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SHORT COMMUNICATION

DWI-MRI vs CT in gastric MALT lymphoma—preliminary results in 19 patients

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Objective: To assess the diagnostic performance of [^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography/CT [^{18}F] FDG-PET/CT] compared to diffusion-weighted imaging (DWI)-MRI of lesion detection in patients with non-FDG avid gastric mucosa-associated lymphoid tissue (MALT) lymphoma.

Methods: 19 patients with histologically proven gastric MALT lymphoma were included in this prospective Institutional Review Board-approved study. Patients underwent [^{18}F]-FDG-PET/CT and consecutive MRI/DWI. Images were evaluated for the presence of gastric lesions in two anatomically defined groups (region 1: cardia, body, fundus; region 2: antrum, pyloric region) by two senior board-certified radiologists, in an

observer-blinded manner. Overall accuracy relative to the reference standard (histology obtained by biopsy) was calculated for each reader and a consensus rating.

Results: We found a statistically significant higher accuracy of lesion detection for lesions in region 1 ($p = 0.030$) and 2 ($p = 0.070$) for DWI-MRI (100%/78.9%) than for CT (68.4%/42.1%).

Conclusion: DWI-MRI seems to be superior accurate to CT for lesion detection in non-FDG avid gastric MALT lymphoma.

Advances in knowledge: DWI-MRI seems to be an alternative reliable imaging method for locoregional disease evaluation of non-FDG avid gastric MALT lymphoma.

INTRODUCTION

About 7% of all non-Hodgkin lymphoma cases are of the extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) type, of which about a third presents as primary gastric lymphoma.¹ Mandatory work-up and initial staging procedures include the patients' history and physical examinations together with histopathology obtained by esophagogastroduodenoscopy and multiple biopsies of each region of the stomach, including a panel of immunohistochemistry. The final diagnosis is made by an expert hematopathologist according to the World Health Organization criteria for hematological malignancies.^{2,3}

According to the Lugano classification, which is in widespread use and contains recommendations for diagnostic imaging of lymphomas, [^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography/CT [^{18}F]FDG-PET/CT] is the standard imaging technique for staging and treatment response assessment of the vast majority of lymphomas due to their high glucose consumption.⁴ MALT lymphoma,

however, is more complex in that regard, and a substantial variability in terms of FDG avidity has been reported: while MALT lymphomas of the head and neck are frequently FDG avid, gastric MALT lymphoma frequently is not.⁵ Because the value of [^{18}F]FDG-PET for MALT lymphoma patients remains subject to debate,^{1,6} the Lugano classification currently recommends contrast-enhanced CT (CE-CT) as the standard imaging test for MALT lymphoma, chiefly because CT is widely available, and no better imaging test has been established so far.⁴ However, recent evidence suggests that MRI, in particular with the addition diffusion-weighted imaging (DWI) which indirectly reflects cell density,⁷ may be useful for the assessment of lymphomas, and thus, also for the locoregional detection of MALT lymphoma.

Based on this assumption, it was the aim of our preliminary study to assess whether DWI-MRI is superior to CE-CT for detection of gastric MALT lymphoma, particularly with

regard to the assignment of the lesion to the correct anatomical segment of the stomach.

METHODS AND MATERIALS

Patients

This study included 19 patients with histologically proven gastric MALT lymphoma who were referred to the Department of Radiology and Nuclear Medicine of the local tertiary care center for staging and follow-up by [^{18}F]FDG-PET/CT and either whole-body DWI-MRI, in the course of a prospective Institutional Review Board-approved trial. The histological diagnosis of MALT lymphoma was based on tissue samples obtained from biopsies, according to the current WHO criteria of hematological and lymphoid malignancies. Patients who gave written, informed consent underwent [^{18}F]FDG-PET/CT and whole-body DWI-MRI, with a maximum of 10 days between the two examinations. Pregnancy, general contraindications to MRI (e.g. claustrophobia, metal or non-MRI conditional implants) and a known adverse reaction to ionized contrast media or any therapeutic intervention between PET/CT and DWI-MRI served as exclusion criteria.

Imaging protocols

[^{18}F]FDG-PET/CT was performed with a fully diagnostic, venous-phase CE-CT, which was also used for PET attenuation correction, covering the anatomy from the superior orbital rim to the upper thigh, using a 64-row multidetector hybrid PET/CT device (Biograph TruePoint 64; Siemens, Erlangen, Germany). CE-CT was obtained after the i.v. injection of 100 ml of a tri-iodinated, non-ionic contrast medium at a rate of 2 ml s^{-1} ; a tube current of 120 mA; a tube voltage of 230 kV; a collimation of $24 \times 1.2\text{ mm}$; a 3 mm slice thickness with a 2 mm increment; and a 512×512 matrix.

Whole-body MRI was performed on a 3-Tesla system (TrioTIM; Siemens, Erlangen, Germany), equipped with a phased array body coil. A single-shot, echo-planar imaging-based, spectral adiabatic inversion recovery-based DWI sequence was obtained during free-breathing, with b -values of 50 and 1000, a repetition time/echo time of 5100/73 ms; five averages; a 192×115 matrix; and a 5 mm slice thickness with no gap. Apparent diffusion coefficient (ADC) maps were calculated, and a T_1 -weighted turbo spin-echo or, in case of breathing difficulties, a fast gradient-echo sequence was obtained for anatomical and morphological correlation.

Image analysis, reference standard, and statistical analysis

Two senior board-certified radiologists specializing in oncological imaging reviewed all CE-CT and DWI-MRI images in a randomized fashion, and blinded to the clinical information, as well as the [^{18}F]FDG-PET data. Images were first evaluated separately by the two readers, followed by a consensus evaluation. The time interval between the evaluation of CE-CT and DWI-MRI (DWI with ADC maps and T_1 -weighted MRI) was 4 weeks. In 14 of 19 patients both examinations were performed on the same day whereas in 5 patients there was a time interval between FDG PET/CT and MRI of a mean of 14.4 days resulting

in overall time interval between examinations of a mean of 3.8 days. Detected lesions were recorded according to their anatomical locations. For statistical evaluation findings were subdivided into two anatomically defined groups (region 1: cardia, body, fundus; region 2: antrum, pyloric region). A maximum of one lesion per anatomical region was taken into subsequent evaluation. The accuracy rate was first calculated independently for two raters, and subsequently for the unblinded consensus evaluation.

Maximum and mean standardized uptake values (SUV_{max} and SUV_{mean}) were measured on [^{18}F]FDG-PET based on isocontour volumes of interest that included all voxels above 41% of the SUV_{max} of the maximum width of wall thickening and in the liver parenchyma, and were constructed using the Syngo MultiModality Workplace environment (Siemens, Erlangen, Germany). Similarly, the mean ADC [ADC_{mean} and min, ($\times 10^{-6}\text{ mm}^2\text{ s}^{-1}$)] of respective lesion were measured on ADC maps, using the interactive level-set method of the MIPAV 7.2.0 software package (Center for Information Technology, NIH, Bethesda, MD).

Pathohistological data obtained from biopsies of each anatomical region of the stomach for each included patient served as the reference standard. McNemar's test was performed to compare accuracy rates on CE-CT and DWI-MRI for each initially-defined anatomical region. A p value equal or below 5% was considered to indicate significant results. Due to the small sample size no multiplicity corrections were performed in order to avoid an increasing error of the second type.

All statistical analyses were performed using IBM SPSS Statistics (v. 24.0, Armonk, NY).

RESULTS

19 patients (7 males and 12 females; mean age, 62.9 ± 14.2 years) with gastric MALT lymphoma fulfilled our inclusion criteria. The vast majority (17/19 patients) of our patients were referred for pre-therapeutic staging by hybrid imaging to our tertiary care hospital, whereas only two patients were referred to imaging for restaging. According to the biopsy results which served as our reference standard, a total of 34 lesions (in 19 patients and 95 histological specimens) were positive for MALT lymphoma in 5 anatomical sites (Table 1).

Table 1. Primary tumor characteristics

	<i>n</i>	%
Region 1		
Cardia	2	5.9
Fundus	9	26.5
Body	13	38.2
Region 2		
Pyloric antrum	5	14.7
Pylorus/proximal duodenum	5	14.7
Total	34	100.0

Localization of primary tumor in the stomach (baseline positive biopsy results $n:95$).

Table 2. Quantitative PET and DWI data for each region of the stomach and the liver parenchyma

Pat. Nr.	Region 1				Region 2				Liver	
	SUV _{max}	SUV _{mean}	ADC _{min}	ADC _{mean}	SUV _{max}	SUV _{mean}	ADC _{min}	ADC _{mean}	SUV _{max}	SUV _{mean}
1	2,7	2,1	1188	1566	2,1	1,6	973	1564	2,7	2,3
2	2,5	1,7	1149	1574	2,2	1,3	717	1057	3	2,3
3	2,4	1,7	1645	1896	3,2	1,2	1137	1416	3,4	2,7
4	4,1	2,7	393	828	2,1	1,1	703	1241	3,7	2,6
5	5,8	3,2	790	1082	6,9	2,9	639	1006	2,9	1,9
6	3,8	2,5	1179	1538	2	0,9	1055	1302	3,8	2,4
7	2,8	1,9	1480	1820	1,9	1,3	1311	1602	3,9	2,8
8	2,9	2,4	1159	1645	1,8	1,1	1085	1537	3,1	2,1
9	11	5,9	598	776	4,6	2	1015	1324	2,7	1,9
10	3,8	2,9	896	1551	2,4	1,2	1268	1861	4,3	2,8
11	6,7	3,4	696	1043	3,2	2,1	1002	1444	3,6	2,3
12	5	3	1609	1887	3,3	2,5	1079	1455	4,4	2,9
13	2,9	1,9	893	1323	2	1,1	1093	1415	4,6	2,8
14	5,3	3,8	614	742	2,4	1,3	1097	1600	3,7	2,5
15	3,6	2,7	1158	1501	2,8	2,1	696	1230	4,5	3,1
16	7,1	5	387	658	3,6	2,2	749	1310	3,8	2,6
17	4,7	2,5	577	896	3,2	1,5	665	1282	4,4	2,3
18	2,7	2	m	m	2,1	1,8	m	m	2,7	2,1
19	2,7	2,1	1095	1414	4,2	2,7	1056	1598	4,2	2,8

[ADC ($\times 10^{-6}$ mm² s⁻¹), apparent diffusion coefficient; DWI, diffusion-weighted imaging; m: data missing; SUV_{max}, maximum standardized uptake values; PET, positron emission tomography; SUV_{mean}, mean standardized uptake values.

Figure 1. Flowchart of MALT lymphoma patients recruitment and general methodology. DWI, diffusion-weighted imaging; MALT, mucosa-associated lymphoid tissue.

Reader 1 achieved a significantly higher patient-based accuracy rate on DWI-MRI [17/19 patients (89.4%)] than on CE-CT [10/19 patients (52.6%)] in region 1 ($p = 0.0160$), whereas in region 2, his accuracy rate was also clearly higher for DWI-MRI, [12/19 (63.2%)] than for CE-CT [6/19 patients (31.4%)], but did not reach statistical significance ($p = 0.508$). Similarly, reader 2 achieved a significantly higher patient-based accuracy rate on DWI-MRI [19/19 patients (100%)] than on CE-CT [12/19 patients (63.2%)] in region 1 ($p = 0.016$), and also a significantly higher patient-based accuracy rate on DWI-MRI [15/19 patients (78.9%)] than on CE-CT [8/19 patients (42.1%)] in region 2 ($p = 0.070$).

Finally, in the consensus reading, DWI-MRI also showed clearly higher accuracy rates than CE-CT in both anatomical regions considered, with patient-based accuracy rates of 19/19 (100%) and 13/19 (68.4%) in region 1 ($p = 0.0310$), and 15/19 (78.9%) and 8/19 (42.1%) in region 2 ($p = 0.070$), respectively.

In region 1 mean $\pm$ standard deviation for SUV_{max} was 4.3 ± 2.2 , for SUV_{mean} 2.8 ± 1.1 and ADC_{mean} and min was 1318.9 ± 413 and 972.6 ± 386.9 ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). Region 2 showed for SUV_{max} values of 2.9 ± 1.3 , for SUV_{mean} 1.7 ± 0.6 and ADC_{mean} and min

was 1402.4 ± 209.8 and 963.3 ± 212.6 ($\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$). 6 out of 19 patients showed pathological focal or diffuse gastric glucose metabolism.

Quantitative PET data as well as ADC values on a per-patient basis can be found in Table 2.

Flow of participants throughout the study is depicted in a STARD diagram (Figure 1).

DISCUSSION

The results of our small-sized study clearly suggest that DWI-MRI may be superior to the currently recommended imaging technique, CE-CT. CE-CT missed approximately 40–50% of all lesions in the present study, whereas MRI with DWI had an overall accuracy rate close to 90%. Notably, the difference between the two readers in terms of accuracy rates was also more pronounced in CE-CT than on DWI-MRI.

Gastric malignancies, and MALT lymphoma in particular, can be difficult to evaluate with anatomical cross-sectional imaging techniques, such as CT.⁸ Detection of gastric MALT lymphoma is particularly challenging due to its morphological and

Figure 2. A 52-year-old female patient with FDG-avid MALT lymphoma in the body of the stomach. PET/CT shows wall thickening on axial plane CT images (A) and corresponding pathological FDG uptake on the fusion images (B). On DWI b800 (C) focal diffusion-restriction (yellow arrow), and corresponding low ADC signal (D) complements diagnosis. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FDG, fluoro-2-deoxy-D-glucose; MALT, mucosa-associated lymphoid tissue; PET/CT, positron emission tomography/CT.

dimensional variability. Furthermore, these tumors show highly variable FDG avidity which can also be masked by elevated glucose metabolism due to physiological contraction or inflammatory changes. Albano et al⁵ recently reported published data from 2005 to 2016 regarding the FDG avidity in gastric MALT lymphoma ranging from as low as 8%⁹ up to 86%,¹⁰ whereas they found a percentage 52% in their own evaluation, which is in the range of our own and other data available.^{11,12} Albano et al⁵ pointed out that the variability of FDG avidity depends on many factors, such as morphology, dimensions, Ann Arbor stage, and the Ki67 proliferation index (Figures 2 and 3). In addition, limiting technical factors in PET data acquisition parameters, including image reconstruction and calibration, as well as the time point for image acquisition (*i.e.* the post-injection delay) have to be considered.¹³

Given the above described uncertainty in FDG avidity in gastric MALT lymphoma, the current Lugano classification recommends the use of CE-CT in non-FDG-avid lymphoma subtypes for staging and treatment response assessment. CT, even with contrast enhancement, frequently shows unspecific stomach wall thickening, which can be difficult to interpret unless clearly asymmetric, and even then, detection of neoplastic lesions depends on factors such as distension of the organ. The latter factor is also the reason why the so-called hydro-CT technique has been proposed for gastric tumors;¹⁴ however, this technique is not considered clinical standard, and even when it is used, it has been shown to be clearly inferior to endosonography for detection of MALT lymphoma.⁸ In our institution endosonography is not routinely performed in MALT lymphoma patients, where imaging and endoscopic biopsies are the standard work-up.

Figure 3. A 70-year-old female patient with FDG-non-avid MALT lymphoma in the body of the stomach. PET/CT does not show any clearly detectable abnormalities on axial plane CT images (A) or pathological FDG uptake on the corresponding fusion images (B). On DWI b800 (C) focal diffusion-restriction (arrow) and corresponding low ADC signal (D) is indicating malignancy. ADC, apparent diffusion coefficient; DWI, diffusion-weighted imaging; FDG, fluoro-2-deoxy-D-glucose; MALT, mucosa-associated lymphoid tissue, PET/CT, .

However, comparing endosonography with CT and MRI is highly desirable for future studies.

MRI, including advanced pulse sequences such as DWI, is, today, almost as widely available as CT. While the examination time for whole-body MRI with DWI exceeds that of CT, it is free of ionizing radiation, which may be a relevant factor for patients with incurable NHL subtypes that require life-long follow-up imaging. Our results confirm our assumption that locoregional accuracy rates may be possibly higher for MRI than for CT, even when the MR protocol consists only of two unenhanced pulse sequences (*i.e.* DWI and a T_1 -weighted sequence), which eliminates the small but recognized risk of contrast media reactions. Our results—which demonstrate higher accuracy rates for DWI-MRI than for CE-CT (up to 100% vs up to 68%, respectively)—are in good accordance with previous studies that reported a superiority of DWI-MRI over [^{18}F]FDG-PET/CT for staging of lymphomas with variable FDG avidity (MALT lymphoma and small-cell lymphocytic lymphoma/chronic lymphocytic leukemia).¹⁵ Also, our evaluation of ADC values of the gastric wall showed values that are in line with most lymphoma subtypes but may be overall a little higher due to morphology of the gastric mucosa and adjacent gastric fluids.

Our preliminary study has limitations, the most obvious of which being the small sample size that did not allow further statistical evaluation regarding the performances of DWI-MRI and CE-CT, nor did it allow a further subdivision of the stomach in terms of anatomy, or a division into tumor stages. Furthermore, more than two readers would have been desirable to enable a better estimation of interobserver variability.

In conclusion, DWI-MRI seems to be a reliable imaging method for locoregional disease evaluation of MALT lymphoma that may possibly be superior to the currently standard technique, CE-CT.

Nevertheless, larger cohorts on this matter are needed to determine whether DWI-MRI should replace CE-CT for imaging of MALT lymphomas.

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