



Ocular Adnexal Marginal Zone Lymphoma: Retrospective Analysis and Clinical-Pathological Features

Fatma Seher Pehlivan¹, Ömer Atmış¹, Hanife Seda Mavili¹

1 Manisa Celal Bayar University, Faculty of Medicine, Department of Pathology, Manisa, Türkiye

Received: 14.09.2025; Revised: 03.11.2025; Accepted: 04.11.2025

Abstract

Objective: Ocular adnexal lymphomas are rare malignancies, accounting for approximately 1–2% of all non-Hodgkin lymphomas and 8–10% of extranodal lymphomas. Among these, ocular adnexal marginal zone lymphoma (OA-MZL) represents the predominant histologic subtype, comprising 55–80% of all orbital/ocular adnexal lymphomas. The aim of this study is to retrospectively evaluate the clinical and histopathological features of cases diagnosed with ocular adnexal marginal zone lymphoma (OA-MZL) and to compare the findings with the current literature.

Methods: A total of 10 OA-MZL cases diagnosed between 2010 and 2025 in the archives of the Department of Pathology, Celal Bayar University, Manisa, with conjunctival and/or lacrimal gland involvement were included in this study. The slides of all cases were retrieved from the archives and re-evaluated under a microscope. Previously prepared hematoxylin–eosin sections and immunohistochemical slides were re-evaluated to confirm the diagnosis. The patients' clinical data, treatment protocols, and follow-up results were obtained from the hospital information system. Clinicopathological parameters were documented, and a descriptive statistical analysis was conducted and the data obtained were compared with the literature.

Results: The mean age of the cases was 65.9 (39-82), and the female/male ratio was 3/7. The most common presenting symptom was orbital swelling. Histopathological examination revealed diffuse monomorphic small lymphoid cell infiltration, and the immunohistochemical panel applied showed tumor cells to be CD20 and BCL2 positive, CD3, CD5, CD21, CD23, Bcl-6, CD10, and Cyclin D1 negative. The mean Ki-67 index was 13.3%. Plasmacytic differentiation was observed in 2 cases. Three patients received definitive radiotherapy, whereas six patients were monitored with active surveillance due to indolent disease behavior. The mean follow-up period was 50 months, and recurrence was detected in 1 case.

Conclusion: Ocular adnexal marginal zone lymphomas are neoplastic proliferations that are clinically indolent but require careful histopathological differential diagnosis. This study aims to contribute by presenting and evaluating the clinical and pathological findings of these rare localizations in the context of the literature.

Keywords: Ocular adnexal marginal zone lymphomas, immunohistochemical stains

DOI: 10.5798/dicletip.1840690

Correspondence / Yazışma Adresi: Fatma Seher Pehlivan, Manisa Celal Bayar University, Faculty of Medicine, Department of Pathology, 45030, Yunusemre/Manisa, Türkiye e-mail: seherfatma@hotmail.com fatma.pehlivan@cbu.edu.tr

Oküler Adneksiyal Marjinal Zon Lenfoma : Retrospektif Analizi ve klinikopatolojik özellikleri

Öz

Amaç: Oküler adneksiyal lenfomalar, tüm non-Hodgkin lenfomaların yaklaşık %1-2'sini ve tüm ektranodal lenfomaların %8-10'unu oluşturan nadir malignitelere aittir. Bu anatomik bölgede en sık görülen histolojik tip ektranodal marginal zon lenfoma olup, olguların %55-80'ini kapsamaktadır. Bu çalışmanın amacı, oküler adneksiyal marjinal zon lenfoma (OA-MZL) tanısı almış olguların klinik ve histopatolojik özelliklerini retrospektif olarak değerlendirmek ve elde edilen bulguları güncel literatür ile karşılaştırmaktır.

Yöntemler: 2010-2025 yılları arasında Manisa Celal Bayar Üniversitesi Patoloji Anabilim Dalı arşivinde tanısı konmuş, konjonktiva ve/veya lakrimal gland yerleşimli toplam 10 OA-MZL olgusu bu çalışmaya dahil edildi. Tüm olgulara ait lamlar arşivden çıkarılarak tekrar değerlendirildi. Tanıların doğrulaması amacıyla mevcut hematoksilen-eozin kesitleri ve immunohistokimyasal boyalı lamlar yeniden gözden geçirildi. Hastaların klinik verileri, tedavi protokolleri ve takip sonuçları hastane bilgi sisteminden elde edildi. Klinikopatolojik bulgular dökümanite edilip tanımlayıcı istatistiksel analiz uygulandı ve elde edilen veriler literatür ile karşılaştırıldı.

Bulgular: Olguların yaş ortalaması 65.9 (39-82) olup, kadın/erkek oranı 3/7 idi. En sık başvuru bulgusu orbitada şişlik olarak kaydedildi. Histopatolojik incelemede diffüz monomorfik küçük lenfoid hücre infiltrasyonu gözlenmiş olup uygulanan immunohistokimyasal panelde tümör hücreleri CD20 ve BCL2 pozitif, CD3, CD5, CD21, CD23, Bcl-6, CD10 ve Siklin D1 negatif olarak değerlendirildi. Ortalama Ki-67 indeksi %13.3 idi. Plazmasitik diferansiyasyon 2 olguda izlendi. Üç hastaya yalnızca radyoterapi uygulanırken, hastalığın indolent seyri nedeniyle altı hasta aktif izlem ile takip edildi. Ortalama takip süresi 50 ay olup, 1 olguda nüks saptandı.

Sonuç: Oküler adneksiyal marjinal zon lenfomalar, klinik olarak yavaş seyirli ancak histopatolojik olarak dikkatli ayırıcı tanı gerektiren neoplastik proliferasyonlardır. Bu çalışma, nadir görülen bu lokalizasyonlara ait klinik ve patolojik bulguları ortaya koyup literatür eşliğinde değerlendirerek katkı sağlamayı hedeflemektedir

Anahtar kelimeler: oküler adneksiyal marjinal zon lenfoma, immunohistokimyasal panel.

INTRODUCTION

Ocular adnexal lymphoma (OAL) is one of the most common malignancies in this location, despite being a rare disease. OALs are neoplasms that arise in lymphoid tissue and affect the structures surrounding and supporting the function of the eyeball. OAL accounts for approximately 3% of lymphomas occurring outside the lymph nodes^{1,2}. The most common histological subtype in this group is extranodal marginal zone B-cell lymphoma. OAMZL (Ocular Adnexal Marginal Zone Lymphoma) accounts for 50-80% of all ocular lymphomas and usually presents as a slow-growing, indolent tumor in older age groups³.

Ocular Adnexal Marginal Zone Lymphoma usually presents with unilateral or bilateral swelling, mass appearance, drooping of the eyelid, or chronic conjunctival inflammation-like findings²⁻⁴. Rarely, invasion of bone,

sinuses, nasopharynx, and cranial cavity may occur. Spread may occur to regional lymph nodes and also to more distant central and peripheral nodes⁵. The disease often remains localized, and systemic spread is rare. However, it has been reported that systemic lymphoma may develop in 10-20% of cases⁶. Therefore, long-term follow-up is critical.

The pathogenesis of OAMZL is multifactorial; chronic antigenic stimulation, infectious agents, immunological mechanisms, genetic/molecular alterations, and interactions with the tumor microenvironment play a role. A strong association with *Chlamydia psittaci* has been reported in OAMZL. Studies have shown that *C. psittaci* DNA is detected at high rates in OAMZL cases and that antibiotic treatment has resulted in tumor regression in some patients^{4,7,8}. Similar to the role of *Helicobacter pylori* in gastric

MALT lymphoma, *Achromobacter xylosoxidans* and *Borrelia burgdorferi* have been associated with OAMZL in some studies^{2,9}. Several precursor lesions with the potential to transform into OAMZL have been identified; these include orbital pseudotumors (idiopathic orbital inflammatory disease (IOID)), reactive lymphoid hyperplasia (RLH), and IgG4-related diseases. As inflammatory non-malignant conditions, precursor lesions in that they lead to chronic antigenic stimulation, which can cause activation of the NF- κ B signaling pathway, chromosomal changes, and other genetic and epigenetic alterations. Chronic infection or inflammation can lead to polyclonal B-cell activation and subsequent monoclonal proliferation by creating continuous antigenic stimulation in the local lymphoid tissue. The association with autoimmune diseases is noteworthy: increased incidence of OAMZL has been reported in patients with Sjögren's syndrome and Hashimoto's thyroiditis. These findings suggest that OAMZL may be an antigen-dependent lymphoma associated with infection and autoimmunity^{2,6,8,10}.

Various translocations and chromosomal alterations have been reported in the molecular pathogenesis. The t(11;18)(q21;q21)/BIRC3-MALT1 translocation suppresses apoptosis by activating the NF- κ B pathway and contributes to lymphoma cell proliferation. The t(14;18)(q32;q21)/IGH-MALT1 translocation prolongs the lifespan of tumor cells by increasing MALT1 expression. Molecular heterogeneity may be important in explaining different clinical courses and treatment responses^{2,11}

The microenvironment also plays a critical role in OAMZL development. Tumor cells interact closely with stromal cells, dendritic cells, and T cells. In particular, the expansion of follicular dendritic cell networks and T-helper cell support contribute to the survival of tumor cells^{6,10}.

Although OAMZL typically follows an indolent clinical course, its diagnosis can be challenging due to overlapping features with benign inflammatory diseases and other low-grade lymphomas. Early and accurate recognition is crucial to prevent unnecessary interventions, to guide appropriate treatment, and to ensure long-term surveillance for potential relapse or systemic involvement.

METHODS

In this study, patients diagnosed with extranodal marginal zone lymphoma between 2010 and 2025 were screened from the archives of the Department of Pathology, Faculty of Medicine, Celal Bayar University. Among these patients, 10 patients with ocular adnexal localization were included in the study. Only biopsy-proven cases with available clinical data, histopathologic slides, and immunohistochemical studies were evaluated. Exclusion criteria included secondary ocular involvement by systemic lymphoma. Tissue samples were fixed in 10% neutral-buffered formalin. Hematoxylin-eosin (H&E)-stained preparations and immunohistochemically stained slides for all cases were retrieved from the pathology archive. All cases were independently reviewed by two pathologists (ÖA, FSP) and no diagnostic discordance was observed. Therefore, inter-observer agreement was assessed qualitatively without the need for statistical concordance analysis. The infiltration patterns of OA MZL, the cytomorphology of neoplastic cells, the presence of reactive germinal centers, lymphoepithelial lesions, stromal changes, and plasmacytic differentiation were reviewed in HE-stained preparations. Clinical data for the cases were obtained from patient files and the hospital electronic record system. The data examined included age, gender, presenting complaints, tumor location (orbit, conjunctiva, eyelid, lacrimal gland), history of accompanying

systemic disease, treatment, and follow-up information.

Ethical approval for the study was granted by The Celal Bayar University Ethics Committee (Approval No: 20.478.486/3341, dated July 30, 2025).

A low-grade B-cell lymphoma panel was applied to all cases. Immunohistochemical staining was performed using an automated immunohistochemistry device (Roche Diagnostics). Immunohistochemical evaluation was performed using the following antibody clones: CD20 (L26), CD3 (2GV6), CD5 (SP19), CD10 (SP67), CD79a (SP18), PAX5 (SP34), BCL2 (124), BCL6 (G1191E/A8), Cyclin D1 (SP4-R), MUM1 (MRQ-8), and Ki-67 (30-9). Appropriate positive and negative control tissues were included for each staining run, and a lymph node with normal morphology was used as the control tissue. All cases were re-evaluated according to the 2017 World Health Organization (WHO) Classification of Hematopoietic and Lymphoid Neoplasms criteria.

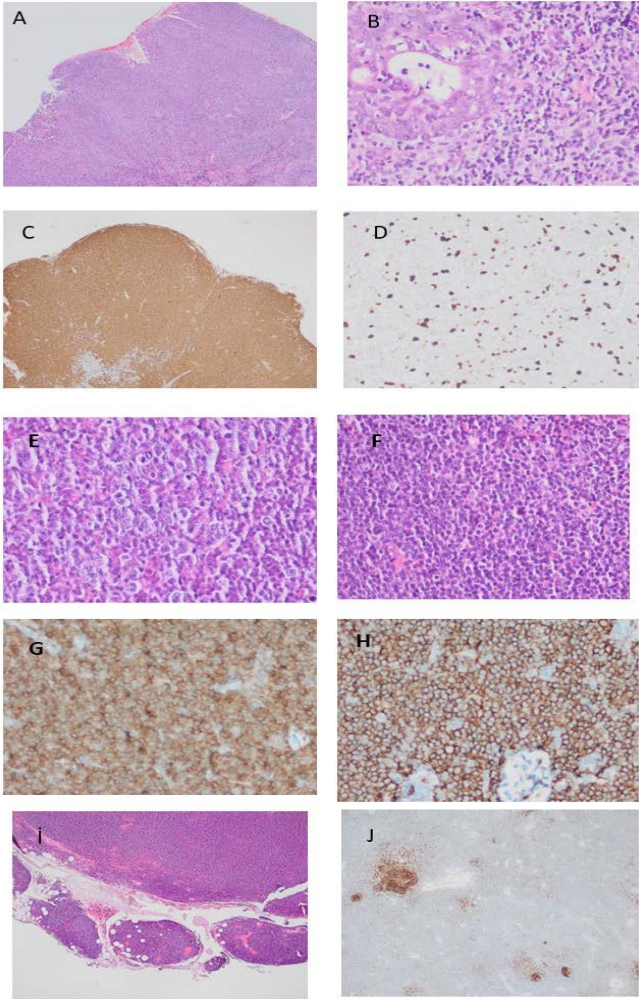
Treatment decisions (active surveillance vs radiotherapy) were based on tumor localization, symptom severity, stage at diagnosis, in line with contemporary international guidelines. Treatment approaches (radiotherapy, chemotherapy, immunotherapy) and follow-up periods, relapse, systemic spread, and survival status were obtained from patient files and electronic archives. Overall survival (OS): The time from diagnosis to death or last follow-up was included

Statistical Analysis

SPSS software was used for statistical evaluations. Given the small sample size and the nature of the study, only descriptive statistics (mean, range, frequency, percentage) were reported. Inferential statistical tests were not applied.

RESULTS

The mean age of the 10 patients included in the study was 65.9 (range: 39-82) years. Three patients were female (30%), and seven were male (70%). Six cases were localized in the left eye, three in the right eye, and one was bilateral. The presenting complaint in all patients was swelling and a mass in the eyelid or orbital region. Some cases also presented with redness and a burning sensation in the eye. In terms of tumor localization, 4 were in the conjunctiva, 3 were in the lower eyelid and soft tissue, 1 involved both the lower and upper eyelids, and 2 were located in the lacrimal gland. No history of systemic lymphoma or concomitant autoimmune disease was detected. Histopathological examination revealed diffuse monomorphic small lymphoid cell infiltration in all cases. Reactive germinal centers were observed in most cases, while lymphoepithelial lesions were detected in two cases. Plasmacytic differentiation was present in 2 cases. A low-grade B-cell lymphoma panel was applied to all cases, and CD20 and Bcl2 were strongly and diffusely positive in all cases. CD3 and CD5 were negative, ruling out T-cell origin. CD10, BCL6, and Cyclin D1 were negative in all cases. CD21 and CD23 showed a disrupted and sometimes enlarged network of follicular dendritic cells. The Ki-67 proliferation index was low to moderate, with a mean of 13.3% (range 5–30%) (Figures A-J) These findings supported the diagnosis of extranodal marginal zone B-cell lymphoma in all cases. Six cases were followed as close follow-up patients. Three were treated with radiotherapy alone, and one was not followed up. The mean follow-up period was 50 months (range 12–120 months). During follow-up, relapse was detected in one case after 5 years, and systemic spread and bone marrow involvement were seen in only one case. One patient in the study died. This patient was 79 years old and died of secondary disease at the end of an 84-month follow-up period.



Figures A-J: a dense infiltrate of small, round-shaped cells in conjunctiva HEx10 and lymphoepithelial lesions HEx100(A-B) the lymphoma cells express CD20 (C). Ki 67 proliferation index %10 (D). Small to medium-sized lymphocytes infiltrate HEx100 (E-F). lymphoma cells immunohistochemistry CD20 and Bcl-2 diffuse positive (G-H). neoplastic cells show adipose tissue infiltration HEx20 (I). CD23 shows irregular follicular dendritic cell meshworks (J).

DISCUSSION

In our study, the majority of OAMZL cases were located in the conjunctiva-eyelid (80%), while lacrimal gland involvement was more limited (20%). This distribution is basically consistent with the localizations reported in large series, but the marked predominance of conjunctival involvement is noteworthy. In the literature, soft tissue of the orbit (40–64%) and conjunctiva (32–40%) are reported as the most

common sites of involvement in OAL; lacrimal gland involvement is reported at lower rates. In the literature, bilateral involvement is ~10–15% in large series and can be seen in the conjunctiva and orbit. In our series, bilateral involvement was seen in only one case¹¹⁻¹³.

The clinical symptoms of conjunctival OAMZL are mostly characterized by swelling, mass effect, and mild irritation; in orbital involvement, ptosis, limited ocular movement, and decreased visual acuity are prominent. The predominance of conjunctival-eyelid localization in our series is consistent with these symptoms; moreover, the ease of biopsy access from these areas may have contributed to the early detection and relative abundance of these lesions for diagnosis.

Histopathologically, all our cases showed typical monomorphic small-to-medium B lymphocyte infiltration, lymphocytic infiltration surrounding reactive germinal centers (germinal center colonization), and, to a lesser extent, lymphoepithelial lesions and plasmacytic differentiation.

These features have been described in the literature as the most important morphological findings in the differential diagnosis of OAMZL^{14,15}. Immunohistochemically, tumor cells in our cases showed strong positivity for CD20, while CD5, CD10, and Cyclin D1 were negative.

BCL2 positivity was observed in all cases, while the Ki-67 proliferative index was low, ranging from 5% to 30%. This profile is consistent with the typical OAMZL phenotype described in the literature and plays a critical role in distinguishing extranodal marginal zone lymphoma from follicular lymphoma or mantle cell lymphoma. Additionally, plasmacytic differentiation was detected in 2 cases. These findings reflect the heterogeneous micromorphological spectrum of OAMZL^{3,16}.

In terms of localization-stage relationship, a significant proportion of OAMZL cases in large cohorts are detected at Ann Arbor IE stage and AJCC T1 (conjunctiva) or T2 (orbit) level. The absence of orbital involvement and conjunctival involvement in our series is consistent with the possibility of earlier stage detection; this is a factor that positively affects prognosis.

Treatment options for OAMZL vary depending on localization, stage, and patient characteristics. In large series, simple excision has been used more frequently for conjunctival lesions, while radiotherapy has been used more frequently for orbital/lacrimal gland involvement¹⁶⁻¹⁸. In our series, despite the predominance of conjunctival involvement, the low recurrence rate (single recurrence), follow-up period, and additional treatment preferences (e.g., application of RT) suggest that these factors contributed to this positive outcome.

In the literature, radiotherapy is the most effective method, especially in limited disease involving the conjunctiva and orbit, providing local control in 85–95% of cases. Even ultra-low-dose RT (e.g., 2x2 Gy) has been reported to have high response rates and has been found to be advantageous in terms of toxicity¹⁷. Rituximab-based combination chemotherapies are preferred in more advanced stages or in cases of systemic involvement. Surgical excision is generally performed for diagnostic purposes; however, when used alone, it has been reported in the literature to carry a high risk of early recurrence. In our series, most conjunctival-predominant cases were treated with RT, and recurrence was observed in only one case. This finding supports the indolent course and responsiveness to treatment of OAMZL. Overall survival rates are reported in the literature to be between 85% and 95%^{19,20}. The absence of deaths in our cohort confirms the good prognosis of OAMZL, despite the limited number of patients.

This study provides long-term clinicopathological data on OAMZL; however, the limited sample size, the single-institution nature of the study, and lack of molecular analyses constitute its main limitations. Despite these constraints, our findings reinforce that OAMZL, although rare, represents the most common lymphoid neoplasm of the ocular adnexa, typically affecting middle-aged to elderly patients and generally following an indolent course with potential for relapse and systemic dissemination. Accurate diagnosis requires careful histopathological and immunohistochemical evaluation. While survival outcomes are favorable, long-term surveillance remains essential. Future research involving multicenter cohorts and integrated molecular approaches is needed to better clarify disease pathogenesis, prognostic markers, and optimal management strategies.

Ethical approval: Ethical approval for the study was granted by The Celal Bayar University Ethics Committee (Approval No: 20.478.486/3341, dated July 30, 2025).

Conflict of Interest: The authors declared no conflicts of interest.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Kirkegaard MK. Ocular adnexal lymphoma: Subtype-specific clinical and genetic features. *Acta Ophthalmol.* 2022;100(Suppl 270):3-37. doi:10.1111/aos.15248
2. Johansson P, Eckstein A, Küppers R. The biology of ocular adnexal marginal zone lymphomas. *Cancers (Basel).* 2022;14(5):1264. doi:10.3390/cancers14051264
3. Choi S, Seo M, Park SH, et al. Clinicopathologic characteristics associated with prognosis in ocular extranodal marginal zone B-cell lymphoma. *Medicina (Kaunas).* 2022;58(6):818. doi:10.3390/medicina5806081
4. Chung HU, Son JH. Ocular adnexal mucosa-associated lymphoid tissue lymphoma: A narrative

- review. *J Yeungnam Med Sci.* 2022;39(1):3-11. doi:10.12701/yujm.2021.01263
5. Desai A, Joag MG, Lekakis L, et al. Long-term course of patients with primary ocular adnexal MALT lymphoma: A large single-institution cohort study. *Blood.* 2017;129(3):324-32. doi:10.1182/blood-2016-05-714584
6. Coupland SE, White VA, Rootman J, Damato B, Finger PT. A TNM-based clinical staging system of ocular adnexal lymphomas. *Arch Pathol Lab Med.* 2009;133(8):1262-7. doi:10.5858/133.8.1262
7. Collina F, De Chiara A, De Renzo A, et al. Chlamydia psittaci in ocular adnexa MALT lymphoma: A possible role in lymphomagenesis and a different geographical distribution. *Infect Agent Cancer.* 2012;7:8. doi:10.1186/1750-9378-7-8
8. Sassone M, Ponzoni M, Ferreri AJ. Ocular adnexal marginal zone lymphoma: Clinical presentation, pathogenesis, diagnosis, prognosis, and treatment. *Best Pract Res Clin Haematol.* 2017;30:118-30.
9. Travaglino A, Pace M, Varricchio S, et al. Involvement of *Helicobacter pylori* in ocular adnexa lymphoma. *Pathol Oncol Res.* 2020;26:2075-81.
10. Coupland SE, Hellmich M, Auw-Haedrich C, Lee WR, Stein H. Prognostic value of cell-cycle markers in ocular adnexal lymphoma: An assessment of 230 cases. *Graefes Arch Clin Exp Ophthalmol.* 2004;42(2):130-45. doi:10.1007/s00417-003-0831-5
11. Takahashi H, Usui Y, Ueda S, et al. Genome-wide analysis of ocular adnexal lymphoproliferative disorders using high-resolution single nucleotide polymorphism array. *Invest Ophthalmol Vis Sci.* 2015;56:4156-65. doi:10.1167/iovs.15-16382
12. Hsu CR, Chen YY, Yao M, et al. Orbital and ocular adnexal lymphoma: A review of epidemiology and prognostic factors in Taiwan. *Eye (Lond).* 2021;35:1946-53. doi:10.1038/s41433-020-01198-y
13. Goto H, Asakage M, Niidime E, et al. Demographics, clinical features and prognosis of patients with primary malignant conjunctival tumors at a tertiary hospital in Japan. *Jpn J Ophthalmol.* 2025;69(2):316-25. doi:10.1007/s10384-025-01165-8
14. Kaya M, Öner FH, Lebe B, et al. İntraoküler lenfoma tanısındaki zorluklar. *Turk J Ophthalmol.* 2021;51(5):317-25. doi:10.4274/tjo.galenos.2021.50607
15. Teles LPM, Lima JCDO, Schmidt LPB, Andrade EP. Orbital mucosa-associated lymphoid tissue lymphoma. *Pan-Am J Ophthalmol.* 2023;5(1):49. doi:10.4103/pajo.pajo_58_23
16. Gao LR, X. Li, X. Wang, et al. Treatment and survival in patients with localized primary ocular adnexal MALT lymphoma: A large bicentric cohort study. *Ann Oncol.* 2023;34(Suppl):S544.
17. Oktariana TP, Andriana A, Nugroho RS. The outcome of radiation therapy as a primary treatment in orbital lymphoma: A systematic review. *Rep Pract Oncol Radiother.* 2022;27(4):724-33. doi:10.5603/RPOR.a2022.0065
18. Lo AC, Holloway CL, Savage KJ, et al. Radioimmunotherapy for orbital marginal zone lymphoma: A retrospective review. *Leuk Lymphoma.* 2022;63(5):1242-5.
19. Liang Y, Fu RY, Liu XL, et al. Long-term survival outcomes of patients with primary ocular adnexal MALT lymphoma: A large single-center cohort study. *Cancer Med.* 2023;12(3):2514-23.
20. Saul EE, Alderuccio JP, Reis IM, et al. Long-term outcomes of patients with conjunctival extranodal marginal zone lymphoma. *Am J Hematol.* 2023;98(1):148-58. doi:10.1002/ajh.26591