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ONCOLOGY

Diagnosis of diffuse spleen involvement in haematological malignancies using a spleen-to-liver attenuation ratio on contrast-enhanced CT images

Christian Philipp Reinert[1] · Clemens Hinterleitner[2] · Jan Fritz[3] · Konstantin Nikolaou[1] · Marius Horger[1]

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Abstract

Objectives We aimed to test the hypothesis that the spleen-to-liver-attenuation ratio on portal-venous enhancement phase CT images can identify diffuse splenic infiltration in subjects with lymphoma.

Methods A database search yielded 70 subjects with malignant haematological diseases who underwent contrast-enhanced CT (CECT) between December 2010 and March 2018. Additionally, consecutive control subjects were evaluated. We compared the splenic volume, splenic attenuation, spleen-to-liver, spleen-to-aorta and spleen-to-musculature ratios on portal-venous phase CECT images, pre- to post-treatment and between the different lymphoma entities. The standard of reference for splenic involvement was normalisation of the spleen volume following chemotherapy or normalisation of FDG-uptake.

Results In subjects with diffuse splenic involvement, the spleen attenuation was significantly lower before treatment (93.48 HU) compared to controls (112.39 HU; $p < .01$) and after successful treatment (113.39 HU; $p < .01$). The spleen-to-liver attenuation ratio significantly increased after treatment ($p < .001$) and proved significantly lower at baseline when compared to control subjects ($p < .01$). The spleen volume significantly decreased after successful treatment (from 586.14.87 cm^3 to 284.90 cm^3; $p < .001$). Spleen-to-liver ratio significantly increased in lymphoma patients after therapy, inversely correlating with the decline in FDG-uptake (n=10) even in patients with normal-sized spleens (2/10), staying unchanged at follow-up. The outcome variables were not significantly different between the lymphoma subtypes.

Conclusions We suggest the additional use of spleen-to-liver attenuation ratio to splenic volume alone for detection of diffuse splenic infiltration in subjects with lymphoma. The course of spleen-to-liver attenuation ratio inversely correlated with that of FDG-uptake in a subgroup of patients working accurately in normal-sized diffusely involved spleens.

Key Points

- *Involvement of the spleen is frequent in haematological malignancies and is important for staging and appropriate treatment.*
- *Diffuse splenic infiltration often results in only homogeneous splenomegaly without a focal lesion, but even no or only minimal increase in splenic volume is possible. In these cases diagnosis of spleen involvement is a challenge for the radiologist.*
- *Our data support the use of the spleen-to-liver attenuation ratio in addition to size measurements for the detection of diffuse splenic infiltration in subjects with lymphoma.*

Keywords Lymphoma · Splenomegaly · Haematological diseases · Follow-up studies

C. Hinterleitner and M. Horger contributed equally to this work.

✉ Christian Philipp Reinert
christian.reinert@med.uni-tuebingen.de

[1] Department of Diagnostic and Interventional Radiology, University Hospital Tuebingen, Hoppe-Seyler-Str.3, 72076 Tuebingen, Germany

[2] Department of Internal Medicine II, University Hospital Tuebingen, Otfried-Müller-Str.10, 72076 Tuebingen, Germany

[3] Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, 601 N. Caroline Street, JHOC 3140A, Baltimore, MD 21287, USA

Abbreviations

CLL Chronic lymphoid leukaemia
GCSF Granulocyte colony stimulating factors
ROI Region of interest

Introduction

Involvement of the spleen is frequent in haematological malignancies and is important for staging and adequate treatment [1, 2]. Different computed tomography (CT) patterns of spleen involvement have been described [3]. While focal nodular (1–10 cm) and large solitary masses are often less of a challenge for the radiologist to diagnose, diffuse infiltration often results in only homogeneous splenomegaly without a focal lesion and may be more difficult to diagnose. The diagnosis may be particularly difficult in cases where the infiltration causes no or only minimal increase in splenic volume [4]. CT is frequently used for the diagnosis and monitoring of haematological and oncological diseases, and therefore tools that can help to improve the accuracy of identifying splenic infiltration are desirable.

FDG-PET is being increasingly used for staging and also for response monitoring, but accuracies for splenic involvement are influenced by the lymphoma subtype and treatment effects on the glucose metabolism of the spleen [5–7]. Low-grade lymphomas and leukaemias show no substantial FDG-uptake and cannot be detected reliably in the spleen, whereas treatment regimens including granulocyte colony stimulating factors (GCSF) temporarily increase glucose metabolism [8, 9]. Moreover, in many leukaemias, such as chronic lymphatic and hairy cell leukaemia, splenomegaly reflects involvement, but the FDG uptake is minimal [10]. The use of ancillary (e.g. T1w- and T2w-signal intensity) MR-image findings has been proposed for the diagnosis of splenic involvement due to their higher soft tissue contrast; however, the complementary use of quantitative measurement techniques (dynamic contrast-enhanced and diffusion-weighted imaging) proved superior for diagnosis [11]. The use of iron particle contrast agents that accumulate in normal reticuloendothelial cells but not in tumour cells was found to be beneficial [12].

Semiquantitative contrast-enhanced CT may be used to identify diffuse splenic involvement, which is based on expected differences in attenuation between normal and infiltrated splenic parenchyma. The spleen is mainly built of red pulp, which consists of vascular flow channels with different velocities, and harbours a large blood volume. Lymphoma and leukaemia infiltrate the white pulp, which then compresses upon the red pulp and vascular channels [13–15]. This effect subsequently results in relatively less contrast containing blood volume in the spleen and overall less attenuation, which could be quantified.

The purpose of our study was to test the hypothesis that the spleen-to-liver-attenuation ratio on portal-venous phase CT images at baseline staging can identify diffuse splenic infiltration in subjects with lymphoma.

Material and methods

Patient characteristics

Our local institutional ethical review committee approved this retrospective study and waived the informed consent requirement (Project Number: 620/2017BO2). We included 70 consecutive subjects [33 male; mean age 53 years (20–82 years)] with haematological malignancies, who underwent contrast-enhanced CT for staging (before treatment) and monitoring of treatment response at our institution between December 2010 and March 2018.

All subjects had malignant haematological diseases with diffuse spleen involvement, including Hodgkin's lymphoma (19/70, 27.1%) (7 × stage IV; 5 × stage III; 3 × stage IIB and 4 × stage IIA), follicular lymphoma (9/70, 12.9%) (7 × stage IV and 2 × stage II), diffuse large B-cell lymphoma (18/70, 25.7%) (9 × stage IV; 7 × stage III; 2 × stage IIA), T-cell lymphoma (5/70, 7.1%) (2 × stage IIB and 3 × stage IV), mantle cell lymphoma (4/70, 5.7%) (2 × stage IV and 2 × stage III), Burkitt's lymphoma (1/70, 2.9%), grey zone lymphoma (1/70, 2.9%), chronic lymphoid leukemia (CLL) (10/70, 14.3%) and acute myeloid leukemia (1/70, 2.9%). Twenty-four of 70 patients had FDG/PET-CT studies, 10/70 patients underwent FDG/PET-CT both at baseline and at follow-up examination.

Subjects with hepatic involvement by lymphoma, liver cirrhosis with portal hypertension or fatty liver disease were excluded. To exclude steatotic liver diseases, liver attenuation was quantified in all patients on non-contrast-enhanced CT-image data. Subjects with liver attenuation higher than 46 HU were considered to have at most mild liver fat content (≤ 9.9%) and were accepted for evaluation [16].

As a control group, we evaluated contrast-enhanced CT examinations of 60 randomly selected subjects, who had no known history of malignant, haematological, hepatic or autoimmune disease, and underwent contrast-enhanced CT with the same protocol.

CT imaging

All CT examinations in the study were performed with the same protocol. Contrast-enhanced CT studies were obtained on MDCT scanners (Somatom Definition AS+ and/or Definition Flash, Siemens Healthineers, Erlangen, Germany) following the intravenous administration of 120 ml non-ionic iodinated contrast material (370 mg/ml iopromide [Ultravist,

Bayer Vital]), which is the in-house standard for oncological contrast-enhance CT (CECT) examinations. The CECT images were all obtained in the portal-venous phase.

Image evaluation

On baseline studies, the mean attenuation of the spleen and liver parenchyma was measured manually in Hounsfield units (HU) by one image reader by drawing regions of interest (ROIs) in the splenic and hepatic parenchyma, thereby excluding parenchymal vessels of the hilar region (Fig. 1). The diameter of the ROIs was chosen as large as possible, but had to be individually adapted to different organ sizes. The spleen-to-liver attenuation ratios were calculated for each patient and examination. In order to correct for potentially existing differences in the circulation time among the subjects we also set ROIs in the abdominal aorta 2 cm below the diaphragm calculating spleen-to-aorta ratios. In addition, we also measured the attenuation of muscle tissue in the erector spinae musculature in each subject calculating spleen-to-muscle ratios. On follow-up studies, the measurements in the splenic parenchyma, liver, aorta and muscle tissue were performed in similar locations. Subsequently, the spleen volume was calculated by the product of the maximum craniocaudal, transverse and anteroposterior diameter and multiplied by 0.523, using an ellipsoid formula.

In addition, we calculated attenuation ratios of contrast-enhanced CT exams that were obtained before and after treatment, between different lymphoma subtypes.

Standard of reference

The spleen was considered involved at baseline either if there was ≥ 20% reduction of the splenic volume or normalisation after chemotherapy, or if there was normalisation of the glucose-uptake at 18F-FDG-PET (n=10) after chemotherapy (down to a Deauville score 1-3 from an initial 4-5) in cases without spleen enlargement at baseline [16, 17].

The liver was considered non-involved if it was normal-sized (midclavicular line average 10–12.5 cm in craniocaudal length, normal-shaped (contours, no rounding of the hepatic inferior border, normal relation between the lobes), patient had no symptoms related to the liver and the liver function tests were within normal ranges including unchanged size after successful lymphoma treatment. Twenty-four patients also had normal liver uptake on FDG-PET.

Statistical analysis

Statistical analyses were performed with SPSS Statistics (IBM). The Wilcoxon rank-sum test for independent variables was used to analyse differences between HU attenuation ratios. The accuracy of spleen HU attenuations was evaluated by examining the area under the receiver-operator characteristic (AUC ROC) curve using a confidence interval (CI) of 95%. Continuous variables in dependent samples were analysed with Friedman's ANOVA. All tests were considered statistically significant for p-values < 0.05.

Results

In subjects with malignant haematological diseases and splenic involvement, the median spleen-to-liver attenuation ratio was 0.94 (95% CI 0.91–0.95), whereas in the control group it was 0.974 (95% CI 0.96–1.01) ($p < .01$) (Fig. 2). The attenuation of the spleen before treatment (median, 93.50 HU; 95% CI 89.60–97.38) was significantly lower than after treatment

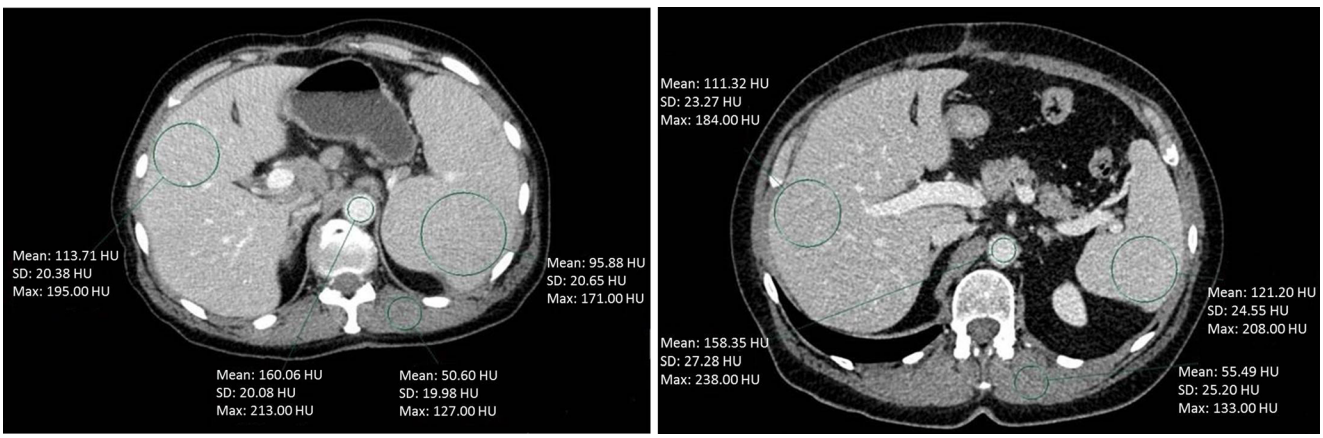

Fig. 1 Placement of regions of interest (ROIs) in the spleen and liver parenchyma for assessment of organ mean attenuation (Hounsfield units, HU) before (**a**) and after (**b**) treatment. The hand-drawn ROIs were set apart from larger parenchymal vessels in the vicinity of the hilar region of the spleen and liver. To correct for differences in circulation time throughout our patient cohort, we additionally measured the attenuation in the abdominal aorta and the paravertebral muscle tissue (erector spinae musculature) generating corresponding ratios

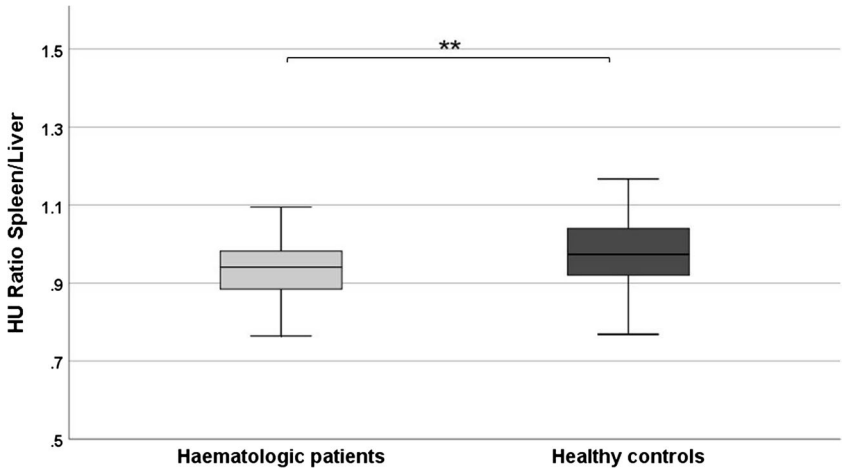

Fig. 2 Median spleen-to-liver attenuation ratios in lymphoma patients (Hounsfield units, HU spleen/liver ratio: 0.94; 95% CI 0.91–0.95) vs. healthy control patients (HU spleen/liver ratio: 0.97; 95% CI 0.96–1.01; ** = $p < .01$

(median, 116.39 HU; 95% CI 109.66–117.11; $p < .01$). Similarly, the spleen-to-liver attenuation ratios were significantly lower before treatment when compared to after treatment (median, 0.94; 95% CI 0.91–0.95 to 1.11, 95% CI 1.13–1.22; $p < .01$) (Fig. 3).

The spleen-to-aorta attenuation ratio before treatment was significantly lower (median, 0.70; 95% CI 0.68–0.73) compared to that after treatment (median, 0.76; 95% CI 0.73–0.78, $p < .01$). The spleen-to-muscle attenuation ratio showed a comparable increase after treatment (median, 1.67; 95% CI 1.59–1.72 to median 1.95; 95% CI 1.90–2.10, $p < .01$) (Fig. 4).

Mean liver attenuation on unenhanced CT at baseline was 67.9 HU.

The spleen-to-liver HU attenuation ratio showed an excellent predictive validity for splenic involvement with a ROC AUC value of 0.95 (95% CI 0.92–0.99) using a cut-off value of 0.99 (Fig. 5).

All 70 haematological subjects with diffuse splenic involvement either showed a significant reduction of the spleen volume (68/70, 97.14%) after chemotherapy or normalisation of diffuse FDG-uptake in 18F-FDG-PET-CT (10/70, 14.29%). Ten of 70 lymphoma patients underwent FDG-PET in the baseline setting and at end-of-treatment. All of them showed initially a Deauville 4 or 5 score in the diffusely involved spleen, which declined after treatment to a score of 1–3. Five of ten FDG-PET-positive spleens were normal-sized at baseline. Eight of 10 subjects (13.3 %) showed both a significant reduction of the spleen volume and a significant reduction of diffuse FDG-uptake in 18F-FDG-PET-CT, whereas in two patients the volume did not change significantly at end-of-treatment (1% in one subject and 9% in the other patient). The mean spleen volume in the entire cohort decreased from 586.14 cm^3 (SD 446.92 cm^3) before treatment to 284.90 cm^3 (SD 144.69 cm^3, $p < .01$) after treatment (Fig. 6a). The reduction of the spleen volume correlated well with a decrease of the splenic tissue attenuation (r=.67 p=.02) (Fig. 6b). In patients with normal-sized spleens before treatment and pathologically increased FDG-uptake (Deauville score 4–5) the spleen-to-liver attenuation ratio normalised inversely correlating with a decrease in FDG-uptake. The median spleen-to-aorta ratio in the FDG-PET-positive subjects was 0.67 (95%

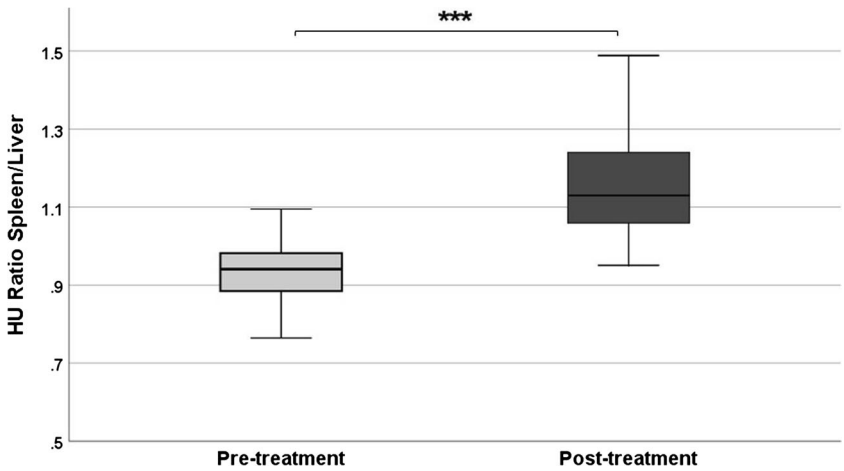

Fig. 3 Median pre-to-post-treatment spleen-to-liver attenuation ratios (Hounsfield units, HU spleen/liver ratio pre-treatment: 0.94; 95% CI 0.91–0.95 vs. post-treatment: 1.11; 95% CI 1.13–1.22; *** = p<.001).

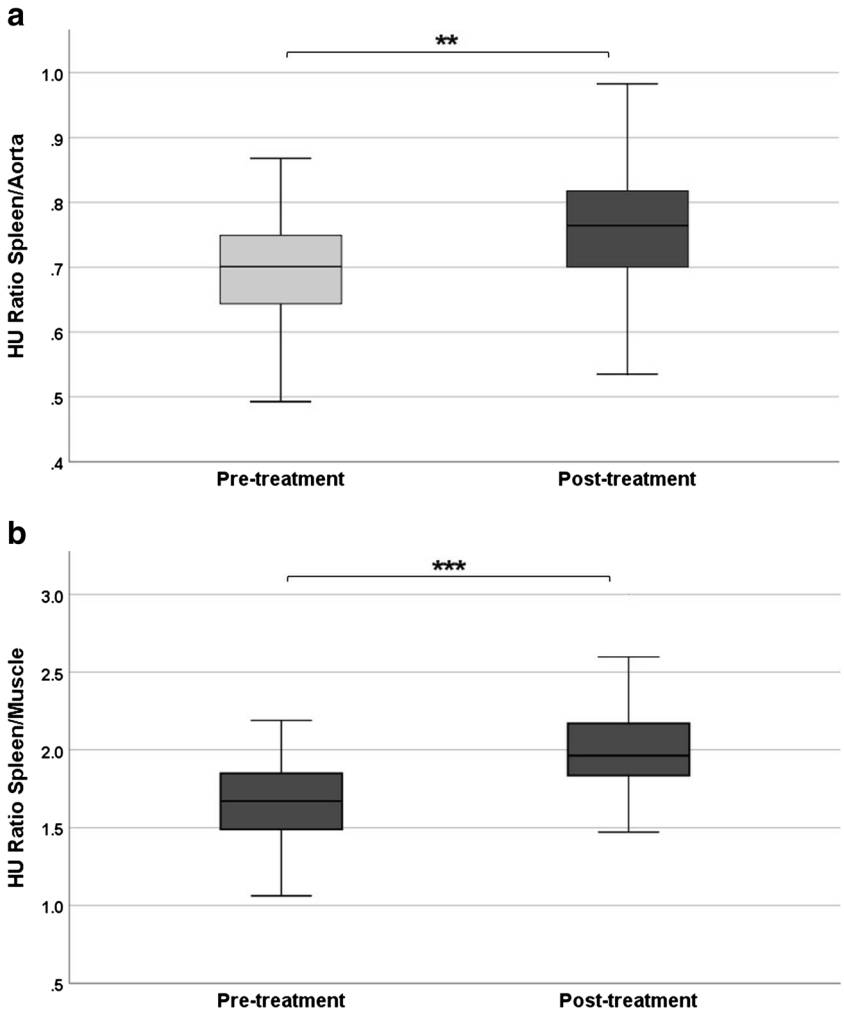

Fig. 4 (**a**) Median pre-treatment spleen-to-aorta attenuation ratio (Hounsfield units, HU spleen/aorta ratio: 0.70; 95% CI 0.68–0.73) vs. post-treatment attenuation ratio (HU spleen/aorta ratio: 0.76; 95% CI 0.73–0.78; ** = $p <$ .01). (**b**) Spleen-to-muscle attenuation ratio pre-treatment (HU spleen/muscle ratio: 1.67; 95% CI 1.59–1.72) to post-treatment (HU spleen/muscle ratio: 1.95; 95% CI 1.90–2.10; *** = $p < .001$) in lymphoma patients

CI 0.61–0.73) at baseline and increased to 0.76 (95% CI 0.71–0.81). In the subgroup of normal-sized (n=5) diffusely involved FDG-PET-positive spleens the median spleen-to-aorta ratio was 0.67 (95% CI 0.62–0.72) at baseline and 0.72 (95% CI 0.64–0.81) at end-of-treatment.

All subjects in the control group had normal-sized spleens (volume).

In subjects with lymphoma and diffusely involved spleen, the lymphoma subtype did not significantly influence the attenuation of the spleen parenchyma (p=.76). There was also no significant difference of the attenuation of the spleen before and after treatment between the lymphoma subtypes.

Discussion

Our results suggest the ability of spleen-to-liver ratios of portal-venous phase contrast-enhanced CT images to detect diffuse splenic involvement in subjects with malignant haematological diseases. Differences between the splenic and hepatic tissue attenuation were highly significant, with a sensitivity of 75% and a specificity of 73% for a cut-off value of 103.3 HU, and the spleen-to-liver attenuation ratio showed an excellent predictive validity with a calculated cut-off AUR ROC value of 0.99. In association, the spleen-to-liver ratio after treatment may also be helpful as there was an increase in spleen attenuation in subjects who achieved tumour remission that was similar to values in subjects with healthy spleens. The spleen-to-aorta and spleen-to-muscle attenuation ratios both confirmed results of direct spleen-to-liver attenuation ratios. In addition, the splenic tissue attenuation parameters correlated well with the spleen volume. The spleen-to-liver ratio also accurately worked in subjects presenting initially with normal-sized spleens, and in showing no change in volume after treatment confirmed by a decline in FDG-uptake at end-of-treatment. The results of our study may provide a simple but efficient means to detect splenic involvement in patients with malignant haematological diseases on CECT images.

Our motivation for this project was to enhance the currently challenging diagnostic ability of CECT for staging and response monitoring of subjects with malignant haematological

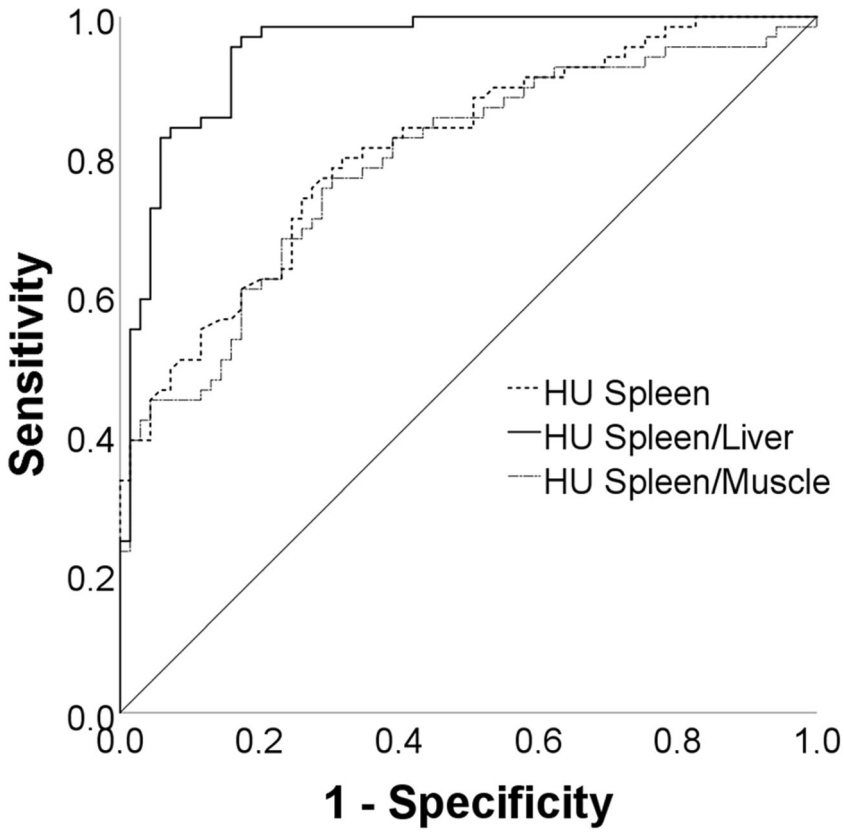

Fig. 5 Receiver-operating characteristic (ROC) curve using a confidence interval of 95%. The spleen-to-liver attenuation ratio showed a predictive validity for splenic involvement with a sensitivity of 0.97 and a specificity of 0.83 using a cut-off value of 0.97

disorders with a more accurate quantitative assessment of diffuse splenic involvement. Diffuse splenic infiltration is present in up to 40% of patients with Hodgkin's lymphoma and present in up to 80% of patients with non-Hodgkin's lymphoma [6, 18, 19]. Hodgkin's lymphoma in the spleen is usually diffuse, and only a small percentage of subjects present with nodular lesions that are larger than 1 cm in diameter [20]. Moreover, 30% of enlarged spleens of unknown origin are caused by lymphoma and in 35% the spleen is the only subdiaphragmatic location affected [19]. Splenic involvement may affect the overall staging and thus also the treatment strategy [21]. Diffuse splenic infiltration is also the most common pattern of infiltration in subjects with leukaemia [22]. While in leukaemia the diagnosis of diffuse splenic infiltration is expected in most cases, and therefore carries a lower clinical significance, we included these cases as a proof of principle. Some aggressive lymphomas, such as T-cell lymphoma of gamma-delta subtype, primarily affect the spleen and the liver causing hepatosplenomegaly without adenopathy, and are therefore even more difficult to diagnose [23].

Despite the increasing use of FDG-PET for staging lymphoma, limitations related to low levels of glucose metabolism in some lymphoma subtypes exist and availability of FDG-PET is still limited. Moreover, FDG-PET is often acquired together with CT simultaneously and thus our results can be used together [10]. While the focal

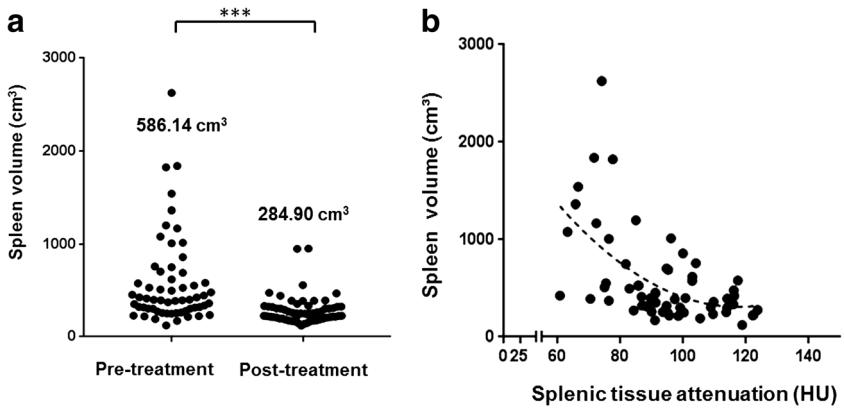

Fig. 6 Spleen volume of the involved group pre-treatment vs. post-treatment (*** = $p < .001$) (**a**), regression analysis (correlation curve) of splenic tissue attenuation and spleen volume (**b**)

involvement of the spleen is easier to detect on CECT, the detection of diffuse infiltration is challenging with CECT images, as indicated by reported sensitivities and specificities of 30–45% and 89–94%, respectively [6]. These data were derived solely from splenic size measurements and detection of focal infiltration. Another method used the obliteration effect of normal heterogeneous enhancement of the spleen in the arterial phase in conjunction with splenomegaly for detection of diffuse splenic lymphoma involvement [24].

The parenchymal attenuation of the spleen and liver vary depending on the contrast delay time. In the portal-venous phase, spleen attenuation is slightly higher than in the liver, because the dually supplied liver receives most of its blood supply through the portal vein. These temporal differences in peak enhancement can be used for quantifying spleen attenuation and related spleen-to-liver ratio. A previous study found that the attenuation values of the spleen are 5–10 HU lower than the liver; however, the contrast delay timing was not specified [25].

Our approach to use CECT for the detection of splenic involvement in lymphomas involving the spleen was also based on the assumption that within the spleen the white pulp would be affected first, leading to cell accumulation compression of the red pulp that consequently displaces the blood out of the sinusoids causing decreased splenic attenuation. This mechanism is expected to occur in normal-sized involved spleens due to the shift in the relationship between the red and the white pulp [13]. Thus, diffuse infiltration of the spleen is expected to lower the splenic tissue attenuation and thus impact the spleen-to-liver ratio. The main requirement for using this approach is a standardised CT-imaging protocol with a fixed delay time and contrast agent volume.

Our results compare favourably with previous reports that evaluated the role of CT for detection of splenic involvement, which did not differentiate between focal and diffuse splenic infiltration, and had lower accuracies compared to 18F-FDG-PET [3, 26, 27]. However, even studies utilising FDG-PET did not specifically differentiate between focal and diffuse splenic involvement, which is essential as focal infiltration is usually readily apparent irrespective of the imaging modality used [26].

Our study had limitations. First, there was no histological proof of splenic involvement. However, splenic tissue sampling is not frequently performed and thus our study set-up mirrors clinical practice. Second, in subjects with a normal-sized spleen and negative FDG-PET results, splenic involvement is not expected; however, it cannot be definitely excluded. Third, some immunological phenomena accompanying lymphoma could have affected the spleen size; however, the effects would have been expected to be small. Fourth, the use of spleen-to-liver attenuation ratios was performed only in subjects who were not suspected of hepatic involvement. Therefore, we excluded all cases with liver enlargement at staging or those with pathological liver laboratory data, which limits the application of our technique in patients with concomitant liver and spleen involvement.

In conclusion, our data support the use of the spleen-to-liver ratio, in addition to size measurements for the detection of diffuse splenic infiltration in subjects with lymphoma, working well even in cases with a normal-sized spleen at baseline.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Prof. Dr. Marius Horger.

Conflict of interest Jan Fritz received institutional research funds and speaker's honorarium from Siemens Healthcare USA and is a scientific advisor of Siemens Healthcare USA and Alexion Pharmaceuticals, Inc

Marius Horger received institutional research funds and speaker's honorarium from Siemens Healthineers Germany and General Electrics

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

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- case-control study
- performed at one institution

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