

Histological response dynamics in gastric extranodal marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue after *Helicobacter pylori* eradication: a single-center longitudinal analysis

Gastric extranodal marginal zone B-cell lymphoma (EMZL) of the mucosa-associated lymphoid tissue (MALT) is unique within all B-cell lymphomas due to its strong pathophysiological connection with chronic antigenic stimulation by *Helicobacter pylori* (HP) infection.¹ Since the seminal discovery that antibiotic eradication of HP can induce durable remissions, HP eradication has become the recommended first-line treatment for gastric EMZL irrespective of stage, achieving long-term disease control and mostly obviating the need for further oncological interventions.²⁻⁵

One of the central challenges in managing gastric EMZL lies in the interpretation of histological response following HP eradication, as the histopathological evolution often follows a non-linear and patient-specific trajectory.^{3,6} The Groupe d'Étude des Lymphomes de l'Adulte (GELA) histological response criteria provide a structured framework for classifying histopathological post-treatment changes as complete remission (CR), probable minimal residual disease (pMRD), responding residual disease (rRD) and no change (NC).⁷ However, little is known about the clinical relevance of fluctuating response depth or transient histological changes over extended follow-up, despite using extensive gastric mapping biopsy protocols.⁸ This uncertainty is particularly important, as histological persistence or relapse after 1 year following HP eradication usually results in oncological therapy.⁹

We therefore conducted a retrospective analysis of patients with primary gastric EMZL treated with first-line HP eradication at a single tertiary center between 1999 and 2024 (Ethics Committee approval number 791/2011).

Histopathological samples of all patients were reviewed by a centralized reference pathologist and response assessed using the GELA classification. Immunohistochemistry for CD20, CD79a, CD5, CD10, CD23, Cyclin D1, Ki-67, evaluation of light chain restriction and molecular analyses to detect t(11;18)(q21;q21) translocation were routinely performed. Clinical characteristics were extracted from medical records. Data on infiltration depth of gastric EMZL was not routinely available and thus not included in our analysis. Patients with absence of HP on histology, absence of gastritis rated as post-HP gastritis and negative serology were rated as HP-negative. Time to next treatment (TTNT) was analyzed as the primary outcome via uni- and multivariable Cox regression analysis to reflect real-world clinical

decision-making. Temporal differences between groups were assessed using the log-rank test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. A two-sided *P* value of <0.05 was considered statistically significant.

Among 498 patients with MALT lymphoma identified at the Medical University of Vienna, 172 had primary gastric involvement; 129 of 172 were treated with upfront HP eradication and 111 of 129 patients had sufficient clinicopathological data available for longitudinal analysis (Table 1). Median follow-up after HP eradication was 28.9 months, with a median of five biopsy time points per patient, resulting in a total of 724 reviewed endoscopic biopsies (Figure 1).

Gastric mapping biopsies were performed in all patients except for 14, who underwent gastroduodenoscopy without known biopsy protocol at external institutions and referred for centralized pathological review to our institution.

Upon HP eradication, 73.9% of patients achieved at least rRD, 56.8% achieved at least pMRD, and 46.8% CR. The median time to first response was 5.6 months for \geq rRD, 6.3 months for \geq pMRD, and 9.9 months for CR, underscoring the gradual deepening of histological response after HP eradication. In contrast, 26.1% of patients showed no histological response (no change [NC]) throughout follow-up (Figure 2A).

At the respective last visit, 72 of 111 patients were still in routine follow-up after HP eradication. In contrast, 39 patients (35.1%) received additional non-antibiotic treatment (Table 1). Among these, 11 patients had histopathological signs of EMZL progression or recurrence within the stomach, while four patients had extragastric progression. Eleven patients received further treatment due to lymphoma persistence after HP eradication. One patient underwent diagnostic resection of a suspicious lung nodule, which was histologically confirmed as EMZL. In three patients, no information on the reason for subsequent therapy was available.

Nine further patients were diagnosed with gastric EMZL-associated secondary malignancies during follow-up, highlighting the importance of continued endoscopic surveillance; seven of 111 patients (7.8%) developed transformation into a diffuse large B-cell lymphoma (DLBCL), which appears slightly higher than expected from earlier series, where it was judged to be between 2-5%.¹⁰ Trans-

formation occurred after a median of 8.7 months after EMZL diagnosis, which is earlier compared to a recently published median time to transformation of 3.67 years in a large retrospective cohort.¹¹ Gastric EMZL of five of those patients did not respond to HP eradication, while one patient each had rRD or CR as best response before DLBCL transformation. Importantly, patients with DLBCL transforming from EMZL restricted to the stomach appear to respond exceptionally well to chemoimmunotherapy¹² - all six patients with a known follow-up are in persisting CR after chemoimmunotherapy at 24+ to 67+ months. Two additional patients were diagnosed with gastric adenocarcinoma 2 months and 11 years after HP eradication; one underwent gastrectomy while the other was treated with systemic chemotherapy, and both had CR with regard to their EMZL in their last specimen. The depth of histological response was strongly associated

with subsequent treatment decisions. Among histological non-responders, 55.2% of patients (16/29) received additional non-antibiotic treatment, whereas significantly less patients that achieved rRD, pMRD or CR were subsequently treated. Specifically, 28.1% of patients (23/82; $P=0.012$) with \geq rRD, 23.8% of patients (15/63; $P=0.004$) with \geq pMRD and 26.9% of patients (14/52; $P=0.016$) with CR received further local or systemic treatment (Figure 2B). That effect largely persisted in uni- and multivariable Cox regression analysis including stage, age, HP status and the presence of concomitant autoimmune disease; CR (hazard ratio [HR]=0.26; 95% confidence interval [CI]: 0.11-0.59; $P=0.001$) and pMRD (HR=0.12; 95% CI: 0.02-0.93; $P=0.042$; Figure 2C). In addition, patients with Lugano stage 2 gastric EMZL were significantly more likely to receive subsequent treatment than stage 1 patients (HR=2.7; 95% CI: 1.3-5.57; $P=0.007$), although ten of 19 patients with Lugano stage 2 achieved \geq rRD and nine

Table 1. Cohort demographics.

Characteristics	Values	Characteristics	Values
MALT lymphoma patients, N	498	Primary gastric MALT lymphoma	
Primary gastric MALT lymphoma, N (%)	172/498 (34.5)	t(11;18)(q21;q21), N (%)	
First-line HP eradication	129/172 (75.0)	Positive	21/57 (36.8)
Excluded from analysis	18/129 (13.9)	Negative	36/57 (63.2)
Insufficient clinicopathological data	15/18 (83.3)	NA	54/111 (48.7)
Unclear timing of HP eradication	2/18 (11.1)	Gastritis at diagnosis, N (%)	70/78 (89.7)
Synchronous breast cancer treatment	1/18 (5.6)	NA	33/111 (29.7)
Primary gastric MALT lymphoma		MALT-associated secondary malignancy, N (%)	9/111 (8.1)
Total study cohort, N (%)	111 (100)	DLBCL transformation	7/9 (77.8)
Median age, years (range)	61.8 (31.5-84.6)	Stomach cancer	2/9 (22.2)
Sex, N (%)		Median follow-up, months (range)	28.9 (1.8-202.4)
Female	55/111 (49.6)	Median number of follow-ups (range)	5 (2-22)
Male	56/111 (50.4)	Median time between follow-ups, months (range)	5.7 (0.2-124.8)
Lugano stage, N (%)		Best histopathological response, N (%)	
1	82/109 (75.2)	NC	29/111 (26.1)
2	19/109 (17.4)	\geq rRD	82/111 (73.9)
4	8/109 (7.3)	\geq pMRD	63/111 (56.8)
NA	2/111 (1.8)	CR	52/111 (46.8)
IPI score, N (%)		Median time to first response, months (range)	
0	66/103 (64.1)	rRD	5.6 (0-124.8)
1	34/103 (33.0)	pMRD	6.3 (0.8-124.8)
2	3/103 (7.3)	CR	9.9 (0.8-126.2)
NA	8/111 (7.2)	Non-antibiotic therapy after HP eradication, N (%)	39/111 (35.1)
HP-status, N (%)		Systemic therapy	35/39 (89.7)
HP-positive	75/109 (68.8)	Chemoimmunotherapy	22/35 (62.9)
HP-negative	34/109 (31.2)	Anti-CD20 therapy	6/35 (17.1)
NA	2/111 (1.8)	Chemotherapy	3/35 (8.6)
First-line HP eradication, N (%)	111/111 (100)	Proteasome inhibitor	2/35 (5.7)
Prior HP eradication	8/111 (7.2)	Immunomodulatory agent	2/35 (5.7)
Median number of cycles (range)	1 (1-4)	Local therapy	4/39 (10.3)
\geq 2 cycles of HP eradication, N (%)	21/111 (18.9)	Surgery	2/4 (50)
Autoimmune disease, N (%)	17/111 (15.3)	Radiotherapy	2/4 (50)

CR: complete remission; DLBCL: diffuse large B-cell lymphoma; HP: *Helicobacter pylori*; IPI: International Prognostic Index; N: number; NA: not applicable; NC: no change; MALT: mucosa-associated lymphoid tissue; pMRD: probable minimal residual disease; rRD: responding residual disease.

did not receive subsequent treatment beyond antibiotics. Longitudinal analysis revealed pronounced intra-patient variability in histological trajectories. Among patients who initially achieved \geq rRD, 25.6% exhibited at least one subsequent biopsy classified as NC that spontaneously reconverted to \geq rRD. Similarly, 30.8% of patients with CR experienced transient histological relapse to pMRD, rRD or NC followed by spontaneous reversion to CR. These fluctuations were typically not accompanied by clinical or radiological progression. Nevertheless, patients with waning histological responses were significantly more likely to receive subsequent therapy than those with sustained or

continuously improving responses (odds ratio =4.15; 95% CI: 1.02-24.70; $P=0.03$), suggesting that dynamic patterns influence treatment decisions despite their often-benign clinical course.

Importantly, a substantial proportion of patients without CR could be managed without further therapy, supporting the concept that complete histological remission is not required for durable clinical benefit in gastric EMZL. Indeed, recent clinical trials have demonstrated that additional (chemo-) therapy following HP eradication offers no significant clinical benefit in patients with gastric EMZL.¹³ At diagnosis, 68.8% of patients were classified as HP-positive, with a

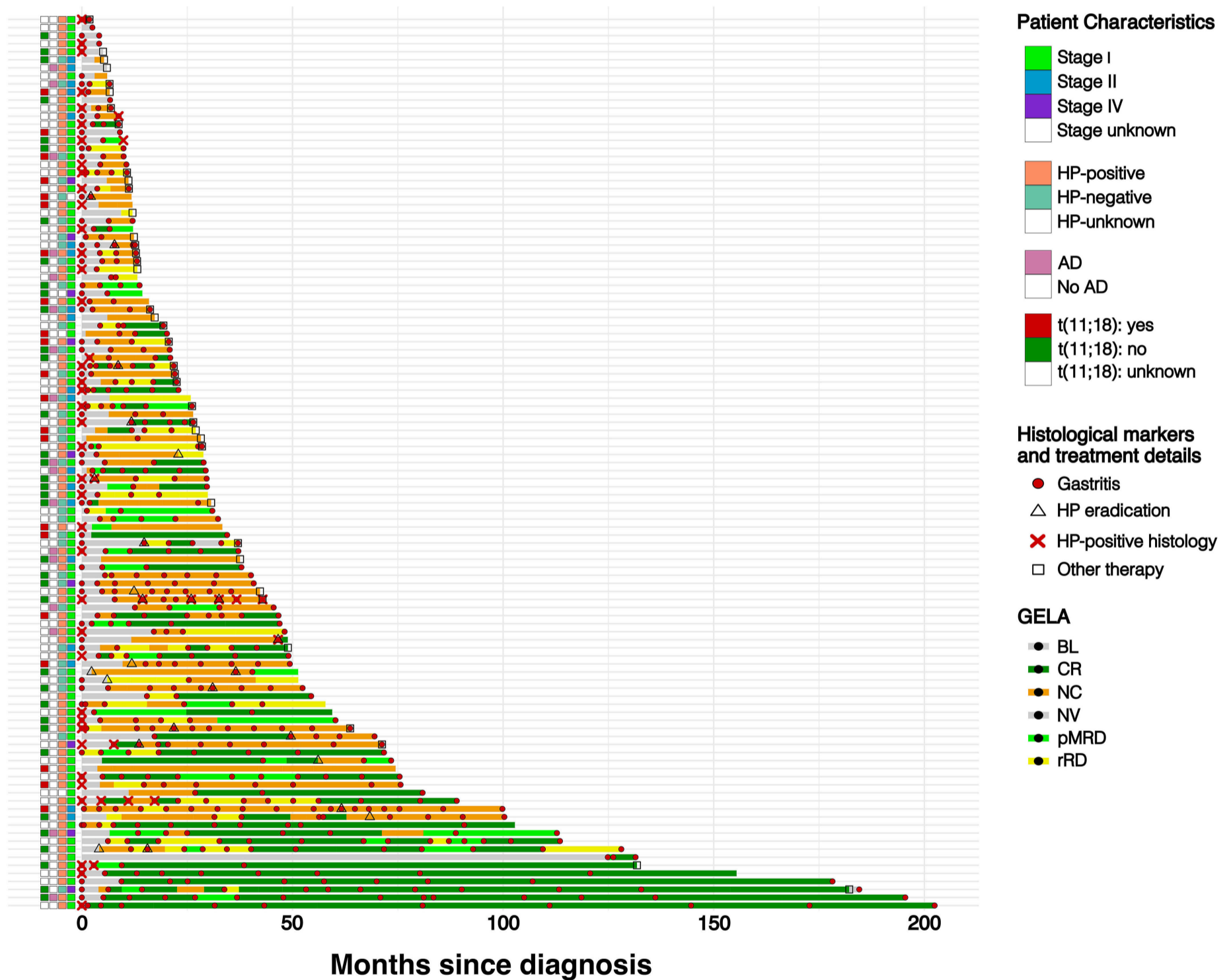


Figure 1. The histopathological response trajectory after first-line *Helicobacter pylori* eradication treatment in patients with primary gastric mucosa-associated lymphoid tissue lymphoma. Each bar represents one patient in the study. The plot depicts relevant clinical co-variates including disease stage (Lugano classification), *Helicobacter pylori* (HP)-status, the presence of concomitant autoimmune diseases (AD) or t(11;18) translocation. Furthermore, the presence of gastritis and HP in each histopathological specimen is noted, where available. We furthermore highlighted the treatment course including consecutive HP-eradications and non-antibiotic treatment per patient. BL: baseline; CR: complete remission; GELA: Groupe d'Étude des Lymphomes de l'Adulte; NC: no change; NA: not available; pMRD: probable minimal residual disease; rRD: responding residual disease.

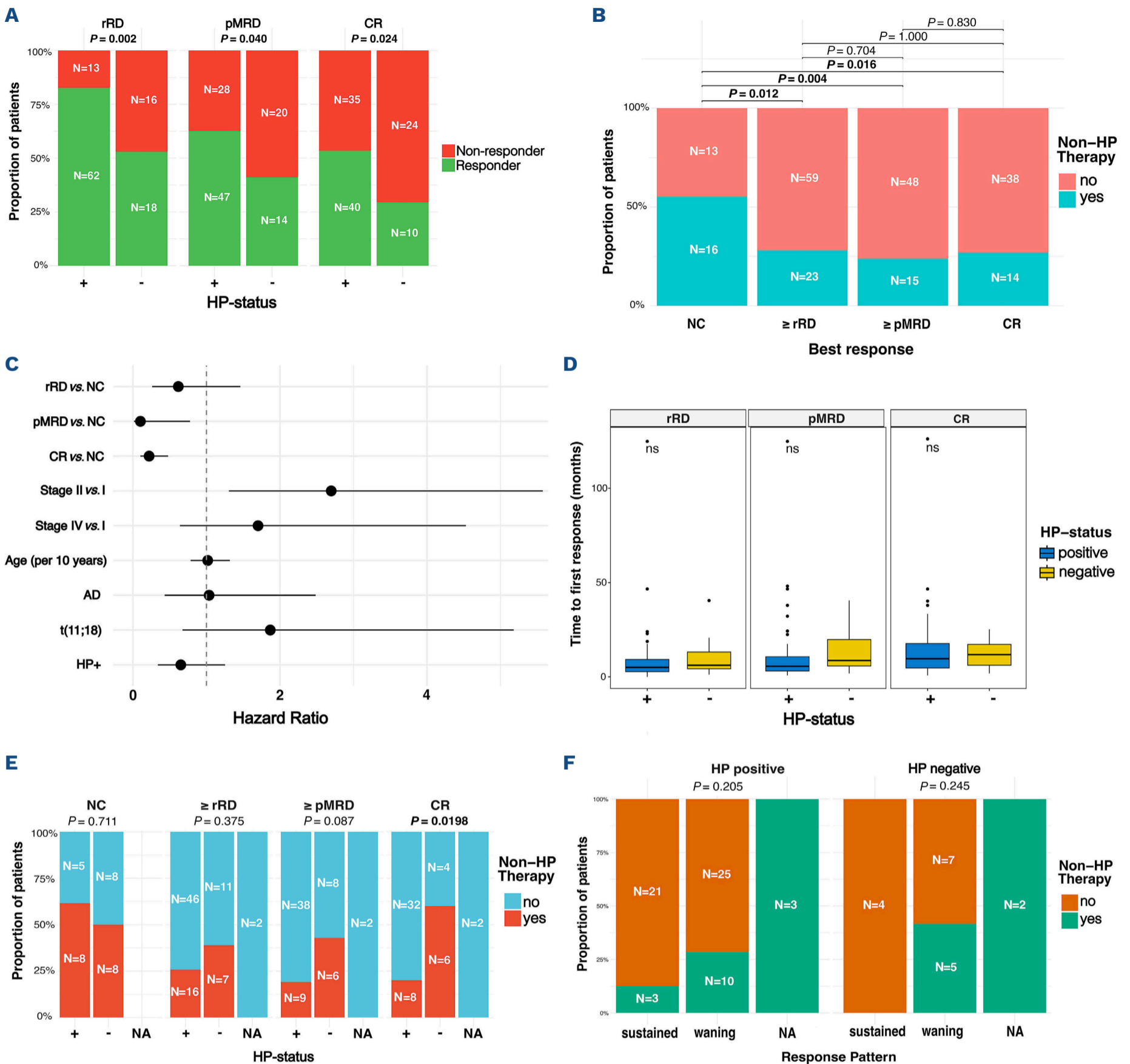


Figure 2. Histopathological response patterns, *Helicobacter pylori* status, and their impact on clinical outcomes in gastric mucosa-associated lymphoid tissue lymphoma patients. (A) The median time to first responding residual disease (rRD), probable minimal residual disease (pMRD) or complete remission (CR) after *Helicobacter pylori* (HP) eradication increases with response depth and is shorter in HP-positive compared to HP-negative patients, although not significantly ($P>0.05$). (B) Patients with rRD, pMRD or CR as best response were significantly less likely to receive subsequent treatment for their mucosa-associated lymphoid tissue (MALT) lymphoma. Notably, 2 patients with rRD or CR and subsequent NC received local radiotherapy. (C) A best histological response of pMRD (hazard ratio [HR]=0.12; 95% confidence interval [CI]: 0.02-0.93; $P=0.042$) or CR (HR=0.26; 95% CI: 0.11- 0.59; $P=0.001$) is associated with a decreased likelihood of receiving subsequent treatment lines in multivariable cox-regression analysis. No significant association of rRD as best response, disease stage, the presence of autoimmune disease (AD) age or HP status was observed. (D) Significantly more HP-positive patients had \geq rRD, \geq pMRD or CR as best response after HP eradication compared to HP-negative patients. (E) Significantly more HP-negative patients with CR as best histopathological response received subsequent treatments compared to HP-positive patients. No significant differences comparing pMRD, rRD or NC with subsequent treatments were observed between HP-positive and HP-negative patients. (F) Fewer patients with a sustained histopathological response received subsequent treatment irrespective of HP-status, although no significant difference was observed for both HP-positive and HP-negative patients ($P>0.05$ each). GELA: Groupe d'Étude des Lymphomes de l'Adulte; NA: not available; NC: no change.

stable incidence over time (*Online Supplementary Figure S1*). HP-positive patients were significantly more likely to achieve \geq rRD, \geq pMRD, and CR ($P=0.002$; $P=0.04$ and $P=0.02$, respectively) compared with HP-negative patients (*Figure 2D*; *Online Supplementary Table S1*) and showed a trend towards faster response onset and deepening (*Figure 2A*), in agreement with historical data.¹⁴ However, responses were not restricted to HP-positive disease: more than half of HP-negative patients achieved \geq rRD, and nearly one-third achieved CR following HP eradication alone, which appears to be higher than in previous publications.¹⁵ Notably, 44% of HP-negative patients did not require any further lymphoma-directed therapy, supporting HP eradication as an appropriate first-line approach even in HP-negative gastric EMZL. Of major clinical impact is the fact that the time to (best) response in HP-negative patients was longer than for HP-positive patients in our series. This challenges the recommended practice of initiating oncological therapies after a shorter follow-up time of only 3–6 months after antibiotic therapy in case of non-response than in HP-positive patients, as suggested in the current European Society for Medical Oncology guidelines.⁵

Despite similar patterns linking deeper histological response to lower treatment rates in both groups, HP-negative patients who achieved CR were more likely to receive subsequent therapy than HP-positive patients with CR (*Figure 2E*). Sustained histological responses were numerically more frequent in HP-positive patients, although differences did not reach statistical significance. Fewer patients with sustained histopathological response received subsequent non-antibiotic treatment than patients with a waning histopathological response in both groups (*Figure 2F*).

In summary, this large single-center longitudinal analysis demonstrates that histological response after HP eradication in gastric EMZL is highly dynamic and frequently fluctuating. Complete histological remission is not a prerequisite for durable disease control, and transient histological persistence or relapse is common and often clinically inconsequential. HP eradication alone provides long-term disease control in most HP-positive patients and a meaningful subset of HP-negative patients. Our findings support a conservative, observation-based strategy after HP eradication, emphasizing the integration of histological findings into the broader clinical context rather than using isolated biopsy results as triggers for immediate therapy.

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Contributions

VS and MR conceived the conceptual idea, designed and performed the analysis. VS, BK, ISK, RB, WD, MM, and MR contributed to data collection and interpretation of the results. VS and MR wrote the manuscript. BK, ISK, RB, WD, and MM critically reviewed the manuscript. All named authors meet all four criteria for (co)-authorship provided by the Good Scientific Practice guidelines of the Medical University of Vienna. All authors read and approved the final manuscript.

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Data-sharing statement

Data may be made available upon reasonable request to the corresponding author, contingent upon approval by the institutional review board and completion of a data-sharing agreement.

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