Review Article

Prognostic factors and risk of transformation in marginal zone lymphoma

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Abstract: Marginal zone lymphomas (MZLs) are a diverse group of indolent non-Hodgkin lymphoma (NHL) sharing a similar immunophenotype but exhibiting unique biology, clinical features and requiring specific treatment approaches. Three subtypes are recognized in the World Health Organization classification including extranodal MZL (EMZL), splenic MZL (SMZL) and nodal MZL (NMZL). MZL represents 10.5% to 11.8% of all B-cell lymphomas and most patients experience long survival. However, there is a subgroup of patients characterized by a more aggressive disease at risk for unfavorable outcomes. Over the last years an effort toward better understanding and identification of these patients was made. Several high-risk features and prognostic models were built to better identify patients at risk for shorter survival earlier in the disease course. However, compared to other low-grade lymphomas, like follicular lymphoma (FL), both survival risk prediction and treatment strategies to overcome poor outcomes have not been optimized yet. The incidence of higher grade transformation (HGT) in MZL is lower than in FL and may occur in all MZL subtypes, however, higher frequency of this event has been observed in SMZL and NMZL compared to EMZL. HGT is an independent risk factor associated with poor outcomes and current knowledge on biology, risks factors and treatment in patients experiencing transformation remains limited. Most recommendations are extrapolated from transformed FL with very few studies assessing treatment strategies in this population. In this review we aim to discuss the current state of the art in prognostic factors and risk stratification in MZL as well as HGT of these lymphomas. We also provide a rational approach to treat MZL patients undergoing HGT.

Keywords: Marginal zone lymphoma (MZL); risk stratification; higher grade transformation (HGT)

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Introduction

Marginal zone lymphoma (MZL) is included in the World Health Organization classification as a mature B-cell lymphoid neoplasm originating from memory B lymphocytes normally present in the marginal zone of the secondary lymphoid follicles (1,2). Marginal zone B cells are continuously exposed to exogenous antigens and have a physiologically reduced threshold for proliferation induction, which may predispose to malignant transformation (3). MZL is subclassified into extranodal MZL (EMZL) of mucosa-associated lymphoid tissue (MALT), splenic MZL (SMZL), and nodal MZL (NMZL) and all share similar immunophenotype but exhibit distinct presentation and behavior (4). EMZL usually remain confined to the site of origin at diagnosis. In contrast, SMZL commonly involves bone marrow and frequently

found in peripheral blood as circulating villous or non-villous lymphocytes, but rarely infiltrates peripheral lymph nodes and extranodal tissue. In contrast, NMZL typically presents with enlarged lymph nodes and only occasionally involves bone marrow and peripheral blood (5).

MZL is a rare disease representing 10.5% to 11.8% of all non-Hodgkin lymphomas (NHLs) with significant variability in incidence by geographic region (1,6). EMZL is the most common subtype accounting for 7% to 8% of all B-cell lymphomas followed by SMZL (2%) and NMZL (1.5% to 1.8%) (1). MZL typically exhibit an indolent course associated with long survival (7-10). In an analysis of the Surveillance, Epidemiology, and End Results (SEER) database, Olszewski *et al.* evaluated the relative survival of MZL patients. The 5-year relative survival rates (adjusted to age, sex and race) for patients with EMZL, SMZL and NMZL were 88.7%, 79.7% and 76.5%, respectively (11). However, a subset of patients exhibits a more aggressive disease course and succumbs early to their disease (12,13). Different prognostic indexes can identify patients with more aggressive disease in individual MZL subtypes.

In this manuscript, we review recent advances in MZL prognostic factors used in stratifying patients and discuss MZL transformation to diffuse large B-cell lymphoma (DLBCL).

Prognosis factors

EMZL

EMZL has been described in virtually all anatomical locations and especially in organs that are normally devoid of lymphatic tissue (3). The stomach is the most common localization in EMZL followed by ocular adnexa, salivary glands, skin, lung, thyroid, upper airways, breast, other gastrointestinal (GI) sites, and liver (8). Gastric EMZL has been commonly associated with chronic gastritis induced by *Helicobacter pylori* (*H. pylori*) (3,14). *H. pylori* can contribute directly to EMZL pathogenesis by acting on normal and transformed B cells and indirectly through T-cell stimulation (15). Over last decade a declining incidence of *H. pylori*-associated gastric EMZL was observed in population-based studies most likely due to a generalized use of proton pump inhibitors (16). Importantly, lymphomas bearing the t(11;18) have a low probability of response to *H. pylori* eradication therapy (17).

Different inflammatory, autoimmune and pathogenic factors have been implicated in individual location sites. However, presence of underlying autoimmune processes was not associated with outcome determination (18). Prognostic scores have been developed in an effort to identify patients with more aggressive disease at the time of initial diagnosis. Thus, in patients with EMZL the MALT-international prognostic index (MALT-IPI), which is based on age ≥70 years, Ann Arbor stage III or IV and elevated lactate dehydrogenase (LDH) level, was designed to identify 3 risk-groups of patients with distinct survival: the low-risk (0 factors), intermediate-risk (1 factor) and high risk (≥2 factors) with 5-year event-free survival (EFS) of 70%, 56%, and 29%, respectively (19).

The prognostic significance of primary anatomical location of EMZL is controversial. Some studies suggested that initial EMZL localization may bear effect on patients' outcomes. Zucca *et al.* evaluated 180 patients with nongastric EMZL and reported 5-year progression-free survival (PFS) at distinct presentation locations: orbit 23%, multiple sites 25%, breast 33%, skin 53%, bowel 63%, salivary gland 67%, and lung 75% (8). Similarly, Thieblemont *et al.* reported shorter freedom-from progression (FFP) in EMZL localized outside of the GI tract (20). Other factors associated with shorter FFP in this analysis were anemia, high β2-microglobulin, and failure to achieve complete response (CR) following initial therapy (20). Concordantly, better EFS, PFS and CR rate were observed in patients with gastric (72%, 95% CI: 65% to 79%) *vs.* primary nongastric EMZL (61%; 95% CI: 54% to 67%) in the IELSG-19 clinical trial (21). A tendency towards shorter EFS was observed in patients with disease primary localized in the lung and skin in this prospective study, (21) contradicting some of the previous observations (8,22,23). In contrast, PFS and overall survival (OS) were similar in patients with localized EMZL treated with radiation therapy (RT) irrespective of primary organ-specific location; however, patients with disease localized in the thyroid and stomach seemed to have a lower risk for disease relapse (7,22,24). Overall, these studies suggest better outcomes in patients with gastric EMZL.

In our study of EMZL patients with stage I disease treated with frontline RT, we did not observe differences in PFS and OS based on the primary anatomical localization of EMZL (7). The reported differences in outcomes in diverse lymphoma sites may be attributed to different therapies used in these patients and studies. Also, a controversial aspect in the treatment of patients with EMZL is the dose of recommended RT. Current international guidelines endorse a radiation dose between 20 and 30 Gy (25).

However, this recommendation is based on randomized studies that mainly included patients with other indolent lymphomas with a primary endpoint of local disease control and not PFS or OS (26,27). In our previously mentioned retrospective analysis of patients with stage I EMZL treated with curative intent, RT dose <30 Gy was associated with a higher risk for disease relapse which was confirmed in various multivariable analyses models (7,28). The incidence of relapse based on radiation field was 17% inside, 17% inside & outside, and 8% outside of all patients treated with radiation for stage I EMZL. Nevertheless, only limited number of patients treated with lower doses of RT were included in this study and thus prospective randomized studies with long follow up are eagerly needed to address this question.

Disease dissemination at diagnosis is observed in 23% to 34% of patients with EMZL and may be associated with worse outcome (8,20). For example, several studies showed that presence of lymph nodes and/or bone marrow involvement at presentation is associated with worse prognosis (8,29). Advanced stage (III/IV) is also incorporated as an unfavorable prognostic factor in the MALT-IPI. However, the prognostic significant of multiple mucosal sites (MMSs) at the time of diagnosis is controversial (8,20,30,31). Few studies evaluated the prognostic significance of MMS and three studies suggested lack of association between the MMS at presentation and outcome (8,20,30), but worse prognosis was found in another study (31). However, these studies included small numbers of MMS patients (n=17 and 24) with a short follow up period precluding robustness of conclusions claimed by the authors. Further, MMS definition varied between these studies. In a large retrospective cohort of EMZL patients (n=405) followed up to 22.3 (range, 0.02–22.3) years we observed that patients presenting with MMS involvement at diagnosis, defined as EMZL in two or more different anatomical organs independent of spleen and BM involvement, exhibited shorter PFS (HR: 5.39, P<0.001) with a median PFS of 1.7 *vs.* 13.2 years in patients without MMS. Similarly, shorter OS (HR: 4.44, P<0.001) with 10-year OS of 40.5% (95% CI: 20.7% to 59.5%) *vs.* 81.1% (95% CI: 75.1% to 85.8%) was observed in patients with and without MMS, respectively. Greater incidence of higher grade transformation (HGT) with a 5-year cumulative incidence of 13.2% (95% CI: 4.7% to 26.1%) was also observed in patients with MMS (13).

In the same study we also observed shorter PFS (HR: 1.82, P=0.016) and OS (HR: 2.25, P=0.033) in patients presenting with monoclonal gammopathy (MG) at diagnosis. MG was present in 10.7% of the patients and was characterized by predominance of immunoglobulin G (IgG) as the most common paraprotein. In other series IgM has been described as the most common MG in EMZL (29,32), but this difference could be secondary to small number of patients incorporated, difference in primary location of EMZL at presentation, and the potential inclusion of some patients with lymphoplasmacytic lymphomas, which may mimic EMZL presentation. We observed a higher incidence of MG in patients with GI-non gastric (12.5%) and MMS (11.6%) presentations. Other studies support this observation, associating presence of MG at diagnosis with worse outcome of patients with EMZL (33,34). Additional reported clinical factors associated with worse outcome are age >60 years, elevated LDH, β2 microglobulin, anemia (hemoglobin <12 g/dL), thrombocytopenia, lymphopenia, low serum albumin, poor performance status, systemic symptoms, failure to achieve CR following initial treatment, follicular lymphoma IPI (FLIPI) >2, and IPI >2 (6,13,35).

There is a limited data on prognostic biomarkers in EMZL. EMZL is typically a CD5 negative neoplasm, however, expression of CD5 in EMZL was associated with nongastric involvement and disease dissemination (36). Similarly, *CXCR4* expression was associated with bone marrow infiltration in gastric EMZL (37). Presence of t(11;18) was associated with a longer median time to disease relapse compared to patients without this translocation (76 *vs.* 29 months; P=0.012) (38). However the presence of t(11;18) in patients with gastric EMZL was associated with resistance to oral alkylating agents and shorter remission duration (39). *FOXP1* expression was associated with a higher relapse rate and shorter disease-free survival, (40) while *BCL10* expression was associated with advanced EMZL (41).

Progression of disease within 24 months (POD24) was associated with a shorter survival in patients with follicular lymphoma (FL) (42,43). Most recently, three independent studies demonstrated that POD24 is also an important marker for shorter survival in patients with MZL (13,35,44). Our group demonstrated that POD24 was associated with shorter survival in patients with EMZL (5-year survival post progression 46.8% *vs.* 91.1% in the reference group) (13). Luminari *et al.* examined the impact of POD24 in patients enrolled in the NF10 prospective international registry. This group reported a 3-year OS for patients with POD24 of 53% (95% CI: 37% to 67%) with a HR of 19.5 (95% CI: 8.4–45.4) compared to 88% (95% CI: 89% to 98%) in

Table 1 Selected prognostic factors in MZL

EMZL	SMZL	NMZL
MALT-IPI (19)	IIL (51)	Poor performance status (52)
POD24 (13,35,44)	HPLL (53)	MALT-IPI (6)
Radiation dose <30 Gy (7)	MALT-IPI (6)	FLIPI (52)
MMS (13)	POD24 (35)	CD5 positive (54)
MG (13)		
CD5 positive (36)		
Elevated β2 microglobulin (20,35)		
Failure to achieve CR following initial treatment (20)		
FLIPI >2 (6,35)		
IPI >2 (6)		

MZL, marginal zone lymphoma; EMZL, extranodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; MALT-IPI, mucosa-associated lymphoid tissue international prognostic index; IIL, Intergruppo Italiano Linfomi; POD24, progression of disease within 24 months; LDH, lactate dehydrogenase; HPLL, hemoglobin concentration, platelet count, elevated LDH, and extrahilar lymphadenopathy; FLIPI, follicular lymphoma international prognostic index; MMS, multiple mucosal site; MG, monoclonal gammopathy; CR, complete remission; IPI, international prognostic index.

patients without POD24. Conconi *et al.* also demonstrated worse outcomes in patients with POD24 enrolled in the IELSG19 clinical trial (n=401) with a 10-year OS of 64% in POD24 group *vs.* 85% in reference group (HR: 2.42, 95% CI: 1.5–4.34, P=0.002). Importantly, this is the only study that validated their results in an independent cohort of patients (n=287) (44). However, all three studies indicate prognostic significance of POD24 in EMZL.

The prognostic significance of positron-emission tomography (PET)/CT in MZL remains debatable. Albano *et al.* attempted to evaluate prognostic impact of qualitative and semi quantitative baseline PET/CT variables such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) in EMZL. One hundred and sixty-one patients were retrospectively evaluated and (^{18}F) fluorodeoxyglucose (FDG)-avidity correlated with Ki67 expression and tumor size, however, no correlation between survival and PET/CT parameters was observed (45). A study carried out by investigators from Memorial Sloan Kettering Cancer Center evaluated the role of PET/CT at the time of EMZL diagnosis in 123 patients. They found that SUV ≥10 was an independent factor associated with significantly shorter 5-year OS (78% *vs.* 92%, P=0.008) and higher rate of subsequent HGT (20% *vs.* 5%, P=0.035) (46). However, 54% (n=314) of the initial EMZL cohort (n=582) was excluded from this analysis because they did not have staging PET/CT rising a concern that patients included in this study might have a more aggressive disease behavior and/or suspicion for HGT that prompted treating physician to request PET/CT and thus may not be representative of the general EMZL population. Only 20 (16%) patients presented with SUV ≥10 and thus this study warrants further validation before reaching any conclusion on prognostic significance of PET/CT is EMZL. In a retrospective study including all three MZL subtypes (n=110), a positive end of treatment PET/CT was associated with shorter PFS with a HR of 3.4 (95% CI: 1.27–9.14, P=0.02). Importantly, this finding did not correlate with OS (47). Another smaller study (n=32) also found better PFS in patients achieving complete metabolic response at the end of treatment PET/CT (48). These findings are consistent with results obtained in FL in the GALLIUM and PRIMA studies (49,50). In these studies, patients achieving PET/CT complete metabolic response attained a 2.5-year PFS of 87.4% (95% CI: 83.7–90.2%) *vs.* 54.9% (40.5% to 67.3%) in non-responders (P<0.0001), and 42 months PFS of 70.7% (95% CI: 59.3% to 79.4%) *vs.* 32.9% (95% CI: 17.2% to 49.5%) (P<0.001), respectively (49,50) (*Tables 1,2*).

SMZL

SMZL is a rear and indolent NHL with a median OS of more than 10 years (11,56). The survival rates have improved with the incorporation of rituximab in the treatment of SMZL (57). A recent SEER database analysis found that age >60 years, Hispanic ethnicity, presence of B symptoms, HGT, and treatment with non-rituximab containing chemotherapy are associated with shorter lymphoma-specific survival (LSS) (58). In another analysis, none of the components of the age-adjusted IPI (aaIPI) scoring (performance status, stage and LDH levels) were associated with shorter OS or PFS (59). Two scores have been proposed to identify SMZL patients at risk for shorter survival (51,53). The first scoring system was developed by the Intergruppo Italiano Linfomi (IIL) (n=309) which identified hemoglobin <12 g/dL, elevated

Table 2 Prognosis of MZL patients based on risk stratification

EMZL	SMZL	NMZL
MALT-IPI (19), 5-y EFS	IIL (51), 5-y CSS	FLIPI (52), 4-y OS
Low-risk: 70%	Low-risk: 88%	Low-risk: 90%
Intermediate-risk: 56%	Intermediate-risk: 73%	Intermediate-risk: 70%
High-risk: 29%	High-risk: 50%	Low-risk: 88%
FLIPI (55), 5-y PFS	HPLL (53), 5-y LSS	
Low/intermediate risk: 92%	Low-risk: 94%	
Poor risk: 62%	Intermediate-risk: 78%	
POD24 (13), 5-y OS	High-risk: 69%	
No POD24: 91.1%	POD24 (35), 3-y OS	
POD24: 46.8%	No POD: 95%	
	POD24: 44%	

MZL, marginal zone lymphoma; EMZL, extranodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma; NMZL, nodal marginal zone lymphoma; MALT-IPI, mucosa-associated lymphoid tissue international prognostic index; EFS, event-free survival; IIL, Intergruppo Italiano Linfomi; CSS, cause-specific survival; FLIPI, follicular lymphoma international prognostic index; OS, overall survival; PFS, progression-free survival; HPLL, hemoglobin concentration, platelet count, elevated LDH, and extrahilar lymphadenopathy; LSS, lymphoma-specific survival; POD24, progression of disease within 24 months.

LDH, and albumin <3.5 g/dL as independent variables associated with poor outcome in SMZL (51). The 5-year cause-specific survival (CSS) rates were 88% for the low-risk group, 73% for the intermediate-risk group, and 50% for the high-risk group. The latter group accounted for 54% of all lymphoma-related deaths (9,51). The HPLL (hemoglobin concentration, platelet count, elevated LDH and extrahilar lymphadenopathy) score was developed based on international analysis of 593 patients. In this index, hemoglobin <9.5 g/dL, splenic extrahilar lymphadenopathy, platelets <80.000/mL and elevated LDH directly correlated with LSS in SMZL and three risk groups with different outcome were identified (5-year LSS of 94%, 78% and 69%, respectively) (53,60). MALT-IPI >1 was also shown to predict shorter PFS but not OS in SMZL (6). FDG-avidity of splenic uptake (homogeneous *vs.* focal) and semi quantitative determinations in PET/CT do not affect survival in SMZL patients (61).

Like EMZL, only limited data on prognostic biomarkers in SMZL is available. The prognosis of *NOTCH2* mutations in SMZL is controversial. Rossi *et al.* reported better PFS and OS in patients harboring *NOTCH2* mutations compared to wild type in a cohort of 94 SMZL patients (5-year PFS 83% *vs.* 44.1%, P=0.020 and OS 93% *vs.* 74.3%, P=0.048, respectively) (62). However, inferior outcomes in patients harboring *NOTCH2* mutation were reported by other investigators and this event seems to be required before lymphoma dissemination to MMSs (63-65). The *NOTCH* pathway is affected in up to 30% of SMZL and among other indolent B-cell lymphoproliferative disorders, *NOTCH2* mutations are more frequently seen in SMZL (62).

Other cytogenetic abnormalities associated with poor prognosis are complex karyotype, 14q aberrations, *TP53* deletions and *KLF2* mutations (63,64,66). Methylation of *CACNB2*, *HTRA1* and *KLF4* identified a group of patients with poor outcome (65). Importantly, the prognostic significance of most of these biological alterations was not confirmed in independent studies.

NMZL

Very few studies evaluated prognostic factors in NMZL. Poor performance status was the only variable associated with significantly worse outcome, while advanced stage showed a trend toward shorter survival but this did not reach statistical significance in a study of 56 patients (67). Starr *et al.* reported age >60 years and elevated LDH associated with inferior OS in NMZL treated in the rituximab era (68). No specific prognostic score has been

Table 3 Series evaluating HGT in MZL

Author	N of patients	Type of MZL	Diagnosis of HGT	Frequency	Median time to HGT
Alderuccio *et al.*, 2018, (6)	453	All MZL	Pathologic	7.5%	2.4 years
Starr *et al.*, 2016, (71)	211	EMZL	N/A	6.6%	N/A
Maeshima *et al.*, 2016, (72)	467	EMZL	Pathologic	8%	4 years
Xing *et al.*, 2015, (73)	107	SMZL	Clinical/pathologic	9% at 5 years; 18% at 10 years	N/A
Conconi *et al.*, 2015, (74)	340	All MZL	Pathologic	3.8%; 5% at 5 years; 10% at 12 years	2.8 years
Lenglet *et al.*, 2014, (59)	100	SMZL	Pathologic	11%	1.9 years
Meyer *et al.*, 2014, (69)	197	All MZL	Pathologic	11.6%; 2.4% per year	N/A
Dungarwalla *et al.*, 2008, (75)	9	SMZL	Pathologic	19%	3.75 years
Zucca *et al.*, 2003, (8)	180	EMZL (nongastric)	Pathologic	3%	N/A
Camacho *et al.*, 2001, (76)	12	SMZL	Pathologic	13%	N/A

HGT, higher grade transformation; MZL, marginal zone lymphoma; N, number; EMZL, extranodal marginal zone lymphoma; SMZL, splenic marginal zone lymphoma; N/A, not available.

developed for NMZL, however, some studies have shown the utility of MALT-IPI and FLIPI to predict outcome in NMZL (6,52,55,68). CD5 positive NMZL was associated with disseminated disease, similarly to EMZL (54).

In summary, clinical prognostic indexes were developed to predict outcome of patients with EMZL and SMZL. However, whether these indices can guide treatment selection was not analyzed. Further, the differences in the outcomes between patients in individual risk groups are generally smaller than outcome differences between FL patients with low and high FLIPI. Consequently, there is a place for improvement and development of novel clinical indices that can better identify patients with short survival that may need different therapeutic approaches. Biologic prognostic biomarkers are largely unknown and further studies of biology of these tumors are needed to identify prognostic and predictive biomarkers.

HGT in MZL

Incidence of MZL transformation

The natural history and clinical course of patients with MZL is characterized by increased risk of transformation to aggressive lymphoma which is an independent risk factor for shorter survival (6,8,69). This phenomenon has been extensively studied in other low-grade lymphomas and the vast majority of clinical data in the literature refers to transformed FL (70). However, only limited data on HGT in MZL is available in the literature (*Table 3*). HGT of MZL, usually to DLBCL, is a rare event occurring in 3.8% to 13% of patients, though, some series in SMZL report transformation in up to 19% (6,8,59,69,71-76). The incidence of HGT in MZL is markedly lower than in patients with FL (77,78). Meyer *et al.* reported an annual frequency of 2.4% (69). In a large study performed by Conconi *et al.* (n=340), HGT was observed in 5% of SMZLs, 4% of EMZLs, and 3% of NMZLs, which suggests a similar incidence across all MZL subtypes (74). However, in our study of 453 patients, a higher incidence of HGT was observed in patients with NMZL and SMZL compared to patients with EMZL (6). Similar to FL patients, the incidence of HGT reaches a plateau after 10 years and HGT is a harbinger of a change in lymphoma course associated with markedly shortened survival (6,59,74,78-80). The median time to HGT was 29 (range, 1.3 to 135) months after MZL diagnosis. The cumulative incidence rate of HGT was 6.6% and 8.4% at 5 and 10 years, respectively, and a 10.1% plateau at 12 years. The corresponding estimated annual incidence rate of HGT was 1.1 (95% CI: 0.7 to 1.5) events per 100 patients per year. Patients experiencing HGT had significantly shorter OS with a 2 and 5-year rate of 57% and 65%, respectively (6,74). Thus, HGT is associated with decreased survival, regardless if it is observed in the context of NMZL, EMZL or SMZL (81).

Importantly, patients who presented with HGT within 12 months from MZL diagnosis had shorter OS than those with HGT at MZL diagnosis and HGT more than 12 months later (4-year rate, 43% *vs.* 84%, P<0.001) (6).

Risks factors associated with MZL transformation

Clinical variables associated with HGT in MZL are elevated LDH, more than 4 nodal sites at diagnosis and failure to achieve CR after initial treatment (6,74). Advanced stage disease was also described as a risk factor for HGT in EMZL (72). Implementing competing risk analysis neither IPI, FLIPI nor MALT-IPI were significant predictors of HGT (6). Elevated LDH and B symptoms are frequently observed at the time of HGT (74). However, clinical and laboratory features at transformation are variable and tissue biopsy is always required. In SMZL with circulating villous lymphocytes presence of peripheral lymphadenopathies has also been associated with a risk of HGT (75). Initial treatment strategy (chemotherapy *vs.* splenectomy) does not seem to affect the incidence of HGT in SMZL (76).

Biology of MZL transformation

The biology of HGT in MZL is largely unknown with only few studies addressing pathogenesis of this event. In EMZL, strong *FOXP1* expression, polymorphic morphology and presence of trisomy 3 and 18 were reported to be associated with a higher risk of transformation to nongerminal center DLBCL (40). In patients with gastric EMZL, transformation to DLBCL was accompanied by upregulation of chemokine receptors *CCR1*, *CCR5*, *CCR8*, *CCR9*, *CXCR7* and *XCR1* (37). Presence of t(14;18) *IGH/BCL2* in primary cutaneous EMZL was reported to increase the risk of HGT (82) but was not confirmed in independent cohorts.

TP53 deletion was described in 40% of patients experiencing HGT in SMZL (83). However, in a cohort of 12 patients with transformed SMZL most patients presented wild type *TP53* and only one patient had p16 deletion. 7q deletion was observed in 42% of cases and a nonsignificant trend towards higher risk for HGT was observed in patients presenting with this abnormality (30% *vs.* 18.2%, P=0.45) (76). Risk for HGT associated with 7q deletion is questionable. Parry *et al.* found higher risk in patients harboring 7q31-32 deletion (64), however, 7q deletion, including chromosome regions 31 and 32, is the most common genetic abnormality found in SMZL and this finding may not represent a true risk factor for transformation (84,85). Mutations of *TNFAIP3* and epigenetic changes including higher-promoter methylation which is associated with IGHV1-02 usage, *NOTCH2* mutations, were also associated with HGT in SMZL (64).

Biology of transformation in NMZL is largely unknown secondary to rarity of this disease. Qian and collaborators evaluated 6 cases of transformed NMZL and found significantly higher incidence of del(20q12) compared to nontransformed NMZL. These cases were significantly enriched in extracellular matrix proteins *COL1A1* and *FN1*, growth factor receptor *PDGFR*β, DNA repair protein *RAD51*, and signaling protein *WNT11* (86).

Diagnosis of MZL transformation

Patients usually present with a rise in LDH level, sudden decline in performance status, rapid localized nodal growth, new extranodal sites of disease, presence of new B symptoms or hypercalcemia (12,74,87). The diagnosis of HGT should wherever possible be based on a biopsy sample rather than relying on cytological samples or on clinical/laboratory criteria (70). Transformed DLBCL usually presents non-germinal center immunophenotype (63%) and double expression of *BCL2* and *MYC* is rarely observed (10%) (72). PET/CT has shown to be an important tool pointing to potential HGT in FL and biopsy should aim to sample a lymph node/extranodal area with highest FDG-avidity on PET/CT. Noy *et al.* analyzed 40 patients with transformed indolent lymphomas including 11 MZL. The authors reported that the observed SUV in biopsy-proven site of transformation ranged from 3 to 38, with a mean of 14; SUV >10 predicted an aggressive lymphoma with >80% certainty and SUV >13 with >90% certainty (88). Other authors confirmed that SUV values ≥10 correlate with more aggressive histology (46,89).

The diagnosis of transformation requires visualization of sheets of large cells (*Figure 1*) (1). An unequivocal definition of transformation requires demonstration of a clonal relationship between the original MZL and subsequent neoplasm. This can be established by molecular techniques demonstrating use of the same immunoglobulin gene comprised of variable (VH), diversity (D) and joining (JH) segments that shares a backbone of common somatic mutations, thus allowing inference of a common progenitor cell. Molecular studies in Richter's transformation of chronic lymphocytic leukemia to DLBCL demonstrated that while some of the paired tumors indeed demonstrate

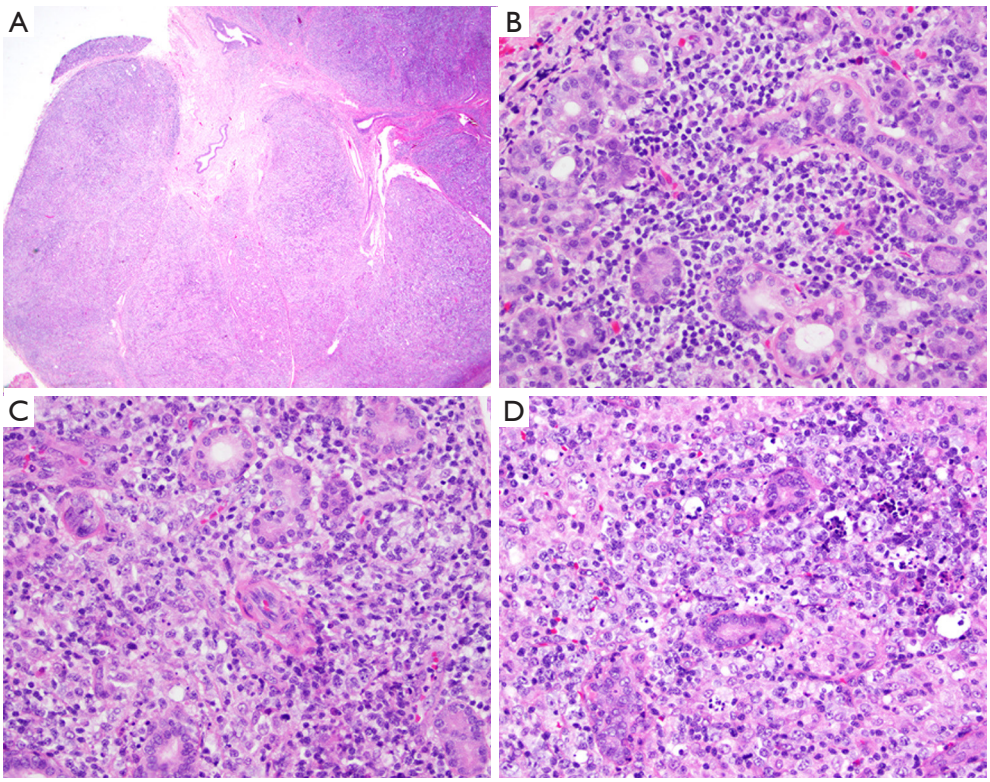

Figure 1 Histologic sections of EMZL of MALT with large cell transformation arising in parotid gland. Hematoxylin and Eosin stained tissue sections show extensive involvement of salivary gland by lymphoma present in a diffuse distribution (A, 40× magnification). The majority of sampled tissue shows involvement by low grade lymphoma composed of small lymphoid cells with moderate cytologic atypia and showing minimal plasmacytic differentiation (B, 400× magnification). Foci of morphologic transition are identified, characterized by the presence of increased large lymphoma cells with vesicular nuclei and conspicuous nucleoli. Mitotic figures and cellular apoptosis are increased in these areas (C, 400× magnification). Foci showing frank morphologic transformation to DLBCL are characterized by the presence of sheets of large lymphoma cells with vesicular nuclei, conspicuous nucleoli and markedly increased cellular apoptosis (D, 400× magnification). EMZL, extranodal marginal zone lymphoma; MALT, mucosa-associated lymphoid tissue; DLBCL, diffuse large B-cell lymphoma.

identical or related IG sequences, confirming a clonal relationship, others showed presence of different molecular B-cell clones, suggesting presence of molecularly unrelated second malignancy (90). However, since in daily clinical practice IG cloning and sequencing are not routinely performed, demonstration of at least light chain restriction by flow cytometry or immunohistochemistry may be sufficient to suggest transformation and rule the appearance of an unrelated second malignancy (91).

Treatment of MZL transformation

There are no prospective studies specifically evaluating treatment strategies in patients with transformed MZL. Efficacy of different therapeutic regimens is reported mostly in small, retrospective cohorts and most approaches to manage transformed MZL are extrapolated from other indolent NHLs (81). In transformed FL anthracycline-containing regimens like rituximab, cyclophosphamide, Adriamycin, vincristine and prednisone (R-CHOP) are recommended, leading to an overall response rate (ORR) and CR of 60% and 40%, respectively (78). Because responses achieved with conventional chemotherapy in patients with transformed FL are frequently of short duration and historically patients with transformed disease exhibit inferior outcomes with conventional therapy, high-dose therapy with autologous stem cell transplant (ASCT) should be considered in young fit patients (12,91). In a cohort of 172 transformed FL patients from the Canadian Blood and Marrow Transplant Group, improved outcomes

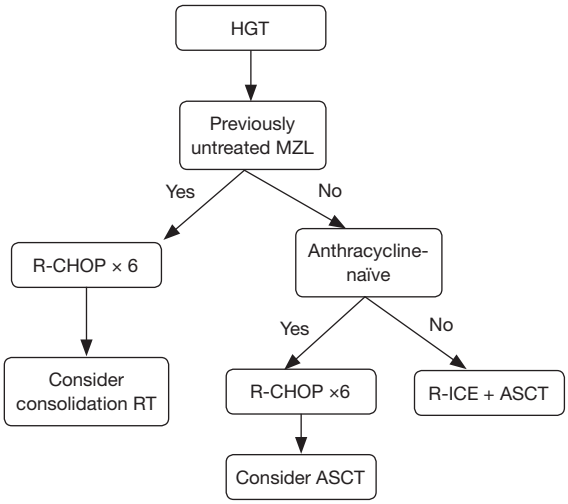

Figure 2 Proposed algorithm in biopsy-proven HGT in MZL. HGT, higher grade transformation; MZL, marginal zone lymphoma; RT, radiation therapy; ASCT, autologous stem cell transplant.

were reported in patients undergoing consolidation with ASCT compared to those treated with rituximab-containing regimens only. Importantly, 85% of the patients presented chemosensitive disease before transplantation and in a multivariable analysis there was no difference in OS between patients treated with allogeneic stem-cell transplant and ASCT (HR: 1.5, 95% CI: 0.65–3.47, P=0.35) (92). Nevertheless, younger patients who were not exposed to chemotherapy prior to HGT seem to have long survival even without transplantation (2-year OS in chemotherapy naïve *vs.* exposed to chemotherapy prior to HGT was 100% *vs.* 35%, P=0.03, respectively) (93).

Compared to FL, there is only limited information on the best treatment strategy in patients with transformed MZL. In the largest study evaluating the role of ASCT in MZL, patients with transformed disease were excluded (94). Response to treatment and long-term outcome seems to be better in previously untreated patients with HGT, similar to findings in transformed FL (6,95). In our analysis of HGT we observed that most previously untreated patients (either diagnosed with HGT at the time of MZL or after active surveillance) achieved a CR rate of 91% with standard frontline DLBCL therapy. Although none of these patients underwent ASCT, we did not observe DLBCL recurrence in any of them during a median follow up of 22.5 (range, 2 to 130) months. Similarly, good results were obtained in another large cohort of transformed EMZL (n=37) patients where the ORR was 97% and 5-year PFS rate of 80% after R-CHOP/CHOP with no patients undergoing ASCT (72). Therefore, untreated patients with HGT may respond to standard DLBCL therapy and may not need consolidation with ASCT. In contrast, the CR rate was less frequent in previously treated patients (52.6%), and eight patients died as a result of DLBCL, even after ASCT (6).

Based on the currently available data which is limited in scope and mostly derived from small retrospective studies we suggest the following treatment algorithm (*Figure 2*):

- Previously untreated MZL patients with HGT or HGT diagnosed at the time of initial MZL diagnosis should be treated with anthracycline-containing regimen such as R-CHOP and considered for consolidation with RT if disease is limited. One exception to this recommendation would be the presence of double hit DLBCL (*MYC* and *BCL2* and/or *BCL6* rearrangements) where more intensive regimen is required and ASCT after frontline therapy should be strongly considered.
- Patients not achieving CR following anthracycline-containing regimen should receive salvage DLBCL treatment and, if chemosensitive disease is demonstrated, proceed with ASCT.
- Patients achieving CR following anthracycline-containing regimen can be observed if they did not receive prior therapy for MZL. ASCT may be considered in selected cases but may not be necessary in majority of these patients.
- Previously treated MZL presenting with HGT should receive anthracycline-containing regimen or DLBCL salvage regimens followed by ASCT.
- Patients treated with anthracycline-containing regimen for MZL prior to HGT should receive standard DLBCL salvage regimen followed by ASCT.

In conclusion, poor risk clinical features in EMZL have been elucidated in recent years. Similarly, characteristics influencing prognosis in SMZL have also been described, however, high risk features in NMZL remain scarce. Compared to FL, MZL biology associated with adverse outcomes and pathogenesis of transformation are largely unknown. Current data attempting to address treatment strategies in high risk patients and in those experiencing HGT is almost inexistent, representing an unmet need in the field. Given the infrequency of MZL and rarity of HGT, it is unlikely that randomized and prospective studies will ever be conducted, thus highlighting the importance of

well design multi-institutional studies attempting to address gaps in the understanding of biology and treatment of high risk/transformed patients with MZL.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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