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^{18}F-FDG-PET/MRI in preoperative staging of oesophageal and gastroesophageal junctional cancer

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ARTICLE INFORMATION

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AIM: To evaluate integrated 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron-emission tomography (PET)/magnetic resonance imaging (MRI), in comparison with the standard technique, integrated ^{18}F-FDG-PET/computed tomography (CT), in preoperative staging of oesophageal or gastroesophageal junctional cancer.

MATERIALS AND METHODS: In the preoperative staging of 16 patients with oesophageal or gastroesophageal junctional cancer, ^{18}F-FDG-PET/MRI was performed immediately following the clinically indicated ^{18}F-FDG-PET/CT. MRI-sequences included T1-weighted fat–water separation (Dixon's technique), T2-weighted, diffusion-weighted imaging (DWI), and gadolinium contrast-enhanced T1-weighted three-dimensional (3D) imaging. PET was performed with ^{18}F-FDG. Two separate teams of radiologists conducted structured blinded readings of ^{18}F-FDG-PET/MRI or ^{18}F-FDG-PET/CT, which were then compared regarding tumour measurements and characteristics as well as assessment of inter-rater agreement (Cohen's kappa) for the clinical tumour, nodal and metastatic (TNM) stage.

RESULTS: There were no medical complications. Comparison of tumour measurements revealed high correlations without significant differences between modalities. The maximum standardised uptake value (SUV_{max}) values of the primary tumour with ^{18}F-FDG-PET/MRI had excellent correlation to those of ^{18}F-FDG-PET/CT (0.912, Spearman's rho). Inter-rater agreement between the techniques regarding T-stage was only fair (Cohen's kappa, 0.333), arguably owing to relative over-classification of the T-stage using ^{18}F-FDG-PET/CT. Agreements in the assessment of N- and M-stage were substantial (Cohen's kappa, 0.849 and 0.871 respectively).

CONCLUSION: Preoperative staging with ^{18}F-FDG-PET/MRI is safe and promising with the potential to enhance tissue resolution in the area of interest. ^{18}F-FDG-PET/MRI and ^{18}F-FDG-PET/CT correlated well for most of the measured values and discrepancies were seen mainly in the assessment of the T-stage. These results facilitate further studies investigating the role of ^{18}F-FDG-PET/MRI in, e.g., predicting or determining the response to neoadjuvant therapy.

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Introduction

Accurate preoperative radiological staging is important to guide the choice of treatment in oesophageal and gastroesophageal junctional (GEJ) cancer. Modern treatments are multimodal, including neoadjuvant chemo- or chemoradiotherapy followed by surgical resection of the tumour or definitive chemoradiotherapy.[1,2] To discriminate patients with curable disease from patients with metastatic disease, the use of whole-body integrated 2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG)-PET (positron-emission tomography)/computed tomography (CT) has in many centres been adopted as clinical reference standard. ^{18}F-FDG-PET/CT is often complemented by endoscopic ultrasonography (EUS) with fine-needle aspiration (FNA) for additional assessment of the primary tumour and local lymph node status.[3]

Whole-body fully integrated ^{18}F-FDG-PET/MRI (magnetic resonance imaging) has recently been introduced in the clinical field. MRI has the advantage of superior soft-tissue contrast, which can provide crucial information on tumour depth and nodal involvement as well as functional information, e.g., diffusion-weighted imaging (DWI). Combining ^{18}F-FDG-PET with MRI in a fully integrated system (henceforth referred to as PET/MRI) in the preoperative staging of oesophageal and GEJ cancers is a potential alternative to standard clinical staging with ^{18}F-FDG-PET/CT (henceforth referred to as PET/CT) as well as EUS with FNA.[4]

PET tracer (^{18}F-FDG) uptake can be quantified, to assess metabolic activity of the tumour and any metastatic manifestations, by means of the standardised uptake value (SUV). Prior comparative studies of SUVs between PET/CT and PET/MRI in healthy individuals as well as in cancer patients[5] have shown adequate agreement. Comparison of PET/CT and PET/MRI in patients with head and neck cancers[6] and the clinical impact of PET/MRI in cancer patients have both shown promising results[7] proposing the usefulness of PET/MRI.

The aim of this prospective study was to perform a structured evaluation of feasibility, safety, **t**umour, nodal and metastatic (TNM) staging and other clinically relevant quantitative or qualitative measures of whole-body fully integrated PET/MRI versus PET/CT in the preoperative staging of patients with cancer in the oesophagus or GEJ.

Materials and methods

Patients and inclusion

A regional ethics committee approved the study and written informed consent was obtained from all participants. Operable patients, diagnosed with potentially resectable ($T_{1–4a}$, $N_{1–3}$, M_0) oesophageal or GEJ cancer, who were to undergo a clinically indicated PET/CT, were scanned for inclusion. Exclusion criteria were pregnancy, claustrophobia, or inability to lay supine for a longer period of time, some implanted metallic artefacts or electronic devices in the thoracic cavity or head, previous history of allergy towards radiological contrast media, manifest renal failure, or inability to provide informed consent (cognitive failure or language inabilities).

Prior to examinations patients were administered an intravenous ^{18}F-FDG injection (mean dose 334±48 mBq) and then underwent a clinical PET/CT and a consecutive PET/MRI immediately afterwards, utilising the same ^{18}F-FDG injection. PET/CT and PET/MRI were performed 64±9 and 109±22 minutes (mean±SD) after ^{18}F-FDG injection, respectively.

PET/CT

The standard clinical PET/CT (Discovery, GE Healthcare, Waukesha, WI, USA) protocol comprised CT (120 kV, 10 mAs) with intravenous contrast medium enhancement for anatomical localisation, guiding, and attenuation correction along with an integrated PET with five bed positions of approximately 120 seconds per bed position. The section thickness was 1 mm. The mean duration of PET/CT imaging was 84±65 minutes (mean±SD), including adequate time for ^{18}F-FDG uptake. In two patients, PET/CT was performed without intravenous contrast medium, and accordingly, the previous clinical diagnostic CT with intravenous contrast medium was added to the PET/CT readings in those patients for evaluation of TNM staging.

PET/MRI

Examinations were performed with a fully integrated combined time-of-flight PET and 3 T MRI (SIGNA, 3 T, 60 cm, GE Healthcare, Waukesha, WI, USA). Whole-body PET imaging required six bed positions, with 180 seconds per bed position, followed by an additional PET sampling over the tumour region for a more detailed study. For attenuation correction, a dedicated T1-weighted sequence, integrated within the vendors software, was used. The extensive study protocol included additional MRI-sequences such as: electrocardiogram (ECG)-gated and breathing-gated images, T2-weighted images, whole-body three-dimensional (3D) Dixon sequences, DWI, and intravenous contrast-enhanced T1-weighted 3D imaging. A hyperosmolar paramagnetic intravenous contrast medium, gadoterate meglumine (Dotarem, Gothia Medical, Billdal, Sweden), was administered. The mean duration of PET/MRI image acquisition was 117±22 minutes.

Radiological reading procedure

All patients were assigned a consecutive number linking them to the examinations performed. Images were stored in a separate study-specific picture archiving and communications system (PACS; Carestream Health, Rochester, NY, USA), for radiological readings. The structured radiological readings were then performed in a blinded fashion by two independent groups of radiologists, where the first group read the PET/CT only and the second group read the PET/MRI only. Consensus readings within each group were performed to form the grounds for the statistical analysis and comparison between the techniques. Both groups

utilised the same study-specific pre-formed protocol for structured readings.

Descriptive tumour characteristics

Tumour measurements, including greatest tumour length and width, tumour wall thickness and distance from the superior tumour border to the tracheal bifurcation as well as the distance from the inferior tumour border to the gastric cardia, were deducted from the structured readings and maximum SUVs were calculated by means of a 3D volume of interest (VOI) model.

Tumour staging

TNM staging was performed according to the 7th edition of the *TNM classification of malignant tumours (TNM7)*.[8] In this study, positive lymph nodes (metastatic) were defined based on a combination of ^{18}F-FDG avidity and lymph node appearance. In PET/CT, a metastatic lymph node was defined as a lymph node with an ^{18}F-FDG uptake above the background uptake, regardless of size and without a specific SUV_{max} cut-off value. In PET/MRI, lymph nodes were defined as metastatic based on whether their outer margin was irregular and/or the internal signal was mixed, regardless of their size. No SUV_{max} cut-off value was utilised, but lymph nodes with altered characteristics and/or an uptake at least higher than the background, were defined as metastatic.

In addition to nodal stage, the total number of radiological positive lymph nodes was deducted from the readings. Non-regional lymph nodes, as specified in *TNM7*, were classified as distant metastatic nodes, and consequently, not included in the nodal stage assessment, but remained in the analysis of the total number of radiologically positive lymph nodes.

Statistical analysis

All continuous data were reported as means ± SD unless otherwise specified. Clinical TNM staging agreements between techniques were calculated separately utilising the readings to assess percentages of exact agreement and inter-rater agreement by weighted and unweighted kappa statistics (Cohen's kappa). Interpretation of Cohen's kappa coefficients were applied as follows: <0 indicating no agreement, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.0 as almost perfect agreement according to well-established criteria.[9]

Correlation assessments between PET/CT and PET/MRI on measured continuous variables were performed with Spearman or Pearson's correlation coefficients and pairwise comparisons of measured tumour characteristics were analysed using paired *t*-test or Wilcoxon's signed rank test. Scatterplots with best-fit lines were used for graphical presentation of radiological estimated tumour measurements and characteristics. A *p*-value of <0.05 was considered statistically significant.

Results

Patients

Nineteen patients were included in the study. The first patient, acting as a pilot, underwent a rudimentary MRI to calibrate the sequencing protocol and thus did not undergo contrast-enhanced imaging or the PET part of the PET/MRI study. This patient was therefore excluded, as were two additional patients who withdrew consent prior to the radiological examinations. Sixteen patients underwent both PET/CT and PET/MRI according to study protocol and formed the basis of the statistical analysis. Patient and clinical characteristics are summarised in Table 1.

Feasibility and safety

No medical- or procedure-related adverse events were observed during PET/MRI or PET/CT. Three patients did not complete the entire PET/MRI protocol due to fatigue, although they did complete the relevant sequences (including the PET sequences) for meaningful comparison between the techniques.

Tumour characteristics

There were no significant differences between techniques in the description of tumour characteristics and measurements when analysed using the paired *t*-test. In the correlation analysis, best correlations were in estimation of tumour length, width, and tumour relation to the tracheal bifurcation (correlation coefficients: 0.857, 0.913, and 0.902, respectively). Least correlations were in the estimation of tumour wall thickness and distance to the gastric cardia (correlation coefficients: 0.640 and 0.675, respectively). Tumour wall thickness had higher absolute estimates in the PET/CT scans; however, this was not significant statistically (Table 2, Fig 1).

Positive lymph nodes

The median number of detected positive lymph nodes were higher with PET/MRI, two (0–5), compared to PET/CT, one (0–2) (median [IQR]; p=0.015, Wilcoxon signed rank test). Non-parametric correlation analysis of the number of

Table 1
Patient characteristics in 16 patients undergoing staging for oesophageal or GEJ cancer.

Characteristic	
Gender (M/F)	15/1
Age, years (median (range))	65 (46–78)
Tumour type	
Adenocarcinoma	13
Squamous cell carcinoma	2
Undifferentiated carcinoma	1
Tumour location in the oesophagus	
Upper	0
Middle	4
Lower	12

Table 2
Estimated measures of tumour characteristics with PET/MRI and PET/CT in preoperative staging of 16 patients with oesophageal and GEJ cancer.

	PET/MRI	PET/CT	Difference (mean ± SE)	*p*-Value[a]	Correlation[b]
Tumour length	73±35	69±33	4±5	0.359	0.857
Tumour width	35±16	34±17	1±2	0.603	0.913
Tumour wall thickness	17±8	20±6	2±2	0.221	0.640
Distance from tracheal bifurcation	55±32	49±34	6±4	0.122	0.902
Distance from gastric cardia	20±28	16±20	4±5	0.437	0.675

Data are in millimetres, mean±SD unless otherwise stated.
PET, positron-emission tomography; MRI, magnetic resonance tomography; CT, computed tomography; SD, standard deviation; SE, standard error.
[a] Paired *t*-test.
[b] Pearson's correlation test.

detected positive lymph nodes revealed a correlation of 0.911 (Spearman's rho correlation).

SUV_{max}

SUV_{max} measured from the VOI in the area of the primary tumour with greatest ^{18}F-FDG uptake was higher with PET/MRI compared to PET/CT (16.5 [10.7–23.1] versus 12.8 [7.1–17.4], median [IQR], $p<0.001$). Even if SUV_{max} values were deemed higher in the PET/MRI readings, correlation between techniques was excellent at 0.912 (Fig 2).

Clinical TNM stage

Agreement in assessment of clinical T-stage between PET/MRI and PET/CT was fair. Exact agreement between readings was 56%. Analysis with unweighted Cohen's kappa resulted in a kappa coefficient of 0.222. Considering the magnitude of discrepancies with weighted Cohen's kappa, the kappa coefficient increased to 0.333. PET/CT readings estimated a higher T-stage than PET/MRI in six patients and vice versa in one. This difference, observed in absolute numbers, was not, however, significant statistically (p=0.053, Wilcoxon signed rank test).

Exact agreements on N-stage and M-stage between PET/MRI and PET/CT exceeded those of T-stage assessments. In this comparison, the exact agreements were 88% and 94% for N-stage and M-stage, respectively. In the kappa analysis of N-stage assessment, the unweighted kappa coefficient was 0.817 and the weighted kappa coefficient was 0.849. As all possible errors in assessment of M-stage were of equal magnitude, due to the fact that M-stage could only assume a

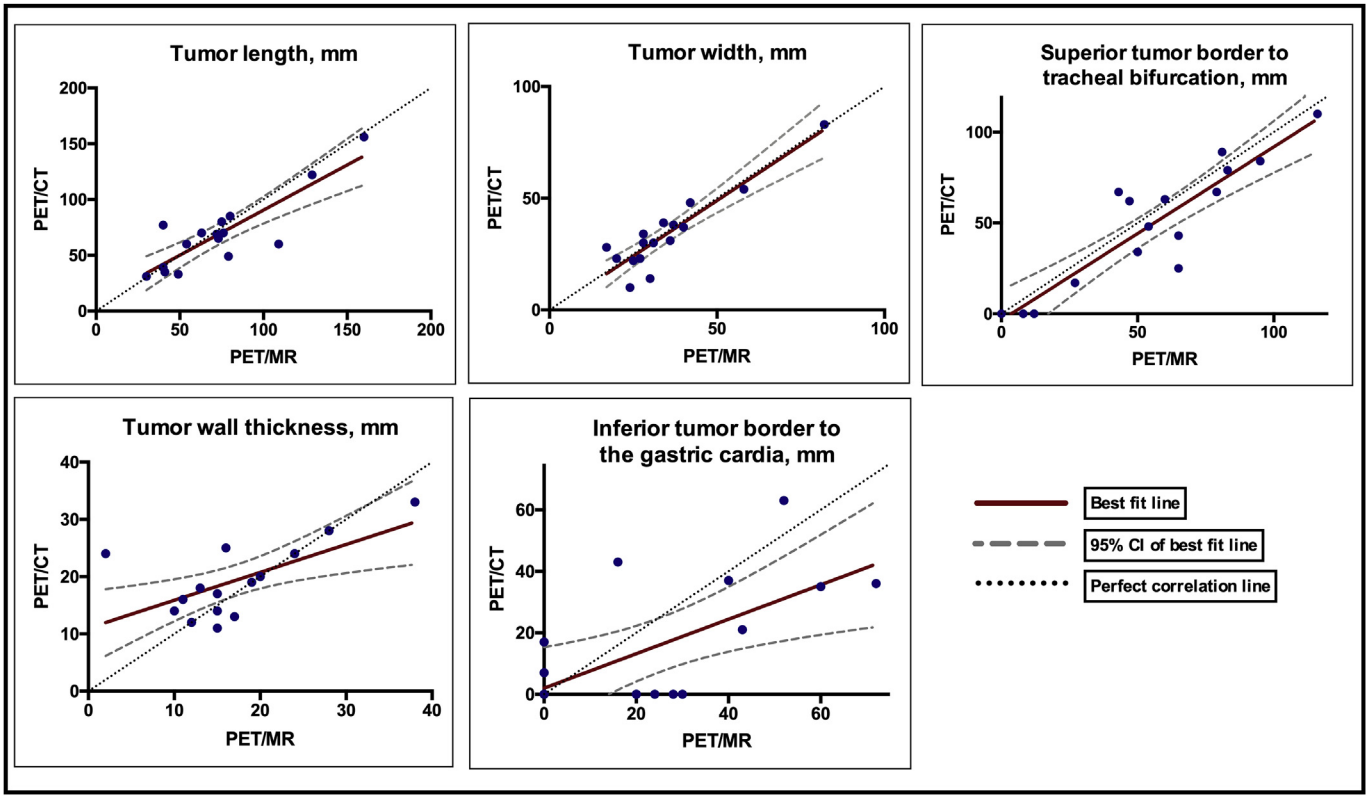

Figure 1 Scatterplots depicting correlation between PET/MRI and PET/CT with best fit lines and 95% confidence interval (CI) of best fit lines from 16 patients undergoing staging for oesophageal and GEJ cancers.

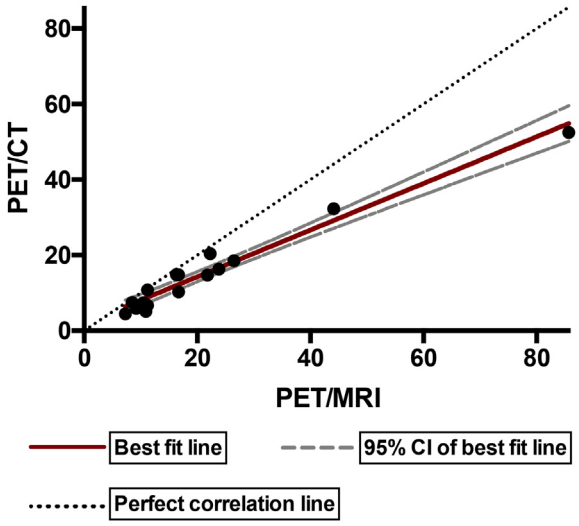

Figure 2 Scatterplot of estimated SUV_{max} for PET/CT and PET/MRI in the preoperative staging of 16 patients with oesophageal and GEJ cancer. The SUV_{max} for PET/MRI (IQR) was 16.5 (10.7–23.1) and that for PET/CT (IQR) was 12.8 (7.1–17.4). Wilcoxon signed ranks test of differences between the two techniques was $p<0.001$ and Spearman's correlation coefficient was 0.912.

value 0 or 1, unweighted and weighted kappa coefficients were equal. The kappa coefficient in assessment of the M-stage was 0.871. A summary of exact agreements, kappa coefficients, and cross-tabulations of qualitative clinical TNM stage assessments can be found in Table 3.

Discussion

This prospective study aimed to assess the role of PET/MRI in a preoperative staging setting. PET/MRI correlated well with the standard method, PET/CT, in regards to tumour measurements, detection of positive lymph nodes, and SUV_{max} values. In T-staging, only fair inter-rater agreement was achieved, although agreements of nodal and metastatic staging were high between the techniques.

The clinical applications of MRI are many; however, MRI is not commonly utilised in the staging of oesophageal and GEJ cancers. There are obstacles to overcome for accurate imaging of the mediastinum and upper gastrointestinal tract, such as free-breathing and the beating of the heart. In the present study, breathing and ECG-gating was applied in a successful manner as described previously by Venkatesh *et al.*[10]

Heeding the drawbacks of MRI, such as the size of the apparatus bore and the longer duration of examination, the advantages are many. Advantages advocated in cancer staging are the enhanced tissue resolution and functional information, such as DWI, which have the potential to better discriminate tumour growth in different gut layers and surrounding tissues of the mediastinum, thorax, and upper gastrointestinal tract.[11] This enables more accurate tumour staging and could guide therapy strategies. The discrimination of an oesophageal tumour growing adjacent to or growing into the aortic adventitia or trachea would most certainly be a separator between the choices of denying or approving treatment with curative intent. MRI has previously been shown to discriminate in this manner.[12,13]

Estimations of tumour measurements with PET/MRI did not significantly differ from PET/CT in the present study. There were, however, no beforehand reasons to believe the techniques would differ much in this respect. The substantial correlations between techniques regarding tumour measurements were instead mainly interpreted as a measure of quality control and a basis for the further inter-rater agreement.

In T-stage assessment, the two investigated techniques diverged. Deductions from the readings showed only fair agreement on T-stage. The tumour walls were deemed thicker with PET/CT compared to PET/MRI. A higher resolution in certain MRI sequences might depict the wall layers

Table 3
Cross-tabulations, exact agreements and kappa coefficients of TNM stage in 16 patients radiologically staged for oesophageal or GEJ cancer.

	PET/MRI				
PET/CT	Radiological T-stage: exact agreement = 56%, Cohen's kappa = 0.333				
		T1	T2	T3	T4
	T1	0	0	0	0
	T2	0	7	1	0
	T3	0	3	1	0
	T4	0	2	1	1
	Radiological N-stage: exact agreement = 88%, Cohen's kappa = 0.849				
		N0	N1	N2	N3
	N0	5	0	0	0
	N1	0	6	1	1
	N2	0	0	1	0
	N3	0	0	0	2
	Radiological M-stage: exact agreement = 94%, Cohen's kappa = 0.871				
		M0		M1	
	M0	9		1	
	M1	0		6	

PET, positron-emission tomography; MRI, magnetic resonance imaging; CT, computed tomography; T-, N-, M-stage, tumour, nodal and metastatic stage according to *TNM Classification Of Malignant Tumours,* 7th edition.

in more detail, thus decreasing the risk of over-staging. In total, there were disagreements for the T-stage between techniques in seven patients of which six were T-staged higher with PET/CT than PET/MRI; however, given the relatively few patients included and the absence of raw evidence, such as the pathological T-stage, the present study is underpowered to draw any firm conclusions in this respect.

There are more subjective values involved in the qualitative assessment of nodal status compared with the quantitative measurement of the primary tumour. It is difficult to find clear consensus on what exactly should determine a positive lymph node, although studies have made attempts to determine the prerequisites.[14] The addition of PET aids the determination of nodal positivity by adding graphics of tumour metabolism to the radiological reading. Even though there were discrepancies in the determination of the total number of positive lymph nodes, correlation was high, and N-stage assessment had both substantial exact agreements and inter-rater reliability between the techniques.

In many countries, PET/CT has become the reference standard for ruling out metastatic disease in patients intended for curative treatment.[15] Due to centralisation to larger-volume centres, PET/CT is available to most patients undergoing preoperative staging in modern healthcare, and many national guidelines on oesophageal cancer recommend the use of PET/CT in staging. In the present study, the inter-rater agreement between PET/MRI and PET/CT is almost perfect for M-stage, indicated by a kappa coefficient of 0.871 and an exact agreement of 94%; thus, PET/MRI is not inferior to PET/CT in detecting metastatic disease. As PET/MRI is a new technique, availability is greatly limited and the cost is higher than that of PET/CT. Other disadvantages of PET/MRI are the long imaging times, depending on protocol lengths. The prolonged PET/MRI imaging times presented in this study even included some alternative MRI sequences that the present authors had hope to utilise but were deemed beyond the scope of the present study; however, dedicated oncological protocols should afford abbreviated imaging times in order to minimise discomfort for patients struggling with claustrophobia or for patients that can be disqualified because of their inability to lay supine for a longer period of time. The noise produced by the scanner can be perceived as problematic, but this is an intrinsic apparatus issue on the same level as a standard MRI system. In addition, PET/MRI may not be feasible in patients with some MRI-incompatible metallic artefacts in the proximity of the investigated area, although adjacent metallic artefacts can greatly reduce CT imaging quality as well. Despite the lack of availability and other above-mentioned disadvantages, the combination of enhanced tissue resolution and the advanced morphological sequences of MRI along with fully integrated PET for evaluation of metastatic disease suggest intriguing advantages for selected patients.

Ongoing European trials, such as SANO[16] and ESOSTRATE,[17] focus on evaluating an active surveillance strategy in patients characterised as complete responders after neoadjuvant chemoradiotherapy (nCRT). In utilising a surgery-as-needed approach, true complete responders must be distinguished from patients that appear to be complete responders, but actually have residual disease. Previous studies using dynamic MRI with intravenous contrast medium have both shown promising results in detecting response to nCRT.[18,19] A fully integrated system including PET and dynamic MRI may therefore be a powerful tool not only in clinical staging, but also in re-staging to assess complete response after nCRT. There are also promising results in introducing the field of radiomics to MRI, such as in the evaluation of complete response after nCRT in rectal cancer.[20]

Limitations

The use of SUV_{max} is widespread, but the application of the value in itself is under debate and known to be subject to many factors unrelated to tumour characteristics.[21] A decline in SUV_{max} from PET investigations prior to given nCRT treatment to after nCRT is proposed to be a predictor of improved survival.[22] In the present study, SUV_{max} values had excellent correlations between PET/MRI and PET/CT, although the estimated SUV_{max} were higher in the PET/MRI readings. One of the important factors for determination of SUV_{max} is the time from the given dose of ^{18}F-FDG to the PET image acquisition.[23] A previous study by Beaulieu *et al.*[24] demonstrated a linear positive correlation between the SUV of the primary tumour and the time to PET image acquisition. As the PET/MRI examinations were performed after the PET/CT, the time from injected ^{18}F-FDG dose to PET/MRI image acquisition was roughly 1 hour longer; thus, an increase in the measured SUV_{max} values was anticipated. This could possibly account for some of the discrepancies noted in TNM stage. In addition, in the PET/MRI readings, an increased number of PET-positive nodes were detected (exemplified by Fig 3), as well as one additional metastatic lesion not detected at PET/CT. This raises some questions regarding the recommended timing of PET imaging from administered dose of ^{18}F-FDG. Previous experimental studies of tumour biology suggest that ^{18}F-FDG uptake in malignant tumours, measured in the SUV, seldom reaches a plateau before 2 hours from injection of ^{18}F-FDG.[25] In standard clinical practice, however, the time to image acquisition is most often 60 minutes, but longer durations have been advocated.[26,27] The results from the present study suggest there could be some value in delaying the PET imaging. Additionally, and maybe equally important, different PET detectors with unequal sensitivity were fitted in the PET/MRI and the PET/CT, which could cloud comparisons of estimated SUV_{max} values; however, given the good correlation between the techniques, the detectors both accurately detected regions of increased ^{18}F-FDG uptake, although to a different extent.

Other limitations of the study are the relatively few numbers of included patients and the fact that there is no comparison of radiological readings to pathological analysis of the surgical specimens (pTNM). There was an initial intent to include pTNM in the analysis; however, all patients

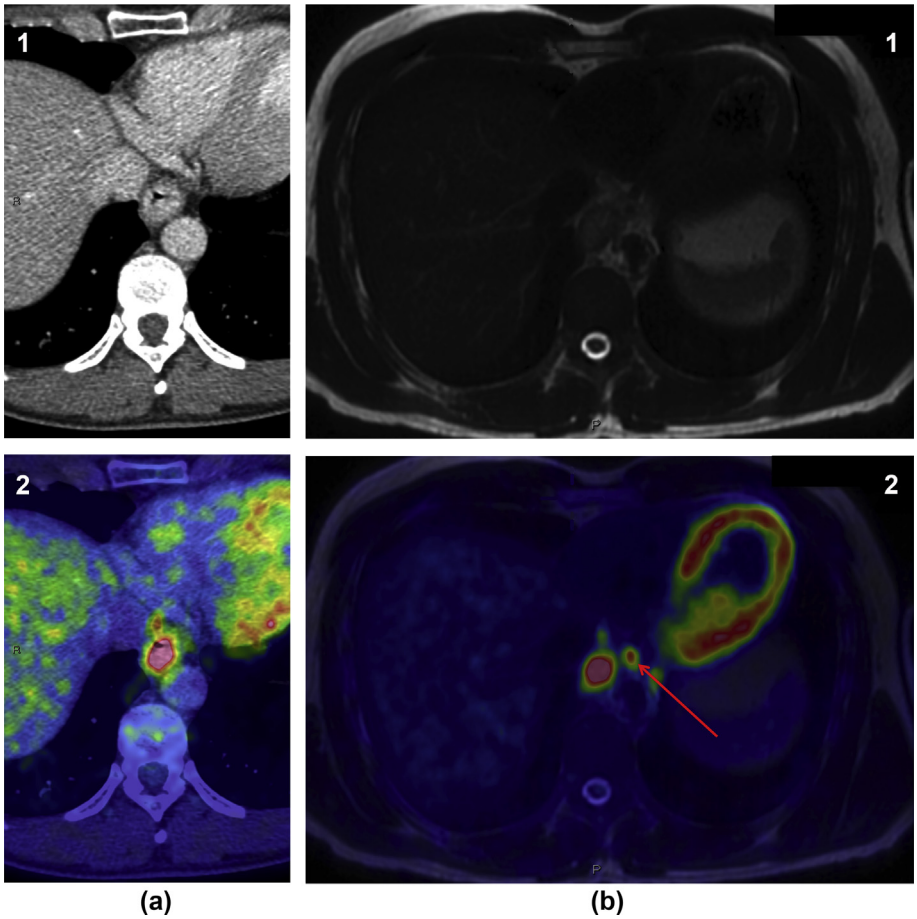

Figure 3 ^{18}F-FDG-PET/CT and ^{18}F-FDG-PET/MRI in a patient with distal oesophageal cancer, where PET/MRI detects a suspected tumour-positive lymph node (arrow) that was not detected with PET/CT. (a1) CT image, (a2) PET/CT fusion image, (b1) MRI image, and (b2) PET/MRI fusion image.

that underwent surgery received nCRT, with a well-known downstaging effect, and the rest were staged as having metastatic disease and so did not undergo surgical resection. The above facts would have made comparison of cTNM to pTNM problematic at best and for a meaningful comparison in this aspect, a second set of examinations would have had to be undertaken after nCRT.

In conclusion, in this prospective study with comparisons of blinded PET/MRI and PET/CT readings, in the preoperative staging of patients with oesophageal and GEJ cancers, PET/MRI was found to be both safe and feasible. Substantial agreements and correlations between the two techniques regarding tumour characteristics, SUV_{max} values, and the number of detected positive lymph nodes were seen; however, the amount of suspected positive lymph nodes was higher with PET/MRI. There was only fair agreement between PET/MRI and PET/CT in the assessment of T-stage owing to the fact that T-stage was assessed higher with PET/CT in 6/16 patients. There was excellent agreement in assessment of N-stage and M-stage.

Ongoing studies evaluating the prospect of active surveillance after nCRT rely heavily on the correct identification of true complete responders as well as differentiation of the patients who are not. These strategies must include reliable diagnostics to early identify signs of disease progression or recurrence. PET/MRI could very well be a suitable radiological technique for determining response to neoadjuvant treatment, identifying complete responders as well as providing a lower radiation dose option than PET/CT for surveillance at narrow intervals.

Conflict of interest

Author HA is medical advisor to Antaros Medical Corporation and author TB is medical advisor to Carestream Health. The above companies had no role in the collection, analysis or interpretation of data in this study. All other authors declare no conflicts of interest.

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