Treatment approaches and clinical outcomes in primary colorectal MALT lymphoma: a single-institution retrospective study of 66 patients

While the pathobiology and treatment approaches for common extranodal marginal zone lymphomas (ENMZL) of mucosa-associated lymphoid tissue (MALT), such as gastric MALT lymphoma, are well described,[1,2] knowledge remains limited regarding primary MALT lymphomas arising in less common sites, such as the colon. Primary colorectal MALT lymphoma is rare, accounting for only 2-3% of MALT lymphomas.[3,4] Most data on colorectal MALT lymphoma comes from case reports, small series, and SEER database analyses, predominantly from Southeast Asia. These studies describe heterogeneous treatments and generally favorable outcomes, but no consensus treatment guidelines exist.[3,5-10] We present the largest single-institution North American cohort of primary colorectal MALT lymphoma, detailing clinicopathologic features, risk factors, treatments and outcomes to inform management strategies.

This institutional review board-approved study retrospectively analyzed 66 patients with stage I-IIE colorectal MALT lymphoma diagnosed at the Mayo Clinic between 1994 and 2024. All diagnostic pathology specimens were reviewed by hematopathologists from the Mayo Clinic. Inclusion criteria were stage I-IIE disease and available treatment records. Patients with a prior MALT lymphoma or stage III-IV disease (e.g., bone marrow or other gastrointestinal involvement) were excluded. Data were analyzed using R version 4.4.3. A two-sided *P* value <0.05 was considered statistically significant. Group comparisons were performed using the Pearson χ^2 and Kruskal-Wallis tests for nominal and continuous variables respectively. Event-free survival (EFS) was defined as the time from treatment initiation to the date of disease progression, subsequent treatment, or death from any cause, censored on the date of last follow-up. Overall survival (OS) was defined from treatment initiation time to date of death, censored on the date of last follow-up. Patients initially observed had survival calculated from the time of diagnosis. Cumulative incidence rates for lymphoma-specific survival were calculated using competing risk model, treating death from non-lymphoma causes as a competing event.

Sixty-six patients with stage I-IIE colorectal MALT lymphoma were identified. The median age at diagnosis was 65 years (interquartile range [IQR], 57-72), and 52% were male. Table 1, summarizes patient and disease characteristics. Among isolated sites of involvement, the rectum was most frequently affected (N=16). The distribution of lymphomatous lesions throughout the colon is shown in Figure 1. Most patients (89%) were diagnosed incidentally during routine colonoscopy. Only seven patients presented with symptoms (hematochezia,

Table 1. Patient and disease characteristics of 66 patients with primary colorectal mucosa-associated lymphoid tissue lymphoma stage I-IIE.

Characteristic	N=66
Age at diagnosis, years, median (IQR)	65 (57-72)
Female, N (%)	32 (48)
ECOG PS, N (%)	
0	57 (86)
1	8 (12)
2	1 (2)
LDH >ULN, N (%)	2 (3)
Unknown	7 (11)
Incidental diagnosis, N (%)	59 (89)
Stage, N (%)	
IE	60 (91)
IIE	6 (9)
BM biopsy performed, N (%)	49 (74)
EGD performed, N (%)	48 (73)
Colonoscopy findings, N (%)	
Single polyp	37 (56)
Multiple polyps	7 (11)
Single mass	7 (11)
Changes in mucosal vascularity	6 (9)
Single nodular/submucosal lesion	4 (6)
Multiple nodular/submucosal lesion	4 (6)
Rectal thickening	1 (2)
Site of disease, N (%)	
Rectum	16 (24)
Cecum	13 (20)
Sigmoid colon	12 (18)
Transverse colon	7 (11)
Ascending colon	4 (6)
Descending colon	3 (5)
Hepatic flexure	1 (2)
Multiple-sites	10 (15)
Ki-67 index, N (%)	
5	10 (15)
10	6 (9)
20	4 (6)
Unknown	46 (70)
Associated M-protein (serum), N (%)	
IgA	1 (2)
IgG	1 (2)
IgM	3 (5)
No monoclonal protein	28 (42)
Not done	33 (50)

ECOG PS: Eastern Cooperative Oncology Group performance status; LDH: lactate dehydrogenase; ULN: upper limit of normal; BM: bone marrow; EGD: esophagogastroduodenoscopy; IQR: interquartile range; M-protein: myeloma protein; Ig: immunoglobulin.

N=5; diarrhea, N=2). Most symptomatic patients (N=6) had disease localized to the rectosigmoid region. No B symptoms or obstruction were reported.

Stage IE disease was present in 91%. Six patients had regional lymph node involvement, including three found post-surgery. Most patients (N=48) presented with a single disease focus: polyp (N=37), mass (N=7) or nodular lesion (N=4). Eighteen patients had either multiple lesions or mucosal changes; ten had >1 colonic section involved. No stage IIE patients had a single polyp; they presented with multiple polyps, diffuse mucosal changes, or a mass.

Forty-eight patients underwent esophagogastroduodenoscopy (EGD). *H. pylori* was detected in two of 43 tested. No patients had HIV. Ten had autoimmune disease or prior solid organ transplant (SOT). Autoimmune conditions included rheumatoid arthritis (N=2), Hashimoto's (N=2), psoriasis, Crohn's, ulcerative colitis and celiac disease (N=1 each). Three had prior SOT (kidney N=2; liver N=1). At diagnosis, six were on immunosuppressants: tacrolimus (N=2), tacrolimus + mycophenolate (N=1), methotrexate (N=2), and etanercept (N=1).

Eleven patients underwent fluorescence *in situ* hybridization testing: five with the *MALT1* probe alone and six with both *MALT1* and *BCL6* probes. Among these, five had abnormalities: two with *MALT1* rearrangement (likely t(11;18)), one with trisomy 3, one with trisomy 18, and one with a *BCL6* rearrangement.

First- and second-line treatments and their associated outcomes are summarized in *Online Supplementary Figure S1*. Five patients were initially observed following a biopsy-confirmed lymphoma, They initially presented with a polyp (N=2), mucosal irregularity (N=1), nodular lesions (N=1), or wall thickening (N=1). Two of five were subsequently treated for disease progression.

Among 33 patients who underwent complete endoscopic resection (including 3 with multiple polyps); three experienced relapse and were treated endoscopically without further therapy. Another patient developed transformation to diffuse large B-cell lymphoma (DLBCL).

Three patients underwent endoscopic resection with residual disease left at diagnosis and were subsequently observed. These included two patients with multiple polyps not fully removed at time of diagnosis, and one patient with persistent fluorodeoxyglucose (FDG) avidity on positron emission tomography/computed tomography. Only the latter received subsequent therapy due to increasing FDG avidity at original disease site and achieved complete remission (CR) with rituximab.

Five patients received frontline radiation including two post endoscopic resection (1 complete, 1 incomplete). All had unifocal disease. Only one of five patients experienced relapse and was re-treated with radiation. Nine patients received frontline rituximab, including three with multifocal lesions and two post complete endoscopic resection. Four had persistent disease post-rituximab and required other systemic therapies. Among the five who achieved CR with rituximab, only one had relapse and was treated with polypectomy alone. Ten had upfront surgery (4 hemicolectomies, 3 transanal excisions, 1 sigmoidectomy, 1 cecectomy, 1 partial cecectomy). Surgical indications included non-specific mucosal changes on colonoscopy (N=4), colonic mass (N=3), mixed polypoid and submucosal lesions (N=1), multiple rectal polyps (N=1), and a lesion not amenable to endoscopic resection (N=1). Three experienced relapse post-surgery but none after hemicolectomy.

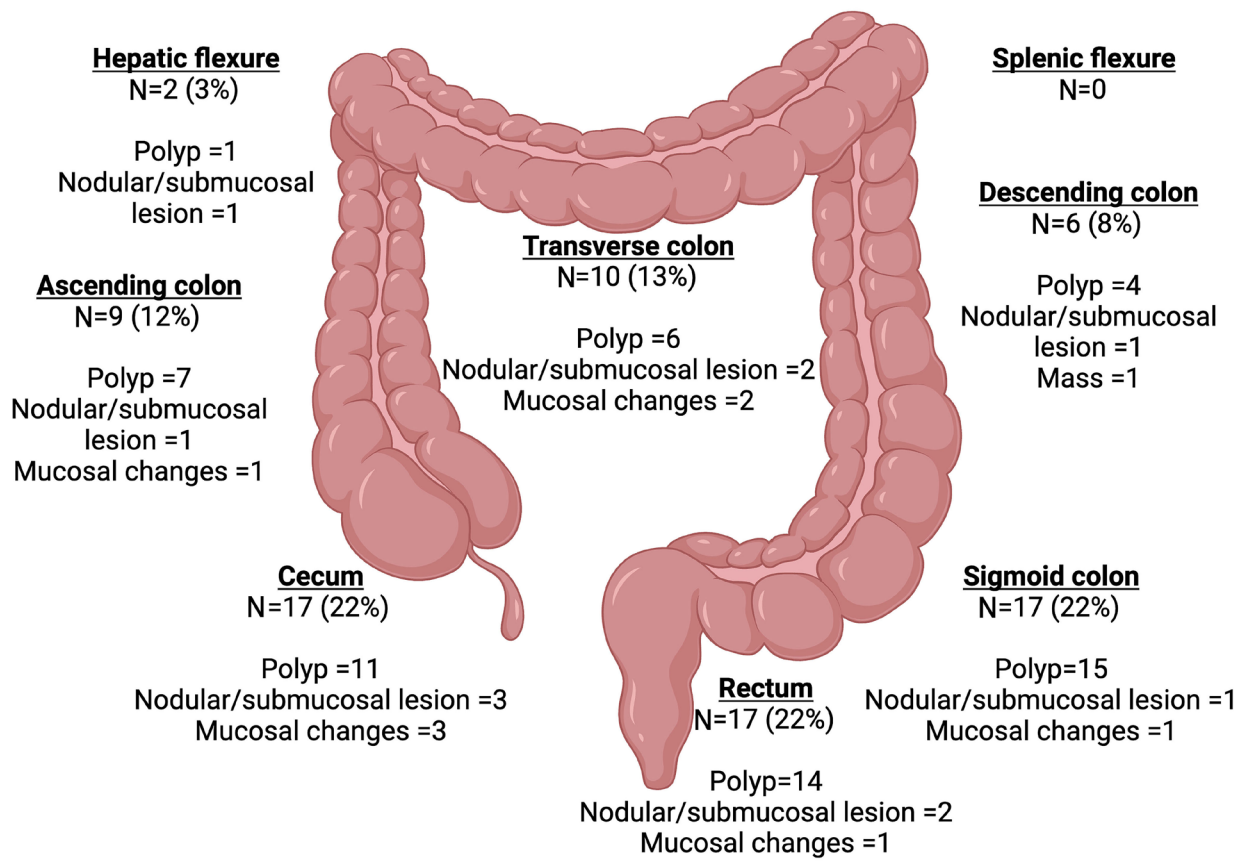

Figure 1. Anatomic location of 78 primary colorectal mucosa-associated lymphoid tissue lymphoma lesions in 66 patients and their endoscopic appearance. Ten patients had >1 site of disease.

Half of the stage IIE patients experienced relapse or progression (N=3) and were initially managed with observation (N=1), rituximab (N=1), or partial cecectomy (N=1). Notably, stage IIE patients who did not have relapse/progression were initially treated with hemicolectomy (N=2) or complete removal of all polyps (N=1).

Median follow-up was 6.1 years (95% confidence interval [CI]: 4.16-8.44); median OS and EFS were 19.3 years (95% CI: 18.7-not reached [NR]) and 12.4 years (95% CI: 6.9-NR), respectively (Figure 2). The 10-year OS and EFS were 88.2% and 57.6%, respectively. The 10-year cumulative incidence of lymphoma-specific and non-lymphoma death were 3.3% and 4.5%, respectively (Figure 2). One patient experienced transformation to DLBCL, which accounted for the only lymphoma-related death. This patient underwent polypectomy at diagnosis then was observed until he developed DLBCL transformation 3.6 years after initial diagnosis of MALT lymphoma.

Our study, the largest North American colorectal MALT lymphoma cohort, highlights several key findings. The median age at diagnosis, balanced sex distribution, predominance of incidental detection, and frequent rectal involvement are consistent with prior small series and SEER database analyses.[3,7-11] The favorable prognosis in our cohort aligns with survival outcomes reported in other studies. The Asan Medical Center study (N=51) reported a 5-year progression-free survival of 92%, and disease-specific survival rate of 98%.[7] A SEER-based study of 361 patients with stage 1 colorectal MALT lymphoma reported a 10-year OS of 73.9% and a 15-year cumulative incidence of lymphoma-specific death of 10.6%, with no OS difference by treatment strategy, including observation, surgery, or combined approaches.[3]

These data suggest that definitive treatment recommendations remain challenging and should be individualized based on patient and disease characteristics. We support complete endoscopic polypectomy/resection followed by observation when feasible, given the excellent outcomes

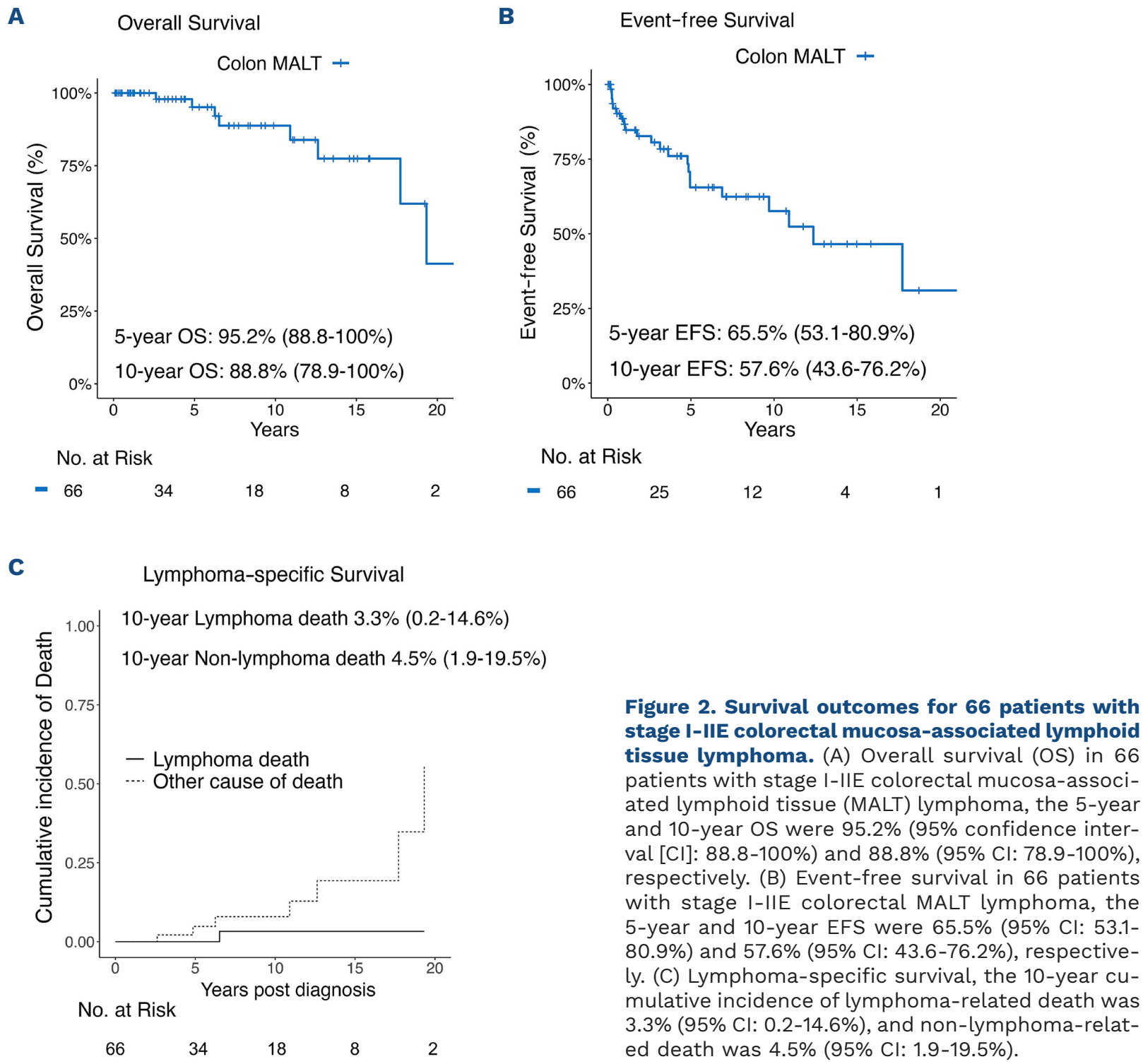

Figure 2. Survival outcomes for 66 patients with stage I-IIE colorectal mucosa-associated lymphoid tissue lymphoma. (A) Overall survival (OS) in 66 patients with stage I-IIE colorectal mucosa-associated lymphoid tissue (MALT) lymphoma, the 5-year and 10-year OS were 95.2% (95% confidence interval [CI]: 88.8-100%) and 88.8% (95% CI: 78.9-100%), respectively. (B) Event-free survival in 66 patients with stage I-IIE colorectal MALT lymphoma, the 5-year and 10-year EFS were 65.5% (95% CI: 53.1-80.9%) and 57.6% (95% CI: 43.6-76.2%), respectively. (C) Lymphoma-specific survival, the 10-year cumulative incidence of lymphoma-related death was 3.3% (95% CI: 0.2-14.6%), and non-lymphoma-related death was 4.5% (95% CI: 1.9-19.5%).

associated with this approach in our cohort and others.[7,9] For patients with residual disease or positive margins, or when complete resection is not feasible, additional locoregional therapies (radiation, surgery) or systemic treatment may be appropriate. Both upfront radiation and surgery are effective treatment options.[3,7] Given the anatomical complexity and bowel motility, radiation should be delivered at experienced centers. Extensive surgeries should be reserved for patients with complications such as obstruction or perforation to avoid surgical complications and overtreatment.

Systemic immunochemotherapy may be appropriate in cases with multifocal or symptomatic disease. Rituximab monotherapy data in colorectal MALT lymphoma are limited. In our cohort, several patients had persistent disease post-rituximab requiring subsequent therapies. However, of five patients who achieved remission post-rituximab, only one experienced relapse, suggesting a potential role for early response assessment in determining subsequent therapy needs. Chemotherapy was administered to only six patients: one at initial diagnosis, four at first relapse or progression, and one as third-line therapy.

The pathogenesis of MALT lymphoma involves chronic antigenic stimulation, often related to infection or immune dysregulation.[1,2,12] In our cohort, 12% of patients had autoimmune disease, and 5% had a prior SOT. MZL-PTLD is rare and, per World Health Organization 2017 criteria, requires Epstein-Barr virus (EBV) positivity for diagnosis. Nonetheless, EBV-negative MALT lymphoma has been reported in SOT recipients.[13] Regression of MZL upon reducing immunosuppression (RIS) in SOT patients was illustrated in some case reports.[14] In our study, one patient had EBV-positive MALT lymphoma early post-transplant and was treated with hemicolectomy. Two others developed disease later post-SOT with no evidence of EBV and were managed with locoregional therapy and RIS. Iatrogenic immunodeficiency-associated lymphoproliferative disorders with indolent B-cell histology are rare and often difficult to distinguish from coincidental MALT lymphoma in immunosuppressed patients.[15] Three patients were on immunosuppressants for autoimmune disease (etanercept, N=1; methotrexate, N=2) and received locoregional therapy at diagnosis. Etanercept was withdrawn, methotrexate continued, and all remained in remission.

Limitations of our study include its retrospective nature, limited molecular testing and inconsistent EGD/bone marrow evaluation, which limits our ability to exclude concurrent MALT lymphoma in other gastrointestinal sites or bone marrow in all cases. The small number of events precluded formal analysis of predictors of relapse or progression.

In conclusion, MALT lymphoma confined to the colon follows an indolent course and can be effectively managed with a range of treatment modalities. However, the heterogeneity of therapies and lack of clinical trials limit the development of standardized guidelines. Given the favorable outcomes with complete endoscopic resection, we support conservative treatments over aggressive approaches. As the largest reported cohort to date, our study may serve as a reference for clinicians managing this rare lymphoma.

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Contributions

GSN and SAAY came up with the conception and design of the study. SAAY collected and assembled data. MJR and SAAY analyzed the data. All authors interpreted the data, provided expert input and approved the final version of the manuscript.

Data-sharing statement

Data is available upon reasonable request.

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