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ORIGINAL ARTICLE

Clinical and pathological predictors for FDG-PET/CT avidity in patients with marginal zone lymphoma—a retrospective cohort study

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Abstract

Background The clinical value of FDG-PET/CT for staging and monitoring treatment response in patients with aggressive lymphoma is well established. Conversely, its role in the assessment and management of marginal zone lymphoma (MZL) is less conclusive. We aimed to assess clinical, laboratory, and pathological predictors for FDG uptake in these patients, in an attempt to identify MZL patients whose management will benefit from this imaging modality.

Methods In this single-center, retrospective cohort study, we included all adult patients diagnosed with MZL at the Rabin Medical Center between January 2006 and December 2020 who underwent FDG-PET/CT at the time of diagnosis. Primary outcomes were FDG avidity (defined as a visual assessment of at least moderate intensity), SUVmax, and SUVliver. Variables such as advanced clinical stage, primary disease site, hemoglobin level (Hb), platelet count (Plt), serum albumin, LDH level, β-2 microglobulin, and Ki 67 index were evaluated univariate and multivariate analysis using logistic and linear regression models. Association between FDG avidity and progression-free and overall survival was evaluated using Kaplan–Meier curves and Cox regression analysis.

Results A total of 207 MZL patients were included in this study, 76 of whom (36.7%) had FDG-avid disease. Baseline patients' characteristics such as age, gender, and comorbid conditions were similar between patients with and without significant FDG uptake. In a multivariate logistic regression model, non-gastric MALT (OR 4.2, 95% CI 1.78–10), Ki 67 index ≥ 15% (OR 3.64, 95% CI 1.36–9.76), and elevated LDH level (OR 8.6, 95% CI 3.2–22.8) were all associated with positive FDG avidity. In a multivariate linear regression model, a combination of advanced clinical stage, specific disease subtypes, LDH level, and Ki 67 index predicted the value of SUVmax (P value < 0.001; adjusted $R^2 = 33.8\%$) and SUVmax/SUVliver (P value < 0.001; adjusted $R^2 = 27\%$). Baseline FDG avidity was associated to PFS and OS only in univariate analyses.

Conclusions In this retrospective cohort study, we present prediction models for positive FDG uptake and SUVmax in MZL patients. These models aim to help clinicians choose patients suitable for incorporation of FDG-PET/CT for staging and monitoring disease and reduce the costs of redundant tests.

Keywords Marginal zone lymphoma · FDG-PET/CT · Prediction · SUV

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Background

Marginal zone lymphoma (MZL) accounts for 5–15% of non-Hodgkin lymphomas in the Western world, and is comprised of three different clinical entities, each with unique clinical and pathophysiological attributes [1]. Prognosis and management of patients with MZL are currently determined using clinical and laboratory findings, such as the Ann Arbor stage, LDH, albumin, hemoglobin level, and platelet count [2–5].

During the last several decades, FDG-PET/CT has revolutionized the management of cancer patients. This imaging technique incorporates mapping of glucose metabolism by fluorine-18–2-fluoro-2-deoxy-d-glucose (^{18}F-FDG) uptake with CT-based anatomical correlation. The role of FDG-PET/CT for staging and treatment response monitoring in aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) and in Hodgkin's disease has been persistently pivotal [6–10].

Current guidelines consider FDG-PET/CT as a modality of little clinical utility in MZL [1], with the main use for establishing a diagnosis of high-grade lymphoma when transformation is suspected. Efforts are being made to re-evaluate this notion with increased sensitivity with modern FDG-PET/CT equipment [11, 12].

Studies in recent years showed conflicting results regarding FDG avidity in MZL patients and underlined various factors that are associated with higher rates of positive FDG uptake in these patients. Such factors include disease stage, primary site, and higher Ki 67 index [11–15].

The clinical benefit of FDG-PET/CT for the staging and prognosis of patients with indolent lymphomas is yet to be determined. Metser et al. [16], showed upstaging in 25% of cases, though most of the patients in this registry had follicular lymphoma. Our group showed an association between FDG uptake following completion of treatment and lower progression-free survival in MZL patients [13].

Our aim in this study is to evaluate clinical and pathological factors associated with FDG-PET/CT avidity in all subtypes of MZL and suggest a prediction tool to identify subgroups of MZL patients whose management will benefit from the incorporation of FDG-PET/CT.

Patients and methods

Study design and patients

This is a single-center, retrospective cohort study that included patients with MZL who underwent FDG-PET/CT at the time of diagnosis between the years 2006 and 2020, and before any treatment. Prior to study entry, the diagnosis was confirmed by inspection of the original pathologic report, according to the WHO 2016 criteria for MZL [17]. Clinical stage was determined by the treating hemato-oncologist, according to the Ann Arbor staging system [18].

We excluded patients diagnosed with concurrent malignancy at the time of diagnosis of MZL and patients with hemolysis (as evident by reticulocytosis, a positive direct Coombs test, and a low level of haptoglobin).

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and approved by the institutional research ethics committee of the Rabin Medical Center.

Data collection

We included patients with a diagnosis of MZL based on the electronic medical records of Rabin Medical Center. We included only patients who had a formal pathological report, for validation of correct diagnosis and for a definition of Ki 67 proliferation index, and for whom an FDG-PET/CT scan was performed within 60 days from diagnosis of MZL and prior to any treatment and was available for revision. Additional data was drawn from the patients' medical records, including demographic data (gender, age, and comorbid conditions), clinical data (MZL subtype, primary disease site, and clinical stage), and laboratory data (blood count, LDH, and albumin).

Definitions

Anemia was defined by a hemoglobin level of less than 12 g/dl. Thrombocytopenia was defined by a platelet count of less than 100,000 per mm^3. Elevated LDH was defined by an LDH level over 480 mg/dl. Hypoalbuminemia was defined by an albumin level of less than 3.6 mg/dl. Elevated Ki 67 index was defined by a value ≥ 15%, according to the accepted cutoffs reported in previous studies [14, 15].

Secondary MALT/MZL was defined by a diagnosis of MZL in a patient diagnosed with *Helicobacter pylori* (HP) infection, viral hepatitis, connective tissue disorder (e.g., Sjogren's syndrome), or with a history of solid organ transplantation.

Progression-free survival (PFS) was defined as the time from diagnosis to the first event of disease progression, relapse, transformation to aggressive lymphoma, or death. Overall survival (OS) was defined as the time from diagnosis to death due to any cause.

FDG-PET/CT data

The FDG-PET/CT of the enrolled patients was performed according to the guidelines in several institutions, as part of the clinical workup. Each FDG-PET/CT was reviewed retrospectively for the study by the same nuclear medicine specialist, blinded to any clinical information.

Results were reported using two methods of evaluation, qualitative and semi-quantitative: visual assessment (VAS) and maximal standardized uptake value (SUVmax), respectively.

Positive FDG avidity was defined as medium-intensity FDG uptake (more than the FDG uptake in the mediastinal blood pool) or high-intensity FDG uptake (more than the FDG uptake in the liver) according to VAS.

SUV—standard uptake value—is a measure of tissue radioactivity concentration relative to the injected dose of radioactivity per kilogram of body weight. SUVmax was calculated using the single maximum pixel count within the defined volume of interest (VOI). SUVliver was measured in $3cm^2$ VOI on segment 7 of the liver.

Statistical analysis

Patients were divided into two groups according to the VAS of FDG-PET/CT avidity. These two groups were compared in regard to clinical, laboratory, and pathological parameters.

Categorical variables were described by numbers and percentages, and the difference between groups was evaluated using the chi-square test (for normally distributed variables) or by the Fischer exact test (for other distributions).

Continuous variables were described by mean and standard deviation and compared using a student *T*-test (for normally distributed parameters), or by medians and interquartile range (IQR) and compared by the Mann–Whitney *U* test (for other distributions).

We conducted a univariable analysis and chose variables that were found to be associated with FDG avidity (P value < 0.05) according to VAS to be further examined in a multivariate logistic model as predictors of a positive FDG uptake. The odds ratio for the various predictors was presented using a log 10 Forest plot.

These predictors were later examined in multivariate linear regression models for the prediction of SUVmax and SUVmax/SUVliver. Model fit was assessed using the Hosmer and Lemeshow test, and the predictive ability of the model was evaluated using the area under the curve (AUC) plotted on a receiver operating characteristic curve (ROC curve).

Because the natural history of PCMZL is significantly different from other types of MZL, these patients were excluded from survival analyses (PFS and OS) in this study.

Survival curves were calculated using the Kaplan–Meier method and Cox regression models were used to evaluate a possible association between FDG avidity and prognostic parameters (PFS and OS) in multivariate analyses.

Statistical analyses were performed using Statistical Package for Social Science (SPSS) version 26.

Results

Descriptive statistics and comparison between groups

A total of 456 patients were diagnosed with MZL at Rabin Medical Center between 2006 and 2020. Of them, 347 underwent FDG-PET/CT at the time of diagnosis. After exclusion of patients with an additional or a possible alternative diagnosis of malignancy (89 patients), hemolysis (12 patients), or missing data (e.g., lack of access to the pathology report, overall, 39 patients), the final evaluation included 207 patients. The rate of positive FDG uptake for the whole cohort was 36.7%.

The median age was 69 ± 15 and 68 ± 21 for patients with positive FDG uptake and no FDG uptake, respectively. Ninety-two (44%) of the patients were male. There were no significant differences between the two groups in terms of baseline parameters and comorbidities.

The cohort included 129 (62.31%) patients with extranodal marginal zone lymphoma (ENMZL), 31 (14.97%) patients with nodal marginal zone lymphoma (NMZL), and 47 (22.7%) patients with splenic marginal zone lymphoma (SMZL). ENMZL patients were further divided according to primary disease site: 46 (22.1%) patients with gastrointestinal (GIT) disease (mainly gastric MALT), 61 (29.4%) with non-gastric MALT (26 pulmonary MALT; 16 orbital disease; 8 head and neck disease; 11 other sites), and 22 (10.5%) with primary cutaneous MZL (PCMZL).

We found a significant difference between positive FDG uptake and no uptake in patients with different primary disease sites. Most patients with PCMZL and GIT ENMZL had no or only mild FDG uptake (10% and 20% positive uptake, respectively), and patients with non-gastric MALT had a higher frequency of FDG-avid disease (~ 50%, Table 1).

One hundred and eight (52%) of the patients had advanced-stage disease, which was associated with higher rates of FDG avidity (49 patients, 45.4%).

In 35 (16.9%) patients in our cohort, MZL was attributed to a predisposing condition such as HP infection or connective tissue disorder. These factors were associated with lower rates of FDG-avid MZL (see Table 1).

Table 1 *Baseline characteristics of patients according to FDG- avidity*

Variable			Total	No FDG uptake	Positive FDG uptake	*P* value
		N (%)	207	131 (63.23)	76 (36.67)	
		Age (median, IQR)	68 (49–87)	68 (47–89)	69 (54–84)	0.636
		Male, *N* (%)	92 (44.4)	62 (67.4)	30 (32.6)	0.36
Disease subtype	ENMZL	Total, *N* (%)	129 (62.3)	88 (68.2)	41 (31.8)	0.001
		GIT, *N* (%)	46 (22.2)	37 (80)	9 (20)	
		Non-gastric MALT, *N* (%)	61 (29.4)	31 (50.8)	30 (49.1)	
		PCMZL, *N* (%)	22 (10.6)	20 (90)	2 (10)	
	NMZL		31 (14.9)	17 (54.8)	14 (45.2)	
	SMZL		47 (22.7)	26 (55.31)	21 (44.68)	
Secondary MZL	Total, *N* (%)		35 (16.9)	27 (77.2)	8 (22.8)	0.06
	HP, *N* (%)		17 (8.2)	13 (76.4)	4 (24.6)	
	Viral hepatitis, *N* (%)		5 (2.4)	4 (80)	1 (20)	
	CTD, *N* (%)		12 (5.7)	9 (75)	3 (25)	
	PTLD, *N* (%)		1 (0.4)	0 (0)	1 (100)	
		Advanced stage, *N* (%)	108 (52.1)	59 (54.6)	49 (45.4)	0.01
		Ki 67 index median (IQR)		5 (5)	10 (15)	
		Hb mean (SD)		12.6 (0.02)	12.4 (0.02)	
		Anemia, *N* (%)	71 (34.2)	44 (131)	27 (76)	
		Plt median (IQR)		198,500 (99,500)	198,000 (108,000)	
		Thrombocytopenia, *N* (%)	12 (5.7)	8 (131)	4 (76)	
		LDH median (IQR)		359.5 (91)	470 (218)	
		Elevated LDH, *N* (%)	47 (22.7)	11 (128)	36 (76)	
		Albumin mean (SD)		4.3 (1)	4.2 (1)	
		Hypoalbuminemia, *N* (%)	16 (7.7)	8 (131)	8 (76)	
		SUVmax median (IQR)		0 (2.7)	7.2 (4.2)	
		SUVmax/liver median (IQR)		0 (1.35)	3.26 (2.32)	

IQR, interquartile range; *ENMZL*, extranodal marginal zone lymphoma; *NMZL,* nodal marginal zone lymphoma; *SMZL*, splenic marginal zone lymphoma; *GIT*, gastrointestinal tract; *MALT*, mucosaassociated lymphoid tissue; *MZL*, marginal zone lymphoma; *HP*, Helicobacter pylori; *CTD*, connective tissue disorders; *PTLD*, post-transplant lymphoproliferative disorder; *Hb*, hemoglobin; *Plt*, platelet count; *LDH*, Lactate dehydrogenase

Table 2 Univariate analysis—predictors for FDG- avidity in MZL

Variable	Univariate analysis (OR, 95% CI)	*P* value
Ki 67 index ≥ 15%	3.7 (1.75–8)	0.001
Advanced clinical stage	2.3 (1.3–4.2)	0.004
Non-gastric MALT	2.4 (1.3–4.4)	0.005
Secondary MALT	0.45 (0.19–1.05)	0.067
Anemia	1.09 (0.6–1.9)	0.77
Thrombocytopenia	0.85 (0.2–2.9)	0.8
Elevated LDH	9.5 (4.4–20.5)	< 0.001
Hypoalbuminemia	1.8 (0.65–5)	0.257
Elevated β 2 microglobulin	2.28 (0.9–5.6)	0.07

OR, odds ratio; *CI*, confidence interval; *MALT*, mucosa- associated lymphoid tissue

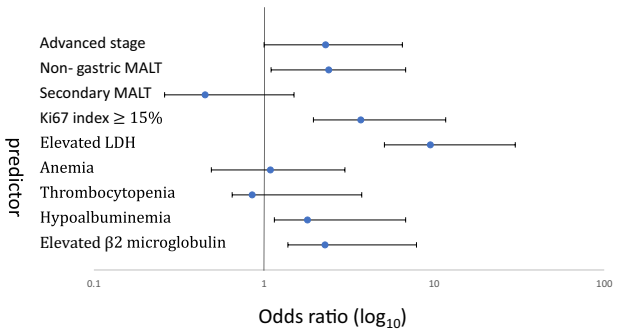

Fig. 1 A log 10 Forest plot presenting odds ratio (OR) for different predictors of positive FDG- avidity according to vusual assesment in MZL patients

Predictors of positive visual assessment

Univariate analyses showed a significant difference between the two groups in the following predictors: clinical stage, Ki 67 index, LDH level, and primary disease site. There was a trend towards reduced FDG avidity in patients with secondary MALT/MZL. There were no

Table 3 Multivariate analysis—predictors of positive FDG avidity in MZL

Variable	OR (95% CI)	*P* value
Advanced stage	2 (0.89–4.9)	0.08
Ki 67 index ≥ 15%	3.64 (1.36–9.76)	0.01
Elevated LDH	8.6 (3.2–22.8)	< 0.001
Non-gastric MALT	4.2 (1.78–10)	0.001

OR, odds ratio; *CI*, confidence intervalModel $\chi 2 = 54.8$, *P* value < 0.001; Nagelkerke's $R^2 = 37\%$; Hosmer and Lemeshow $\chi 2 = 3.8$, *P* value = 0.566

Table 4 Linear regression model for prediction of SUVmax

Variable	*B* (95% CI)	*P* value
Constant	−2.745	< 0.001
Stage	1.86 (0.7–3)	0.002
Ki 67 index (%)	0.123 (0.06–0.18)	< 0.001
LDH	0.009 (0.006–0.01)	< 0.001
Disease subtype	1.92 (0.7–3)	0.002

Prediction equation: SUVmax = −2.745 + 1.86 [stage*] + 0.123 [Ki67] + 0.009 [LDH] + 1.92 [disease subtype**]

*Stage = 1 if advanced, 0 if early; **disease subtype = 1 if disease subtype is non-gastric MALT, 0 if any other disease type

Model: F (4, 166) = 22.7, P value < 0.001; adjusted $R^2 = 33.8\%$

significant differences in hemoglobin level, platelet count, and serum albumin (see Table 2).

A log 10 Forest plot was formed in order to graphically present odds ratio (OR) and 95% confidence interval (CI) for the various predictors of FDG avidity in MZL patients (see Fig. 1).

A binomial logistic regression was performed to evaluate these factors in a multivariate analysis (see Table 3). The model explained 37% (Nagelkerke's R^2) of the variance in VAS and correctly classified 74.4% of cases. Sensitivity was 55.2% and specificity was 86.7%. The following predictors were significantly associated with FDG avidity: Ki 67 index ≥ 15% (OR 3.64, CI 1.36–9.76, *P* = 0.01), elevated LDH (OR 8.6, CI 3.2–22.8, *P* value < 0.001), and non-gastric MALT (OR 4.2, CI 1.78–10, *P* = 0.001).

Prediction of SUVmax and SUVmax/SUVliver

A multiple linear regression model was formed in order to predict SUVmax. Predictor variables included Ki 67 index, LDH level, clinical stage, and primary disease site (the latter two variables were dichotomous, with possible values of 0 or 1).

A prediction equation was generated by SPSS' linear regression model, and was statistically significant; *F* (4, 166) = 22.7; *P* value < 0.001; adjusted $R^2 = 33.8\%$.

The equation is as follows: Predicted SUVmax = −2.745 + 1.86 [stage*] + 0.123 [Ki67index] + 0.009 [LDH] + 1.92 [primary site**].

*Stage = 1 if advanced clinical stage, 0 if early clinical stage.

**Primary site = 1 if non-gastric MALT, 0 = any other type of MZL.

Regression coefficients and standard errors can be found in Table 4.

Examples of FDG-PET/CT tests of patients included in the study with a comparison between the predicted and actual SUVmax can be seen in Figs. 2, 3, and 4.

A similar model for the prediction of SUVmax/SUVliver can be seen in Table 5.

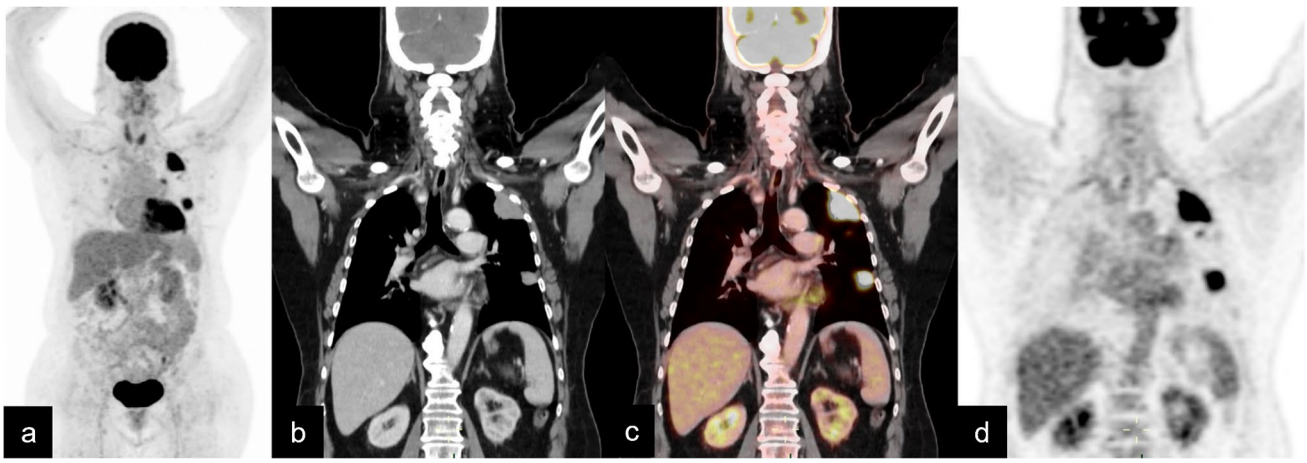

Fig. 2 A representative case FDG-avid ENMZL. A 67-year-old woman with a biopsy-proven, advanced-stage, ENMZL of the lung. Ki 67 index was 30%, and LDH level was 651. Predicted SUVmax = −2.745 + 1.86 [1] + 0.123 [30] + 0.009 [651] + 1.92 [1] = 10.5. Actual SUVmax = 8.2. Maximum intensity projection image, MIP (**a**); axial CT (**b**); axial PET (**c**); and axial fusion images (**d**)

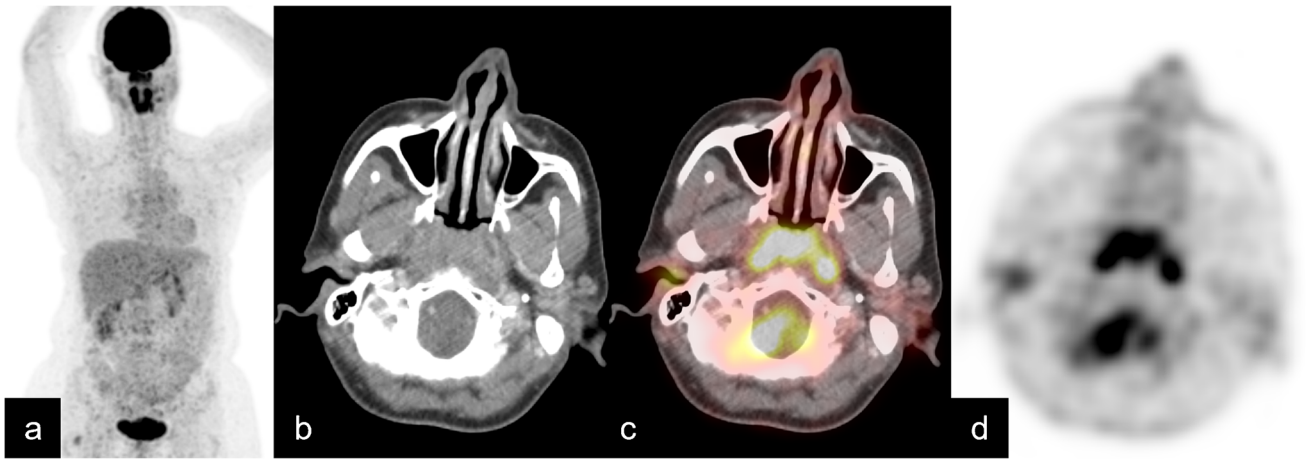

Fig. 3 A representative case FDG-avid ENMZL. A 50-year-old woman with a biopsy-proven, advanced-stage, ENMZL of the nasopharynx. Ki 67 index was 5%, and LDH level was 425. Predicted SUVmax = −2.745 + 1.86 [1] + 0.123 [5] + 0.009 [425] + 1.92 [1] = 8.22. Actual SUVmax = 8.8. Maximum intensity projection image, MIP (**a**); axial CT (**b**); axial PET (**c**); and axial fusion images (**d**)

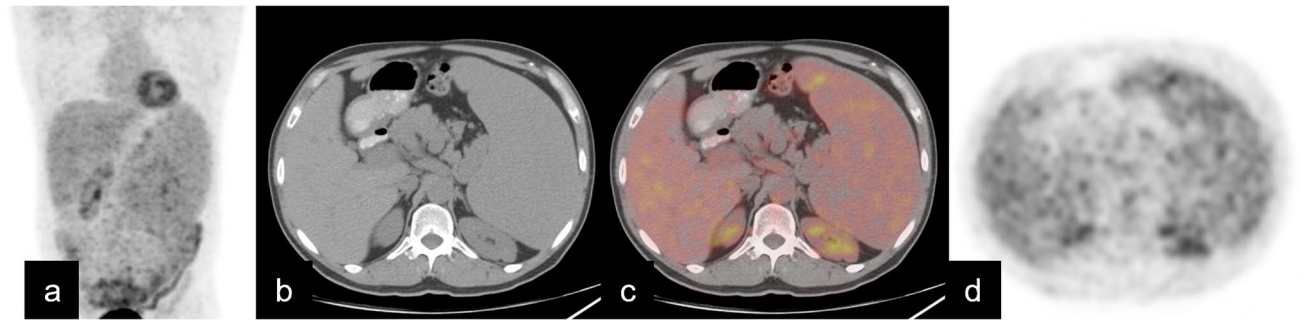

Fig. 4 A representative case of non-FDG-avid MZL. A 52-year-old man with a biopsy-proven, early-stage, SMZL. Ki 67 index was 5%, and LDH level was 402. Predicted SUVmax = −2.745 + 1.86 [0] + 0.123 [5] + 0.009 [402] + 1.92 [0] = 1.48. Actual SUVmax = 0. Maximum intensity projection image, MIP (**a**); axial CT (**b**); axial PET (**c**); and axial fusion images (**d**)

Table 5 Linear regression model for prediction of SUVmax/SUVliver

Variable	*B* (95% CI)	*P* value
Constant	−1	0.006
Stage	0.87 (0.27–1.48)	0.005
Ki 67 index (%)	0.04 (0.008–0.07)	0.01
LDH	0.004 (0.003–0.006)	< 0.001
Disease subtype	0.98 (0.36–1.6)	< 0.002

Prediction equation: SUVmax/SUVliver = −1 + 0.87 [stage*] + 0.04 [Ki 67 index] + 0.004 [LDH] + 0.98 [disease subtype**]

*Stage = 1 if advanced, 0 if early; **disease subtype = 1 if disease subtype is non-gastric MALT, 0 if any other disease type

Model: F (4, 166) = 16.7, P value < 0.001; adjusted R^2 = 27%, Durbin-Watson = 1.94

Progression-free and overall survival

Most MZL patients with baseline positive FDG uptake were treated with systemic therapeutic regimens, mainly Rituximab plus chemotherapy (see Table 6). Patients without FDG uptake were mostly treated with localized therapy (HP eradication or radiation) or no therapy. When these patients were assigned for systemic therapy, most were treated with rituximab monotherapy.

The median follow-up time was 7 years (range, 0.5–19.5 years). Forty-eight patients in the cohort died during the follow-up period, but mortality was attributed directly to the lymphoma only in 10. Relapse rates were similar between the two groups, but rates of progression, transformation to aggressive lymphomas, and death (and notably, death that was attributed to lymphoma) were all higher in patients with positive FDG uptake (see Table 6).

Table 6 Treatment and prognosis of MZL patients according to FDG avidity

Variable			Total	No FDG uptake	Positive FDG uptake	*P* value
First Tx	Non		36 (17.3)	26 (19.8)	10 (13.1)	0.004
	Local Tx	HP eradication	8 (3.8)	7 (5.3)	1 (1.3)	
		Surgery or radiation	58 (28)	42 (32)	16 (21)	
	Systemic Tx	Total, *N* (%)	105 (50.7)	56 (42.7)	49 (64.4)	
		R, *N* (%)	46 (22.2)	36 (27.4)	10 (13.1)	
		C, *N* (%)	6 (2.8)	1 (0.7)	5 (6)	
		R + C, *N* (%)	53 (25)	19 (14.5)	34 (44.7)	
PFS		Total median (range)	7 (5.5–8.4)	8.1 (6–10.2)	5.7 (4.1–7.3)	0.037
		Any event, *N* (%)	107 (51.6)	62 (47.3)	45 (59)	0.09
		Relapse, *N* (%)	73 (35.2)	44 (33.5)	29 (38.1)	0.5
		Progression, *N* (%)	9 (4.3)	5 (3.8)	4 (5.2)	0.6
		Transformation, *N* (%)	12 (5.7)	5 (3.8)	7 (9.2)	0.1
OS		Total median (range)	18.8 (9–28)	21.2 (10–35)	18.8 (4–33)	0.017
		Death	48 (23)	26 (20)	22 (28.9)	0.14
		Death attributed to lymphoma	10 (4.8)	3 (2.2)	7 (9.2)	0.025

MZL marginal zone lymphoma; *Tx* treatment; *HP Helicobacter pylori*; *R* rituximab; *C* chemotherapy; *PFS* progression-free survival; *OS* overall survival

After exclusion of PCMZL, MZL patients with baseline positive FDG avidity had a median time to any event (relapse, progression, transformation, or death) of 5.75 years (95% CI, 4.1–7.3 years), as opposed to patients without baseline FDG uptake, who had a median time of 8.1 years (95% CI. 6–10.2 years). The survival distributions for the two groups were statistically significantly different; $\chi^2 = 4.33$; $P = 0.037$. In the Cox regression analysis, positive FDG avidity was predictive of PFS (HR 1.53, 95% CI 1.02–2.29, $P = 0.04$, Fig. 5). However, in a multivariate analysis using Cox regression, the only factors that were predictive of PFS were elevated LDH (HR 1.74, 95% CI 1.02–2.96, $P = 0.04$) and advanced clinical stage (HR 1.77, 95% CI 1.06–2.95, $P = 0.027$).

Kaplan–Meier curves of OS in MZL patients according to FDG avidity showed statistically significant differences ($P = 0.02$), but these differences were not repeated even in a univariate analysis using Cox regression (HR 1.5, 95% CI 0.84–2.7, $P = 0.15$). Graphic representations of Kaplan–Meier curves of PFS and OS can be seen in Fig. 5.

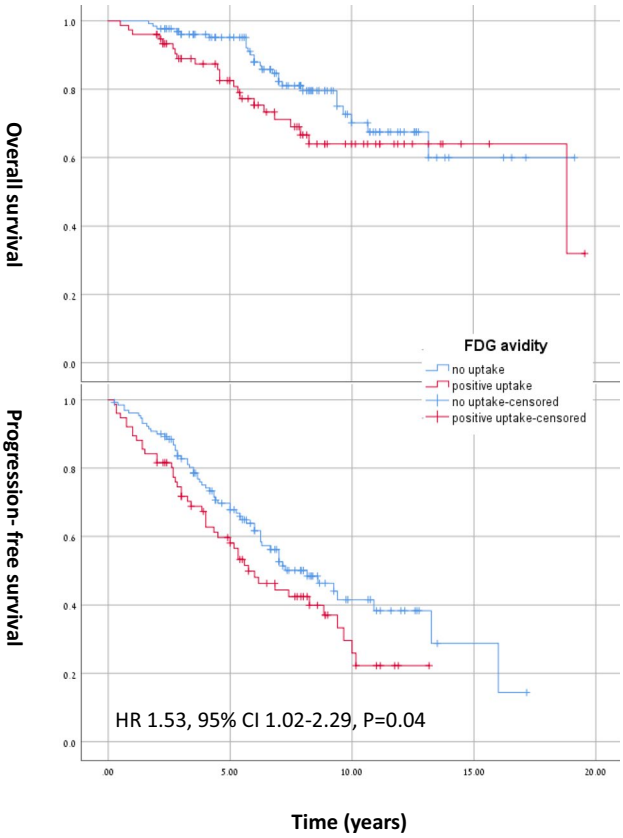

Fig. 5 Progression-free survival (PFS) and overall survival (OS) of MZL patients with and without positive baseline FDG avidity according to visual assessment

Discussion

In this retrospective study of 207 patients with MZL, we present a significant association between certain primary disease sites, Ki 67 proliferation index, and LDH level and FDG uptake in patients with MZL. Other factors such as MZL subtype, Hb level, platelet count, serum albumin, and β-2 microglobulin were not found to be associated

with FDG avidity. Our statistical analyses enabled us to create models for the prediction of positive FDG avidity and SUVmax according to the above predictor variables.

The FDG avidity in our study was 36.7%, in line with some of the reported frequency in the literature [19] while others demonstrated higher avidity rates [12, 13]. We believe these differences are mainly related to cutoff values, as we chose to define positive FDG uptake by a VAS of at least moderate intensity. Another possible explanation is related to the selection of patients with different proportions of specific disease sites, which is associated with FDG avidity as we mention below. An important strength of our study is the fact that we used two different methods for the assessment of avidity, both VAS and semi-quantitative SUVmax.

Several studies focused on identifying predictor variables for FDG avidity in MZL. Similar to our results, others underlined an association between primary disease site [19, 20] and FDG avidity, with higher rates of FDG avidity in lung and head and neck disease, and lower rates in cutaneous and gastric disease. As for the advanced stage, others found an association between the advanced stage and FDG avidity [11]. In our study, we show an association between the advanced stage and FDG avidity in univariate analysis, but not in a multivariate analysis. We do show an association between the advanced stage and SUVmax in a multivariate analysis.

In accordance with our results, Qi et al. [20] also showed an association between elevated LDH and FDG avidity.

Albano et al. [14, 15] published several studies focusing on factors associated with FDG avidity in ENMZL. They presented an association between tumor size, morphological features, Ki 67 index, and FDG avidity in gastric MALT [15], and Ki 67 index but not plasmacytic differentiation in other ENMZL sites [14]. Ki 67 index was also significantly associated with FDG avidity in our study. However, plasmacytic differentiation was not evaluated in our study, but found to be associated with FDG avidity in a few studies [21].

All the predictor variables we found were previously described in different studies, although inconsistently. We offer their incorporation as significant independent predictors for FDG avidity, as part of multivariate models with statistical significance.

Recently, Albano et al. [22] showed an association between baseline FDG avidity and PFS and OS in MZL patients, but it was only valid on a univariate analysis, whereas in a multivariate analysis, the only prognostic predictors were clinical stage and non-gastric MALT.

This is similar to our study. We present an association between baseline FDG avidity and PFS and OS. Both associations were not significant in the multivariate Cox regression analyses. These results are also in accordance with our previous study [13] which also did not show an association between baseline avidity and prognosis, as opposed with the end of therapy FDG uptake that was associated with progression-free survival.

This is the first study to evaluate the association between clinical, pathological, and laboratory parameters to FDG avidity in all types of MZL, both nodal and extranodal. We evaluated a larger cohort than most of the previous similar studies and created statistical models with high specificity in the prediction of positive FDG uptake and SUVmax.

Several limitations merit consideration. A major weakness in this study is due to study design, retrospective and single-centered. There is a possibility that clinicians chose to perform FDG-PET/CT in patients with a more aggressive disease behavior, where an alternative diagnosis of aggressive lymphoma was suspected which may have resulted in selection bias.

In some of our predictor variable subgroups, we had very low numbers of patients (for instance, only 10 patients with hypoalbuminemia, and 12 with thrombocytopenia).

We almost did not have patients with a description of plasmacytic differentiation in their pathology report, and therefore did not analyze the effect of this parameter on FDG avidity. In many of the patients, we lacked data such as Coombs' test or haptoglobin level and more. The effect of missing data might explain some of the weaknesses of our prediction models. For instance, OR for elevated LDH was largely distributed, perhaps partly due to failure to recognize patients with hemolysis (which increases LDH level without an association to the metabolic activity of the cancer cells).

Another limitation of our study is the inability to assess the reproducibility of FDG-PET/CT findings, given that a single nuclear medicine specialist reviewed all the tests.

Our model for predicting FDG avidity according to VAS was specific but lacked sensitivity, mainly because of the cutoff we defined. Therefore, this model is not sufficient as a screening tool for MZL patients. On the other hand, our model for predicting SUVmax is not dependent on cutoff values and therefore shows more promise. Due to high specificity, it would be safe to say that both models can help identify patients that will benefit from incorporating FDG-PET/CT in their staging and monitoring.

The role and significance of FDG-PET/CT in staging and monitoring treatment response in MZL patients are yet to be determined, mainly due to high variability in rates and intensity of FDG uptake in these patients and lack of evidence supporting a prognostic significance. Meanwhile, clinicians use FDG-PET/CT in MZL patients without a clear indication or stratification system (in our cohort, about 50% of MZL patients underwent FDG-PET/CT at the time of diagnosis).

Our prediction models incorporating significant independent predictors for FDG avidity may help clinicians choose which MZL patients are more likely to have FDG-avid disease and implement FDG-PET/CT as an integral component of their staging and monitoring of treatment response. Implementation of our prediction model has the potential to improve patients' care when the test is expected to be positive, and to reduce radiation exposure and financial costs of redundant tests.

MZL that is secondary to chronic inflammatory conditions might be less FDG-avid, but due to the relatively small number of cases, this should be interpreted with caution. This point requires further investigation.

Large, prospective studies are needed in order to create a reliable predictive model for FDG avidity in MZL.

In conclusion, this study presents predictive tools for FDG avidity in MZL, based on multivariate analyses of clinical and pathological predictors. These findings offer clinicians an opportunity to choose MZL patients suitable for FDG-PET/CT-based staging and monitoring. It appears that positive baseline FDG avidity in MZL patients is associated with prognosis, but this seems to be more because of associations to several factors that are better prognostic markers, such as LDH level and clinical stage.

Declarations

Conflict of interest The authors declare no competing interests.

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