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# Chemokine Receptor PET/CT Provides Relevant Staging and Management Changes in Marginal Zone Lymphoma

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Because of gastral and extranodal manifestations, guideline-compatible diagnostic work-up of marginal zone lymphoma is challenging. We aimed to determine the diagnostic performance of C-X-C motif chemokine receptor 4 (CXCR4)-directed PET/CT compared with routine diagnostics, along with PET/CT-based retrospective changes in therapeutic management. The predictive potential of the PET signal was also investigated, and the number of patients eligible for CXCR4-directed radioligand therapy in a theranostic setting was determined. **Methods:** For this study, 100 marginal zone lymphoma patients underwent CXCR4-directed PET/CT. We compared staging results and treatment decisions from molecular imaging with respective results from guideline-compatible work-up (CT, esophagogastroduodenoscopy, and bone marrow-derived biopsy). Prognostic performance of the in vivo CXCR4 PET signal for progression-free survival (PFS) was evaluated (using log-rank test and Kaplan–Meier curves). **Results:** Relative to CT, CXCR4-directed imaging led to Ann Arbor (AA) staging changes for 27 of 100 patients (27.0%). Among those, clinically relevant upstaging from AA I or AA II to AA III or AA IV was observed for 23 patients (85.2%), along with respective changes in therapeutic management (escalation, 6/23 [26.1%]; deescalation, 17/23 [73.9%]). CXCR4 PET/CT yielded diagnostic accuracy of 94.0% relative to esophagogastroduodenoscopy and 76.8% relative to bone marrow-derived biopsy. An increased CXCR4 PET signal was linked to shorter PFS (707 d vs. median PFS not reached; hazard ratio, 3.18; 95% CI, 1.37–7.35;  $P = 0.01$ ). CXCR4-directed radioligand therapy would have been feasible for 18 of 100 patients (18.0%). **Conclusion:** Relative to CT, CXCR4-directed PET/CT led to AA changes for 27 of 100 patients. Chemokine receptor PET/CT may improve current diagnostic algorithms and influence management relative to CT alone, potentially obviating some biopsies.

**Key Words:** marginal zone lymphoma; mucosa-associated lymphoid tissue lymphoma; PET/CT; CXCR4; theranostics

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**A**mong all non-Hodgkin lymphomas, approximately 7% are classified as marginal zone lymphomas (MZLs) and thereby represent the second most common type of indolent lymphoma. Subtypes include (extranodal) mucosa-associated lymphoid tissue lymphoma followed by splenic and nodal MZL (1). Current practice guidelines recommend an extensive work-up, including esophagogastroduodenoscopy (including colonoscopy), bone marrow-derived biopsy (BMB), and CT (2). In this regard, PET/CT using the most common oncologic radiotracer, [<sup>18</sup>F]FDG, is not fully established as the imaging modality of choice, partly because only about 60%–85% of MZLs show relevant tracer uptake and limited clinical utility has been reported for diagnostic work-up of certain MZL subtypes (2–5).

Immunohistochemistry studies already provided evidence that C-X-C motif chemokine receptor 4 (CXCR4) is substantially upregulated in mucosa-associated lymphoid tissue lymphomas (6); thus, this receptor has emerged as a promising target in the context of MZL (7–9). Not surprisingly, recent studies reported on excellent tumor-to-background ratios using the novel CXCR4-targeting PET probe [<sup>68</sup>Ga]Ga-pentixafor, which provided favorable readout capabilities, along with superior contrast relative to physiologic background radiotracer accumulation (10), and rendered this radiotracer a noninvasive biomarker for therapeutic monitoring. [<sup>68</sup>Ga]Ga-pentixafor can also identify residual disease after *Helicobacter pylori* eradication, which would then potentially allow noninvasive follow-up through imaging instead of repeated endoscopy (11). Moreover, in a recent pilot study with a limited number of 22 patients, this PET probe provided better diagnostic performance in different MZL subtypes, particularly compared with guideline-compatible diagnostic procedures, and even triggering a change in management in a substantial fraction of patients (4). Those considerations are important because patients with limited disease (stage I or II), especially with extranodal MZL, may undergo external-beam radiation therapy (RTx), whereas subjects with stage III or stage IV are scheduled either for watch-and-wait strategies or for chemotherapy with or without rituximab (2,4).

In the present study, comprising (to our knowledge) the largest cohort of MZL patients imaged with [<sup>68</sup>Ga]Ga-pentixafor PET/CT to date, we aimed to determine the diagnostic performance of CXCR4-directed molecular imaging relative to routine work-up, including esophagogastroduodenoscopy, BMB, and CT. Beyond staging changes, we determined the retrospective impact on the

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therapeutic algorithm because of [<sup>68</sup>Ga]Ga-pentixafor. In addition, the predictive potential of the quantified CXCR4 PET signal for progression-free survival (PFS) was assessed. Moreover, PET results showed that patients can be scheduled for treatment using the therapeutic compound [<sup>177</sup>Lu]Lu-pentixather, which exhibits DNA strand breaks via β-emission, ultimately causing substantial antilymphoma effects (12–14). Because such a theranostic approach has already been reported to be promising in the treatment for other lymphomas, achieving partial or even complete remission (12–14), we aimed to determine the portion of patients potentially eligible for CXCR4-directed radioligand therapy (RLT) because of their [<sup>68</sup>Ga]Ga-pentixafor PET/CT results.

## MATERIALS AND METHODS

### Patients

In this retrospective, single-center study, we included 100 patients (women, 55/100 [55%]; mean age, 66 ± 13 y; age range, 24–86 y) with MZL who had been imaged with [<sup>68</sup>Ga]Ga-pentixafor as part of routine care (primary staging, 92/100 [92%]; restaging, 8/100 [8%]). In all cases, MZL was histologically confirmed. All subjects provided written consent for the conducted procedures. The local ethics committee waived the need for further approval (number 20220414 01). Parts of the investigated cohort also underwent the analyses provided in Duell et al. (4) and Buck et al. (10).

### Radiotracer Preparation

[<sup>68</sup>Ga]Ga-pentixafor was prepared in-house for all subjects in accordance with Buck et al. (10) and Lapa et al. (15). We used a dedicated synthesis module provided by Scintomics, along with single-use cassette kits (ABX). A detailed description can be found in Lapa et al. (15).

### Diagnostic Work-up, Including CXCR4-Targeted PET/CT, Esophagogastroduodenoscopy, and BMB

[<sup>68</sup>Ga]Ga-pentixafor was performed on a Biograph mCT 64 or 128 scanner (Siemens Healthineers). As described in Buck et al. (10), we performed scans that covered the whole body, reaching from the vertex of the skull to the upper part of the thighs, approximately 60 min after application of 123 (±23.2) MBq of [<sup>68</sup>Ga]Ga-pentixafor. We used the manufacturer's protocol to reconstruct images (3-dimensional mode, 200 × 200 matrix, 3 iterations, and 24 or 21 subsets [mCT 64 or mCT 128], with gaussian filtering of 2.0 mm), including CT-based correction for attenuation, scatter, and random events. If not performed as part of CXCR4-directed PET/CT, separate full-dose diagnostic CT imaging within 30 d of PET/CT was available from our imaging database for each patient. In addition, we searched our medical archive for esophagogastroduodenoscopy (including colonoscopy) and BMB results within 30 d of CXCR4-targeted PET/CT for every patient. Individuals remained treatment-naïve between procedures.

### Quantification of [<sup>68</sup>Ga]Ga-Pentixafor PET

To investigate a potential predictive role of [<sup>68</sup>Ga]Ga-pentixafor PET/CT, we quantified the obtained PET signal in all sites of disease, consulting an expert reader and board-certified nuclear medicine physician in inconclusive cases. For this purpose, we used a workstation equipped with dedicated software packages (Syngo.via version VB60; Siemens Healthineers), which provided the following parameters by drawing 3-dimensional volumes of interest that applied an isocontour threshold of 40%: SUV<sub>mean</sub>, SUV<sub>max</sub>, SUV<sub>peak</sub>, lymphoma volume (in cm<sup>3</sup>), and fractional lymphoma activity (FLA, defined as lymphoma volume × SUV<sub>mean</sub>) (10,16,17).

### Visual Analyses of Diagnostic Procedures, Including Staging and Therapy Changes and Eligibility for CXCR4-Targeted RLT

One board-certified radiologist reviewed diagnostic CT imaging masked to clinical data and CXCR4 PET/CT results in a randomized order. [<sup>68</sup>Ga]Ga-pentixafor PET/CT scans were reviewed randomly in an interdisciplinary consensus setting by 2 board-certified nuclear medicine physicians, a board-certified radiologist, and a dual board-certified internal medicine physician and hematologist masked to other clinical data. In addition, imaging experts classified patients eligible for CXCR4-directed RLT according to intensity and widespread disease. Eligibility criteria for RLT were SUV<sub>max</sub> of 10 and Ann Arbor (AA) classification stage IV (derived from PET/CT alone). Finally, taking histologic results at baseline staging into account, AA classification staging for both full-dose diagnostic CT and CXCR4-directed PET/CT were recorded separately. Rates of no change, upstaging, or downstaging after reviewing PET/CT were documented. When current guidelines were reviewed, we considered reclassification from AA I or AA II to AA III or AA IV to be clinically relevant, because those reclassifications are generally associated with treatment changes (2). In addition, a dual board-certified internal medicine physician and gastroenterologist with extensive experience in hematology reviewed results of BMB and esophagogastroduodenoscopy, and findings relative to CXCR4-directed PET/CT were recorded. Results were verified by another dual board-certified internal medicine physician and hematologist running the local MZL outpatient unit. Both experts proposed oncologic management with routine diagnostic work-up (CT, BMB, and esophagogastroduodenoscopy) versus PET/CT, and respective therapeutic modifications were recorded and rated as either deescalation or escalation, as described in Duell et al. (4).

### Statistical Analyses

Descriptive analyses were conducted for head-to-head comparisons of PET/CT with other diagnostic procedures, therapy modifications, and eligibility for CXCR4-directed RLT. We used the Shapiro–Wilk test to determine normal distribution and report mean ± SD for normally distributed variables (otherwise, median and range) (18). The Fisher exact test was used to evaluate the diagnostic performance of CXCR4-directed PET/CT compared with esophagogastroduodenoscopy and BMB. We used Kaplan–Meier curves to assess the predictive potential of the quantified PET signal and to compare PFS between groups provided by the median of quantified PET parameters. We present median PFS in days, along with hazard ratios and 95% CIs (19). PFS was defined as the time between CXCR4-directed PET/CT and the date of progression on follow-up imaging. We used GraphPad Prism version 9.3.1 (GraphPad Software), and a *P* value of less than 0.05 was considered statistically significant.

## RESULTS

### Staging Changes Resulting from [<sup>68</sup>Ga]Ga-Pentixafor PET/CT

Full-dose diagnostic CT showed MZL manifestations in 60 of 100 patients (60%), whereas PET/CT revealed CXCR4-expressing MZL manifestations in 83 of 100 patients (83%). PET/CT findings showed that the distribution of lymphoma manifestations was as follows: lymph nodes, 51 of 100 patients (51%); bone and bone marrow, 20 of 100 patients (20%); orbit, 19 of 100 patients (19%); gastrointestinal tract, 18 of 100 patients (18%); salivary glands, 14 of 100 patients (14%); spleen, 12 of 100 patients (12%); lung, 7 of 100 patients (7%); and kidneys, 5 of 100 patients (5%), followed by other soft-tissue sites (including cutis or subcutis, muscle, and pleura), 19 of 100 patients (19%; Table 1).

Taking histologic results at baseline staging into account, full-dose diagnostic CT alone revealed the following AA classifications: AA I, 57 of 100 patients (57%); AA II, 5 of 100 patients (5%); AA III, 7

**TABLE 1**

Numbers of Organ Systems Affected as Detected by [<sup>68</sup>Ga]Ga-Pentixafor PET/CT and Diagnostic CT Alone

Organ	Concordant	Pentixafor+ /CT-	Sum
Lymph nodes	41	10	51
Bone and bone marrow	0	20	20
Orbit	12	7	19
Gastrointestinal tract	2	16	18
Salivary glands	7	7	14
Spleen	9	3	12
Lung	7	0	7
Kidneys	5	0	5
Other soft tissue	14	5	19

of 100 patients (7%); and AA IV, 31 of 100 patients (31%). On CXCR4-directed PET/CT, distribution among stage classifications was as follows: AA I, 36 of 100 patients (36%); AA II, 4 of 100 patients (4%); AA III, 4 of 100 patients (4%); and AA IV, 56 of 100 patients (56%). Figure 1 provides an overview of AA classifications using PET/CT. Relative to CT, [<sup>68</sup>Ga]Ga-pentixafor PET/CT led to no staging changes for 73 of 100 patients (73%) and upstaging in the remaining 27 patients (27%; Fig. 2). In those 27 cases, upstaging from CT AA I to PET/CT AA IV was recorded for 19 patients (70.4%), followed by CT AA III to PET/CT AA IV for 4 patients (14.8%), CT AA II to PET/CT AA IV for 2 patients (7.4%; Fig. 3), CT AA I to PET/CT AA III for 1 patient (3.7%), and CT AA I to PET/CT AA II for 1 patient (3.7%). Altogether, clinically relevant upstaging from CT AA I or AA II to PET/CT AA III or AA IV occurred for 23 of 27 patients (85.2%) with staging changes.

### Retrospective Impact on Oncologic Management Because of [<sup>68</sup>Ga]Ga-Pentixafor PET/CT

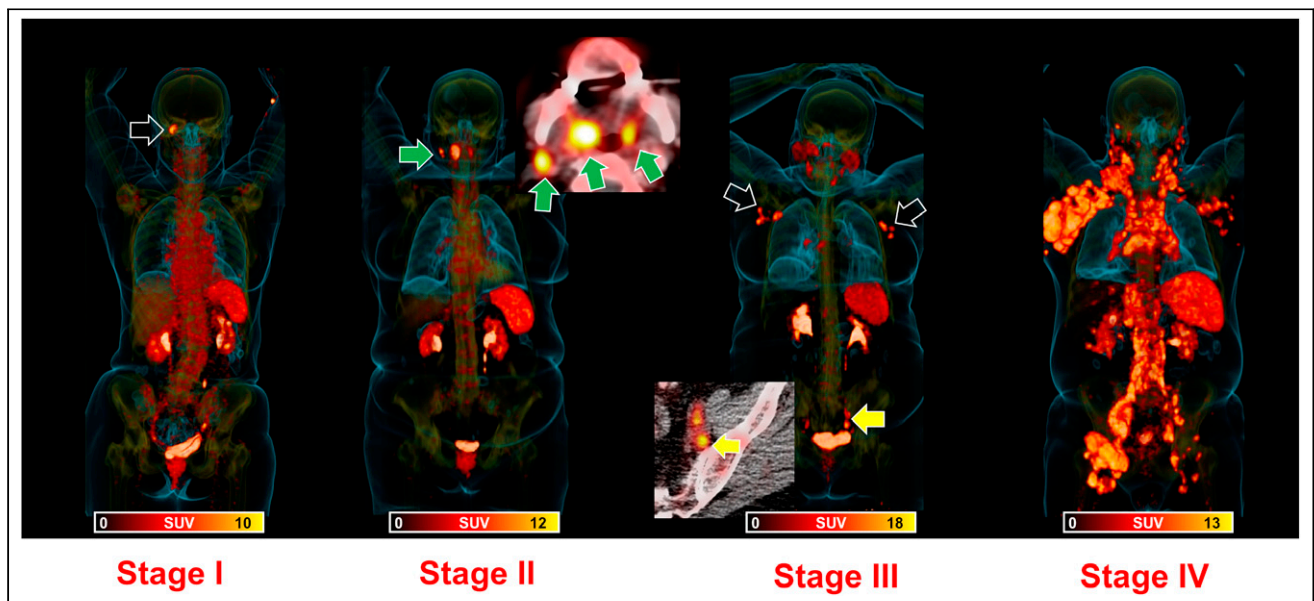
Among the 27 patients with AA classification staging changes, no therapeutic management changes were seen for 4 patients (14.8%, all with changes from CT AA III to PET/CT AA IV). In the remaining 23 patients (85.2%), clinically relevant staging changes (CT AA I or AA II to PET/CT AA III or AA IV) would also have resulted in modifications in oncologic management. Among those, deescalation of treatment would have occurred for 17 of 23 patients (73.9%) and escalation would have occurred for 6 of 23 patients (26.1%). In all 17 deescalation cases (100%), intended RTx would have been changed to a watch-and-wait approach. For therapeutic escalation, the following modifications were noted: extension of the initially planned radiation field for 5 of 6 patients (83.3%) and additional chemotherapy accompanying initially planned radiation for 1 of 6 patients (16.7%).

### Diagnostic Performance of [<sup>68</sup>Ga]Ga-Pentixafor PET/CT Compared with Esophagogastroduodenoscopy and BMB

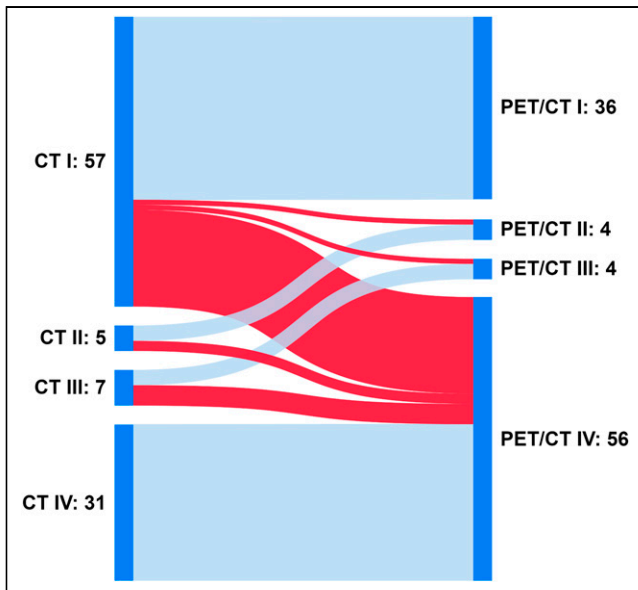
Histologic results within 30 d of the PET/CT scan were available for esophagogastroduodenoscopy of 67 of 100 patients and for BMB of 56 of 100 patients. Diagnostic performance of CXCR4-directed PET/CT for the detection of gastrointestinal MZL manifestations ( $P < 0.01$ ) and bone marrow infiltration ( $P = 0.09$ ) is shown in Table 2.

### Predictive Potential of [<sup>68</sup>Ga]Ga-Pentixafor PET/CT and Identification of Patients Eligible for CXCR4 RLT

Quantitative PET parameters for MZL manifestations were as follows: median SUV<sub>mean</sub>, 5.34 (range, 0.68–22.1); SUV<sub>max</sub>, 9.58 (range, 2.53–44.9); SUV<sub>peak</sub>, 5.58 (range, 1.32–26.3); lymphoma volume, 25.9 (range, 0.60–969); and FLA, 176 (range, 1.74–8,854). Follow-up imaging was available for 81 of 100 patients (81%). Median PFS was 548 d, with observed disease progression in 24 of 81 patients (29.6%). When Kaplan–Meier analyses were used to compare PFS between groups as provided by the median of

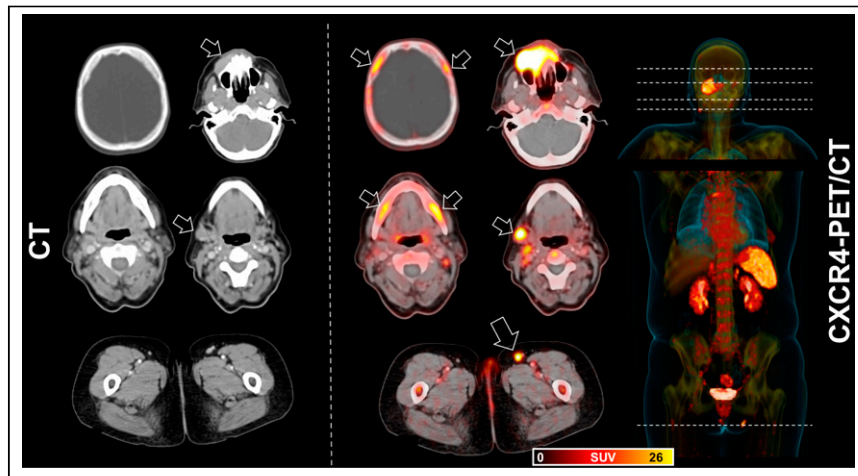


**FIGURE 1.** AA stages with CXCR4-directed PET/CT using [<sup>68</sup>Ga]Ga-pentixafor. For stage I, single extralymphatic manifestation in right orbit was found (empty arrow). For stage II, bilateral CXCR4-positive manifestations in tonsillar region and locoregional affected lymph node were seen (green arrows). For stage III, affected lymph nodes located on both sides of diaphragm were noted (empty and yellow arrows). For stage IV, widespread disease, including muscle and subcutaneous infiltration, was recorded.



**FIGURE 2.** AA reclassification chart. AA staging changes from CT to CXCR4-directed PET/CT are shown. Most staging changes occurred from CT AA I to PET/CT AA IV.

quantified PET parameters, increased CXCR4 FLA was significantly linked to decreased PFS (707 d vs. median PFS not reached; hazard ratio of progress, 3.18; 95% CI, 1.37–7.35;  $P = 0.01$ ). Moreover, CXCR4 lymphoma volume showed borderline significance, with higher values linked to shorter PFS (716 d vs. median PFS not reached; hazard ratio of progress, 2.36; 95% CI, 1.02–5.45;  $P = 0.05$ ; Fig. 4). Respective Kaplan–Meier curves for  $SUV_{mean}$ ,  $SUV_{max}$ , and  $SUV_{peak}$  achieved no significant separation between subgroups ( $P \geq 0.57$ ; Supplemental Fig. 1 [supplemental materials are available at <http://jnm.snmjournals.org>]).



**FIGURE 3.** Image of 57-y-old female patient with MZL and AA reclassification after CXCR4-directed PET/CT. On CT alone (left), disease manifestations in ventral to right maxilla (arrow, top row) and behind right mandible (arrow, middle row) were recorded, without visible lymphoma manifestations in inguinal region (bottom row). Thus, CT showed that this patient was classified as AA II. However, on [ $^{68}\text{Ga}$ ]Ga-pentixafor PET/CT (right), identical disease sites with more extensive involvement ventral to right and left maxilla (arrows, top row) and behind right mandible (arrows, middle row, right) were recorded. Relative to CT alone, additional PET-avid findings included skull (top row), mandibles (middle row, left), and intense inguinal lymph node (bottom row). These findings allowed patient to be reclassified as AA IV. Maximum intensity projection of [ $^{68}\text{Ga}$ ]Ga-pentixafor PET (far right), with dotted line, indicating respective transaxial PET/CT portions.

In addition, because of the intensity of radiotracer uptake and widespread disease on CXCR4-directed PET/CT, 18 of 100 patients (18%) were rated as eligible for RLT.

## DISCUSSION

In the largest cohort imaged with [ $^{68}\text{Ga}$ ]Ga-pentixafor to date, molecular imaging led to AA staging changes for 27 of 100 investigated MZL patients relative to CT (taking baseline histologic biopsy results into account), particularly for clinically relevant reclassification from AA I or AA II to AA III or AA IV. Among those patients experiencing upstaging, we recorded management changes in 23 of 27 cases (mainly deescalation from RTx to watch and wait), rendering CXCR4-directed PET/CT a clinical tool for adequate staging and therapeutic modifications. In a further head-to-head comparison with guideline-compatible procedures, [ $^{68}\text{Ga}$ ]Ga-pentixafor demonstrated diagnostic performance similar to that of esophagogastroduodenoscopy or BMB, with diagnostic accuracy of up to 94%. Beyond such visual assessments, quantification of the PET signal demonstrated that FLA, an in vivo biomarker of receptor expression on the lymphoma cell surface, was closely linked to shorter PFS. Finally, 18 of 100 patients would have been eligible for CXCR4-directed RLT; thus, treatment with  $\beta$ -emitting therapeutic equivalents (e.g., with [ $^{90}\text{Y}$ ]Y-pentixather) may be feasible.

In patients with MZL, current guidelines recommend the use of CT, esophagogastroduodenoscopy, and BMB, allowing a comprehensive readout of the status quo (2). However, such an intensive diagnostic work-up may put a high burden on both patients and personnel; thus, a 1-stop-shop solution combining all of those routine procedures is intensively sought. In this regard, molecular imaging with the most commonly used radiotracer in oncology, [ $^{18}\text{F}$ ]FDG, has provided inadequate diagnostic performance, particularly because of relatively low in vivo glucose consumption in extranodal MZL (2,3). A recent study that investigated human tissue samples of both gastric

and extragastric mucosa-associated lymphoid tissue lymphoma reported on substantial upregulation of the G protein-coupled receptor CXCR4 in most cases (6), thereby rendering this chemokine receptor an attractive target for both imaging and treatment. CXCR4-targeting PET using [ $^{68}\text{Ga}$ ]Ga-pentixafor has already been applied in a small cohort of 22 MZL patients. This pilot study demonstrated superior quantitative and diagnostic performance relative to [ $^{18}\text{F}$ ]FDG PET (including the respective CT portion of hybrid imaging) and accuracy that is comparable to that of both esophagogastroduodenoscopy and BMB (4). In the present analysis, we aimed to expand our initial findings. We investigated 100 MZL patients and showed CXCR4 PET/CT to lead to upstaging in 27 cases. After further analyzing guideline-compatible diagnostic procedures, including BMB and esophagogastroduodenoscopy, [ $^{68}\text{Ga}$ ]Ga-pentixafor demonstrated comparable results, indicating that chemokine receptor imaging may add diagnostic information or even substitute for the currently used diagnostic triple assessment.

**TABLE 2**  
Gastrointestinal Manifestation and Bone Marrow Infiltration on PET/CT

Parameter	Gastrointestinal manifestation*	Bone marrow infiltration*
Sensitivity (%)	77.8 (40.0–97.2) [7/9]	36.4 (10.9–69.2) [4/11]
Specificity (%)	96.6 (88.1–99.6) [56/58]	86.7 (73.2–95.0) [39/45]
PPV (%)	77.8 (46.2–93.5) [7/9]	40.0 (18.5–66.3) [4/10]
NPV (%)	96.6 (89.2–99.0) [56/58]	84.4 (77.8–89.8) [39/46]
Accuracy (%)	94.0 (85.4–98.4) [63/67]	76.8 (63.6–87.0) [43/56]

\*With histologic results within 30 d of PET/CT scan as standard of reference.

PPV = positive predictive value; NPV = negative predictive value.

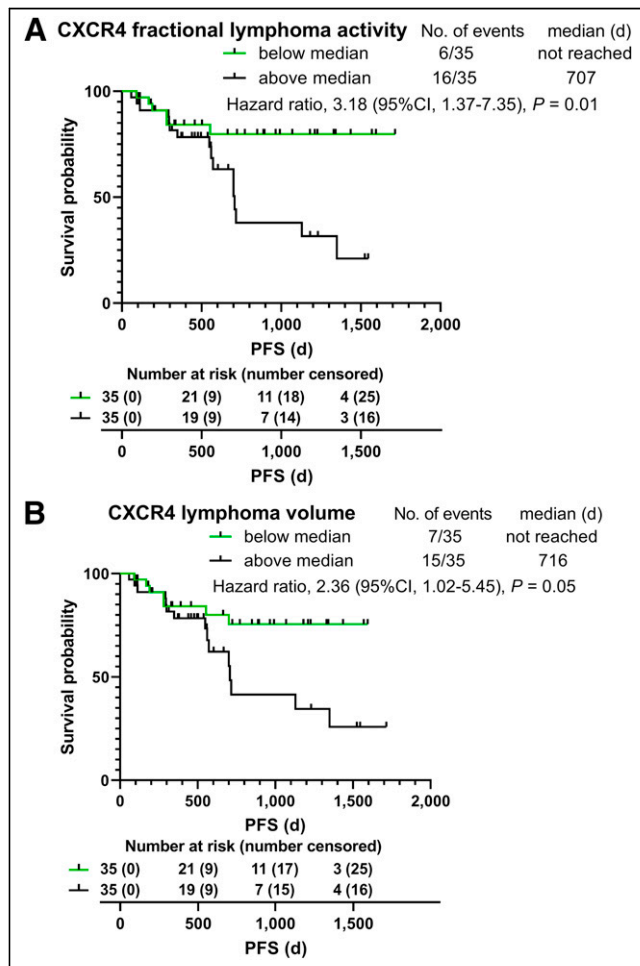
Data are mean percentages, with 95% CIs in parentheses and numerators and denominators in brackets.

Beyond an impact on AA reclassification, patients imaged with [<sup>68</sup>Ga]Ga-pentixafor would have experienced relevant therapeutic modifications, which included deescalation in 17 of 23 cases. In all of those cases, oncologic management would have been

changed from RTx to observation only. Because advanced disease is not always linked to decreasing survival (20), current guidelines recommend RTx exclusively in localized disease (2). In this regard, [<sup>68</sup>Ga]Ga-pentixafor PET/CT identified otherwise-occult lesions; thus, local RTx was not needed, suggesting that CXCR4-directed PET/CT may avoid unnecessary therapeutic interventions. Nonetheless, 6 of 23 patients experiencing therapeutically relevant AA upstaging still would have undergone intensified treatment. Those changes included extension of the initially planned radiation field or onset of chemotherapy, supporting the notion that PET/CT may serve as a therapeutic decision aid.

A recent study explored a panel of varying chemokine receptors in human tissue samples and provided evidence that ex vivo CXCR4 expression may be linked to nodal manifestation and advanced disease (21). Therefore, we aimed to determine whether the derived CXCR4 PET signal also holds prognostic potential. Increasing imaging-derived FLA was linked to shorter PFS, indicating that PET-based quantification may also allow identification of high-risk patients prone to radiographic progression. CXCR4-targeted RLT using hot, β-emitting, CXCR4-directed therapeutic equivalents ([<sup>90</sup>Y]Y-pentixather) has already led to remarkable outcome benefits in other hematologic neoplasms, including complete remission in refractory T-cell lymphoma (13). If [<sup>68</sup>Ga]Ga-pentixafor PET/CT were used, 18 of 100 investigated MZL patients would have been eligible for such a theranostic approach, inducing antilymphoma efficacy. Such a therapeutic approach using [<sup>90</sup>Y]Y-pentixather also causes bone marrow ablation, and myeloablative efficacy can prepare the patient for stem cell transplantation. This effect may be valuable for selected cases that have failed multiple previous lines of chemoimmunotherapy, with CXCR4-directed RLT serving as an adjunct to the high-dose regimen commonly applied before transplantation (22). In addition, the quantified PET signal may allow assessment of retention capacities for other emerging treatment options in patients with advanced indolent non-Hodgkin lymphoma, such as chimeric antigen receptor T-cell therapy (23). In this regard, a recent study demonstrated that CXCR4-directed PET/CT allows differentiation between relapse or autoimmune-related off-target effects caused in multiple myeloma (24). Thus, further studies may apply [<sup>68</sup>Ga]Ga-pentixafor PET/CT in MZL patients scheduled for such innovative treatment options.

Our study is limited by its retrospective design and resulting lack of randomization. Furthermore, a single board-certified radiologist analyzed diagnostic CT scans. Not all lesions seen on CXCR4-directed imaging were biopsied, especially in patients



**FIGURE 4.** Kaplan-Meier curves and log-rank comparisons for PFS using median of [<sup>68</sup>Ga]Ga-pentixafor PET-derived FLA (A) and lymphoma volume (LV) (B). Significant separation was recorded for FLA, with patients above median FLA experiencing shorter PFS. Borderline-significant separation was noted for LV, with patients above median LV showing trend toward shorter PFS.

with widespread disease; therefore, the true extent of lymphoma infiltration cannot be definitively determined in all cases. In addition, because of the limited number of patients with concurrent histologic results in esophagogastroduodenoscopy and BMB, the respective results have to be interpreted with caution. The SUV<sub>max</sub> cutoff was chosen using a previously established approach (10,25,26). Nonetheless, higher physiologic uptake may affect our quantitative results; thus, our analysis may be repeated using varying thresholds, preferably in a prospective setup.

## CONCLUSION

When the CXCR4-targeting PET probe [<sup>68</sup>Ga]Ga-pentixafor was applied in 100 MZL patients, molecular imaging led to AA staging changes for 27 patients relative to CT (taking baseline histologic biopsy results into account), particularly for clinically relevant reclassification from AA I or AA II to AA III or AA IV. Our results also show that CXCR4-directed PET/CT may improve staging and influence management relative to CT alone, potentially obviating some biopsies. Finally, in a theranostic approach, 18 of 100 patients would have been eligible for RLT using CXCR4-targeting β-emitters, causing both antilymphoma and myeloablative efficacy.

## DISCLOSURE

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## KEY POINTS

**QUESTION:** Can CXCR4-directed PET/CT affect staging and oncologic management in patients with MZL, along with identifying candidates eligible for a theranostic approach?

**PERTINENT FINDINGS:** Relative to guideline-compatible diagnostic work-up, the CXCR4 PET probe [<sup>68</sup>Ga]Ga-pentixafor triggered AA staging changes for 27 of 100 MZL patients, particularly for clinically relevant reclassification from AA I or AA II to AA III or AA IV. In addition, 18 of 100 patients would have been eligible for RLT using CXCR4-targeting β-emitters in a theranostic approach.

**IMPLICATIONS FOR PATIENT CARE:** In patients with MZL, CXCR4-directed PET/CT triggered upstaging and therapeutic modifications in a substantial portion of patients, identified high-risk patients prone to progressive disease, and determined candidates for CXCR4 theranostics.

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