcinoma and tumor-positive biopsies at 5 weeks after nCRT. Both teams correctly classified the primary tumor area (a–d; arrows) as malignant on ^{18}F-FDG PET/MRI. The esophageal wall at the primary tumor location was thickened on the T2w PROPELLER image (a). Focal uptake was seen on ^{18}F-FDG PET (b), with hyperintense DWI $b = 800$ s/mm^2 (c) and hypointense ADC (d), suspect for tumor (ypT3N2; >50% residual tumor). ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; nCRT, neoadjuvant chemoradiotherapy; PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction; T2w, T2-weighted.

Fig. 5



Patient with cTxN0M0 adenocarcinoma, who underwent surgery for a positive lymph node (ypT0N1). Both teams correctly classified the primary tumor area (a–d; arrows) as benign on ^{18}F-FDG PET/MRI. Some hyperintense signal in the esophageal wall was observed on the T2-weighted PROPELLER image (a). This was considered more likely to be reactive than suggestive for residual tumor: linear, ^{18}F-FDG uptake was observed (b), without clear diffusion restriction (c,d). PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction.

assessment of ^{18}F-FDG PET/MRI was performed instead of assessing MRI alone. This might partially explain the discrepancy between results because the interpretation of the ^{18}F-FDG PET might have influenced the integrated conclusion of the scan. In addition, with a different implementation of the DWI of another scanner, a higher-quality image might be achieved in terms of less artifacts or distortions. Additional data on the value of MRI post-treatment is expected, because two studies are currently investigating (^{18}F-FDG PET/) MRI in patients treated with nCRT [17,18].

An important strength of our study was the prospective design, allowing similar scanning protocols and a similar follow-up protocol in all patients. Furthermore, between scans, patients were allowed to eat and drink. This contributed to the toleration of another hour of scanning. Furthermore, two teams of readers were involved in

a learning curve may play a role. The obvious advantage of ^{18}F-FDG PET/MRI is the perfect alignment between the PET and MR images, which aids the characterization of ^{18}F-FDG PET-avid lesions. The methodology for the interpretation of a residual tumor, however, requires further investigation.

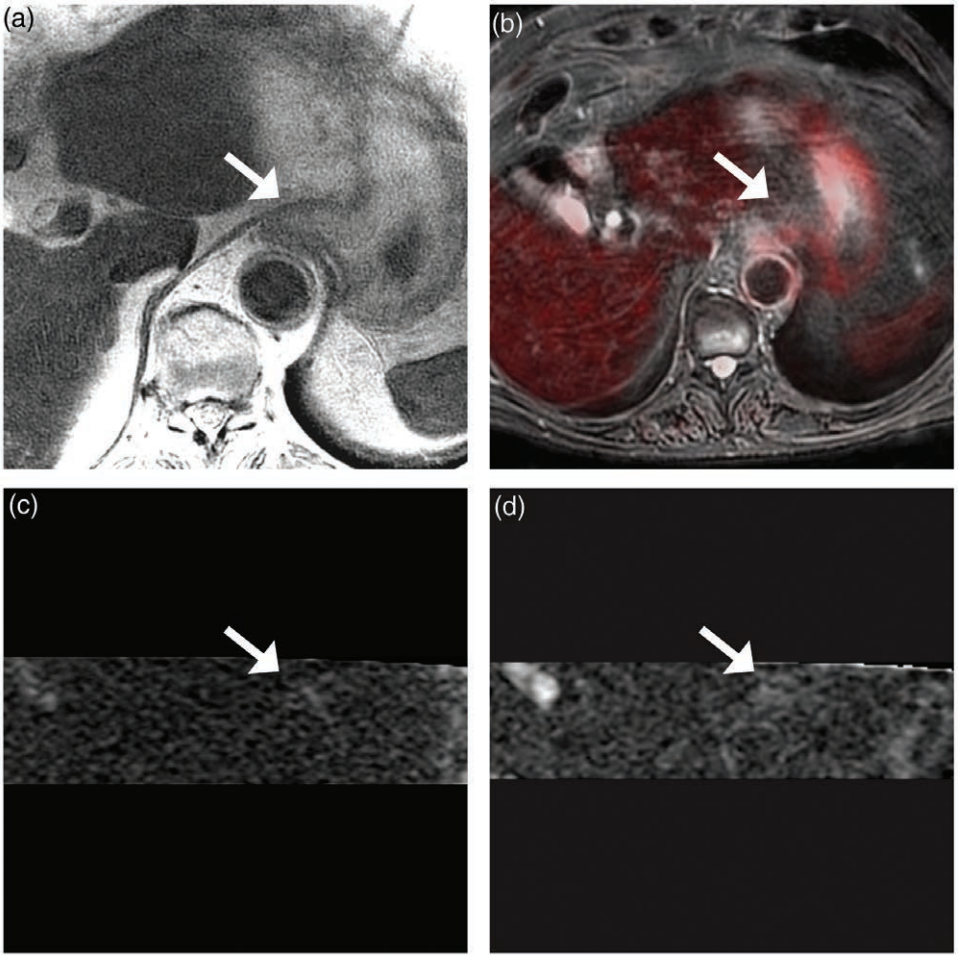
Overall, the present study indicates a sensitivity for yp/ycT+ of 36/78% (team 1/team 2) with ^{18}F-FDG PET/MRI, and a specificity of 43/14%, compared with 86/86% sensitivity and 57/14% specificity with ^{18}F-FDG PET/CT. In contrast, another study demonstrated better sensitivity and specificity for ypT+ with DWI than with ^{18}F-FDG PET/CT (sensitivity reader 1/reader 2 : 92/96% vs. 69/62%, resp.; specificity: 57/43% vs. 43/43%, resp.) after nCRT [6]. MRI has thus been shown to achieve high sensitivity at the cost of low specificity [16]. Notably, in the present study, an integrated

reading the scans. This was advantageous for assessing intra- and inter-team comparisons.

Some limitations should be taken into consideration. The sample size was limited, which fit the purpose of a feasibility study. As indicated by wide confidence intervals, the parameters for diagnostic accuracy thus only provide a gross estimation of the expected diagnostic performance of ^{18}F-FDG PET/MRI. Moreover, the reference standard was not available at the same time point for all patients. A proxy until 9-month follow-up had to be defined in patients without surgery. However, such a choice was unavoidable in an active surveillance setting. Moreover, ^{18}F-FDG PET/CT was performed first in all patients to retain it as the standard of care. This may have introduced bias regarding the perceived burden, which was more favorable with ^{18}F-FDG PET/CT. The standard longer uptake time for ^{18}F-FDG PET/MRI also affected distribution. Different tumor/background ratios might have impacted assessments, although it is unclear to what extent. Finally, baseline ^{18}F-FDG PET/MRI and dynamic contrast-enhanced (DCE) MRI were not performed in this study. Therefore, it was not possible to exploit delta-ADC and dynamic contrast-enhanced parameters.

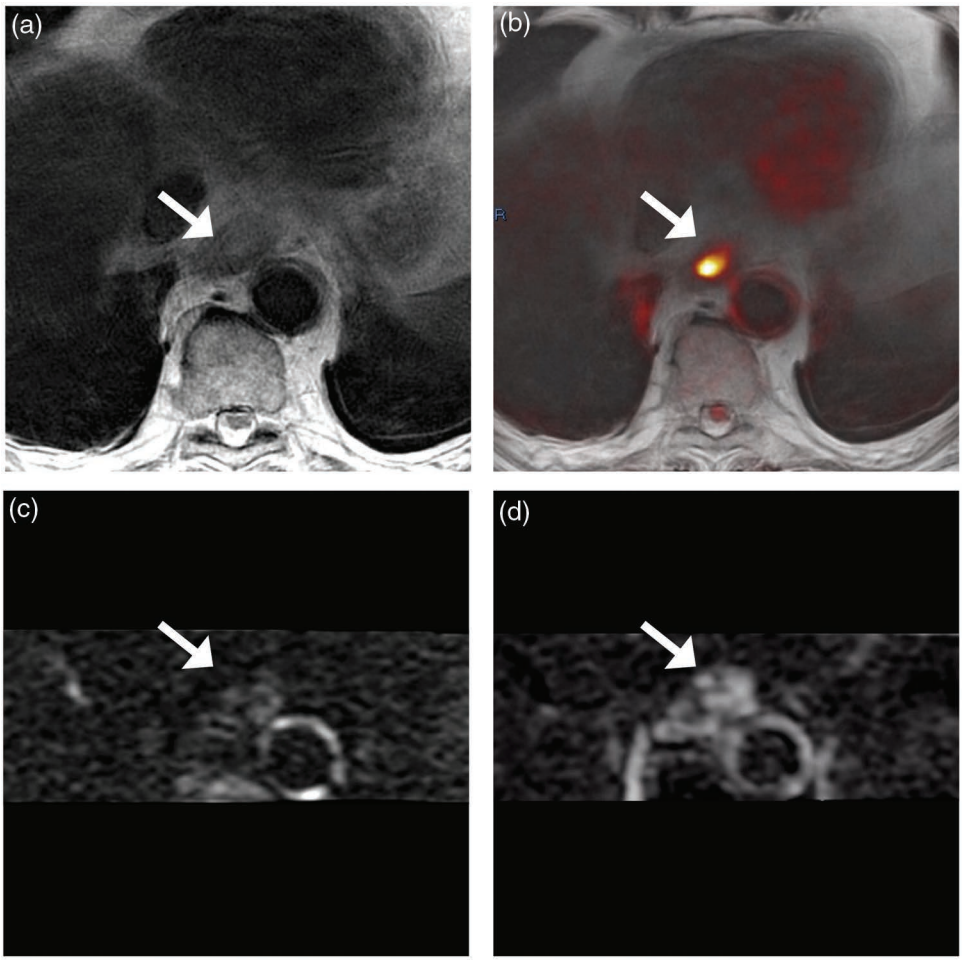
This was our first experience with post-treatment ^{18}F-FDG PET/MRI, and several aspects could be considered in future studies. Scanning the mediastinum with ^{18}F-FDG PET/MRI remains challenging, and the scanning protocol needs to be optimized to reduce artifacts. The addition of filling liquid in the esophageal lumen might be considered to optimize tissue contrast. The possibility of serial scanning, exploring delta-MRI features, might provide more guidance in assessing response during active surveillance [19]. Eventually, the best improvement in specificity might be obtained with another, more

Fig. 6



Patient with cT3N0M0 adenocarcinoma and tumor-positive biopsies at 6 months after nCRT (ypT1bN0; >50% residual tumor). Both teams incorrectly classified the primary tumor area as benign (a–d; arrows). On the T2-weighted PROPELLER image (a) separate esophageal layers could be recognized and no residual tumor mass was observed. No suspect ^{18}F-FDG uptake (b) nor diffusion restriction was observed (c,d). nCRT, neoadjuvant chemoradiotherapy; PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction.

Fig. 7



Patient with cT3N0M0 adenocarcinoma, with a persistent clinically complete response until last available follow-up 16 months after nCRT. Both teams incorrectly classified the primary tumor area as malignant (a–d; arrows). The esophageal wall appeared thickened on T2-weighted PROPELLER image (a). Moderate ^{18}F-FDG uptake (b) and suggestion of diffusion restriction (c,d) were considered suspect for residual tumor. nCRT, neoadjuvant chemoradiotherapy; PROPELLER, periodically rotated overlapping parallel lines with enhanced reconstruction.

Table 4 Quantitative assessments of the primary tumor location

	ypT0 ($n=7$)	ypT+ ($n=14$)	*P*	
SUL_{max} on ^{18}F-FDG PET/CT	2.63 (2.33–2.98)	2.65 (2.39–3.01)	0.64	
SUL_{max} on ^{18}F-FDG PET/MRI	1.90 (1.81–2.71)	2.05 (1.89–2.41)	1	Nonparametric*
ADC_{mean} tumor team 1	2.25 (2.10–2.39)	2.20 (2.13–2.41)	0.55	
ADC_{mean} tumor team 2	2.28 (1.97–2.47)	2.11 (1.90–2.49)	0.82	

Data are median, interquartile range.
**P* value calculated with Mann–Whitney *U* test.

tumor-selective tracer. Fibroblast activation protein inhibitor may be a candidate, as well as other radiotracers in the future, which needs to be confirmed in new studies [20].

Conclusion

The current study indicates that the novel ^{18}F-FDG PET/MRI and the present standard ^{18}F-FDG PET/CT show similar performance in terms of accuracy of locoregional esophageal cancer detection after nCRT. Improvements in technique, reader experience and application of serial scanning offer potential sources for improvement of the performance of ^{18}F-FDG PET/MRI.

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Data generated or analyzed during the study are available from the corresponding author on request.

All procedures performed in the patients described herein were in accordance with the principles of the 1964 Declaration of Helsinki and its later amendments or comparable standards. The study was approved by the Medical Ethical Committee of the Erasmus MC (MEC-2020-0784). Written informed consent for participation and for publication was obtained from all patients in this study.

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Conflicts of interest

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