January 2021

Epidemiology, Outcomes And Prognostic Factors In Orbital Lymphoma In The United States

Osama Muneer Ahmed

Epidemiology, outcomes and prognostic factors in orbital lymphoma in the United States

A Thesis Submitted to the

Yale University School of Medicine

in Partial Fulfillment of the Requirements for the

Degree of Doctor of Medicine

by

Osama M. Ahmed

May 2021

Abstract

Purpose: We performed an epidemiological study of orbital lymphoma in the United States to determine how histological subtypes confer differing prognosis, and understand other factors associated with survival.

Methods: All patients in the Surveillance, Epidemiology and End Results database diagnosed with a histologically confirmed orbital lymphoma between 1973 and 2014 were included. Exclusion criteria included diagnosis at autopsy and the presence of other malignancies. Measures included patient demographic information, histological subtype and treatment modalities. Outcomes included overall and disease specific survival.

Results: Of the 1504 cases identified, 702 were male (46.7%, mean age: 64.4 years, standard deviation [SD]: 15.3) and 802 were female (53.3%, mean age: 67.5 years, SD: 14.3). Mucosal associated lymphoid tissue (MALT) (49.5%) and diffuse large B cell lymphoma (DLBCL) (19.5%) were the two most common histologic subtypes. MALT lymphoma conferred the best prognosis (10-year cancer specific survival [CSS] 90.2%, 95% Confidence Interval [CI] 87.4% – 93.1%) and DLBCL conferred the worst prognosis (10-year CSS 68.6%, 95% CI 62.5% – 75.3%) (p<0.001, log-rank test). Older age above 50 (Hazard Ratio [HR]: 3.71, 95% Confidence Interval [CI]: 2.94-4.66, p<0.001), male sex (HR: 1.22, 95% CI: 1.039-1.441, p = 0.015), no radiation (HR: 1.72, 95% CI: 1.46-2.02, p<0.001) and DLBCL histology were significant predictors of worse overall survival.

Conclusions: DLBCL histology confers the worst outcomes whereas MALT lymphoma confers the best outcome in orbital lymphoma. Age, gender, and radiation treatment also influence survival. These epidemiological results can be used clinically to communicate outcomes on the basis of patient characteristics and disease histology.

Acknowledgements

I would like to sincerely thank my thesis adviser and research mentor, Dr. Renelle Lim in the Department of Ophthalmology and Visual Science at Yale University School of Medicine. Dr. Lim's mentorship, advice and commitment to my learning throughout my four years at Yale made it possible for me to build confidence in my research abilities in oculoplastics and ocular oncology. Ultimately, she played a crucial role in helping me envision my future potential as an ophthalmologist and an academic. She consistently allowed me to claim full ownership over my research project but was always there to clarify complex topics and steer me in the right direction. Thank you so much for being an incredible mentor.

I would also like to thank Anthony K. Ma, (YSM '22) for his expertise in computer programming and big data analysis. Completing this project would have not been possible without his valuable feedback and assistance. I would also like to thank my brother Taha M. Ahmed, for sanity checking my thought process and assisting with , literature search, and manuscript writing of our study that was published in the Journal *Orbit*.

Lastly, I am incredibly grateful to my parents Siraj Muneer and Shehla Alam and my wife Maham Ahmad for their continual support throughout my time in medical school. Their constant encouragement made it possible for me to excel in research and complete this project. Thank you all.

TABLE OF CONTENTS

Introduction

Orbital lymphoma (OL) accounts for the majority of orbital malignancies in adults.[1,2] However, it is still a rare disease, accounting for less than 1% of all Non-Hodgkin's Lymphoma (NHL).[3] Due to its rarity, efforts to document its presentation and epidemiology have relied primarily on case reports or cohorts of patients pooled from around the world.[2,4–11] Although, conjunctival and ocular adnexal lymphoma are thought to be along the same spectrum as OL, the prognosis of purely conjunctival lymphoma tends to be better.[4]

It has been observed that the various histologic subtypes of OL confer different overall survival rates.[4,10–12] In the largest study reporting the effect of histologic subtype of OL on survival, Olsen et al found extranodal marginal zone B cell lymphoma (which is also known as Mucosa Associated Lymphoid Tissue [MALT] lymphoma) to confer the best prognosis and mantle cell lymphoma (MCL) to confer the worst prognosis in a cohort of 797 patients from seven international cancer centers.[11] However, patients in the United States accounted for only 30% of their cohort and were included from only three regional cancer centers. Moreover, no subgroup analysis was performed in their study for survival amongst the American cohort. Although prognostication is of great importance in oncologic care, due to the rarity of this disease in the United States, there is no large study that provides prognostication by histological type of the disease. Although disease staging can currently offer prognostic value it is not as predictive of survival in OL as disease histology.[10] Further survival data based off disease histology could offer more information to prognosticate with.

Background

Early History

The earliest mention of "orbital lymphoma" in PubMed indexed journals dates back to 1965, when Jortay described a case of unilateral exophthalmos that was thought to be a chronic granuloma or orbital lymphoma.[13] Reese et al in 1971 also identified orbital lymphomas compromising 10% of the 504 primary orbital tumors in their study whereas Henderson et al in 1974 diagnosed orbital lymphomas comprising 8% of their series of 465 orbital tumors. In Henderson's studies, orbital lymphoma was seen in patients mostly younger than 20.[14]

In 1978, Jakobiec and colleagues from the Harkness Eye Institute at Columbia-Presbyterian Medical Center published a review of lymphoid lesions of the orbit, identifying 13 orbital lymphomas from 410 cases of orbital lymphoid lesions accumulated over 40 years in their pathology laboratory.[15] They noted that the disease was more commonly occurring in older adults above the age of 50. Furthermore, they noted that the diagnosis and prognosis of these lesions was challenging for the clinician and the pathologist because of difficulty in identifying frankly neoplastic cellular details in the lesions and discerning whether the orbital lesion is primary or a manifestation of systemic diseases. In 8 of the 13 patients with initially presumed primary orbital lymphoma, metastasis to other sites was usually found at the time of diagnosis, with all cases having metastasized within 1 year and 3 months of initial diagnosis. Treatment of the disease involved radiotherapy with 2000-5000 rads (equivalent to 20-50 Gy), exenteration in some cases and systemic chemotherapy reserved for treatment resistant

tumors. Survival from time of diagnosis ranged from 5 months to 6 ½ years – the cause of death in all patients was directly related to the tumor or the side effects of treatment.[15]

Disease Histopathologic Classifications

WHO Classification

Lymphomas are malignancies due to abnormal clonal proliferation of lymphocytes. Although there have been many classification systems in the past for lymphomas (which are covered later in this thesis), the most updated system is the WHO classification, which was majorly updated in 2016.[16] In this classification, lymphomas can be divided into Hodgkin's lymphoma, which consists of B-cells and Non-Hodgkin's lymphoma which includes B-Cell, T-Cell and rarely NK cell lymphomas. These types can be further subdivided based on histo-cytologic criteria.[10] There are over 40 sub-categorizations, many of which are beyond the scope of this study due to the rarity of their occurrence in the orbit (for more information, see Caponetti and Bagg 2017).[17] In particular, this thesis focuses on Non-Hodgkin B-Cell lymphomas – for more information on T cell lymphomas and beyond, see Olsen et al 2019, which is referenced in this thesis.[10]

In the orbit, the following histological subtypes of NHL are frequently encountered: follicular lymphoma (FL - *International Classification of Diseases for Oncology 3* [ICD-O-3]: 9695/3, 9690/3, 9691/3, 9698/3), extranodal marginal zone lymphoma of mucosal associated lymphoid tissue (MALT - ICD-O-3: 9699/3), diffuse large B cell lymphoma (DLBCL - ICD-O-3: 9680/3, 9684/3), lymphoplasmacytic

lymphoma (LPL - ICD-O-3:9671/3), small lymphocytic lymphoma (SLL - ICD-O-3: 9670/3) and mantle cell lymphoma (MCL - ICD-O-3: 9673/3). Figure 1 demonstrates how these histological subtypes are categorized.

Follicular lymphomas (FL) are of B cell lineage that demonstrate follicular architecture. These follicles are uniform, densely packed to the point that they often obliterate nodal architecture. They are composed of proportions of small cleaved cells and some large cells that may or may not be cleaved. Grading of the lymphoma is based on the proportion of large cells, as seen in table 1. Disease staging is not based on histopathologic features but rather the Ann Arbor or AJCC Staging system, which will be discussed later.[18]

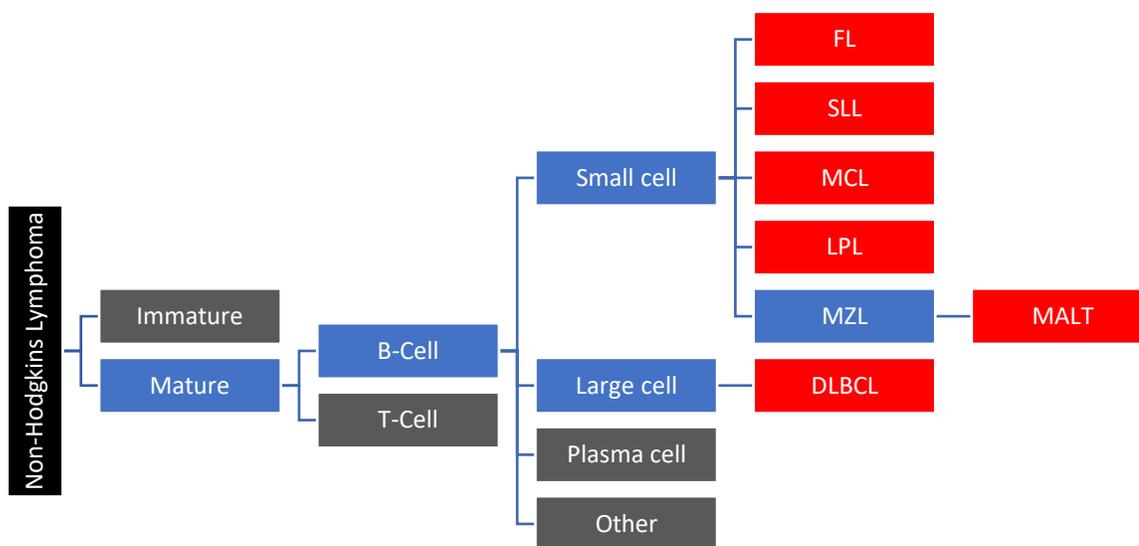*Figure 1:WHO Classification of Non-Hodgkin Lymphomas. Grey boxes indicate histological types not found commonly in the orbit. Red indicates common orbital lymphoma histologies. FL=Follicular Lymphoma, SLL = Small Lymphocytic Lymphoma, MCL = Mantle Cell Lymphoma, LPL = Lymphoplasmacytic Lymphoma, MZL = Marginal Zone Lymphoma, MALT = Mucosa Associated Lymphoid Tissue Lymphoma, DLBCL = Diffuse Large B Cell Lymphoma*

Histopathologic Grade of Follicular Lymphoma	% of Large Cells
1	Under 25
2	25-50
3	Over 50

Table 1: Histopathologic Grading of Follicular Lymphomas

Marginal Zone Lymphomas are composed of small B lymphocytes with pale cytoplasm known as monocytoid cells. They have an affinity for mucosal sites, hence the designation of the specific subtype MALT lymphoma. These neoplastic cells may involve marginal zones of reactive follicles and colonize adjacent follicles. There is no consensus grading criteria for MALT lymphoma, but it is generally considered a 'low grade' neoplasm. Staging is based on the Ann Arbor criteria or the AJCC criteria.[18]

Small Lymphocytic Lymphoma, also known as chronic lymphocytic leukemia when identified in non-solid tumor form, is a neoplasm made of mostly small round B cells. Diagnostic criteria includes effacement of nodal architecture by sheets of small B lymphocytes, pseudo-follicular proliferation. There is no consensus grading criteria for this disease, but it is generally considered as a 'low-grade' neoplasm. Staging is based on the Ann Arbor criteria or the AJCC criteria.[18]

MCL is a B cell neoplasm containing small to medium sized cells with mild or moderate nuclear irregularities. The neoplasm commonly involves and expands the mantle zone and compressing the germinal center in a lymph node. A key feature of this subtype is its genetic expression of bcl1, which is discussed in the section on disease pathogenesis. There is no consensus grading criteria for MALT lymphoma, but it is

generally considered a 'high grade' neoplasm. Staging is based on the Ann Arbor criteria or the AJCC criteria.[18]

LPL is a B cell neoplasm composed of small round B cells that display prominent plasmacytoid differentiation. These cells also lack defining features of other small B cell lymphomas. Many cases can express IgM and cause hyper-viscosity syndromes. There is no consensus grading criteria for this neoplasm, though it is generally regarded as 'low-grade'. Staging is based on the Ann Arbor criteria or AJCC criteria.[18]

DLBCL is an aggressive neoplasm that consists of large cells that show a diffuse pattern of growth that effaces normal nodal architecture. Although there are no formal consensus grading criteria, it is considered 'high grade.' Staging is based off Ann Arbor criteria or AJCC criteria.

Older Classifications

The Rappaport classification was amongst the earliest modern classifications used to describe lymphomas and was proposed in 1956. Henry Rappaport and colleagues argued for a clinically useful classification that was accurate, reproducible, easily taught and learned. Using these principles, they classified NHL into two subtypes: nodular, in which the neoplasm retained nodal architecture, and diffuse, which was characterized by effacement of the lymph node architecture.[19] Furthermore, they subclassified neoplasms as 'well-differentiated', 'poorly-differentiated', and 'histiocytic.' This classification fell out of favor with the realization that all lymphomas were of lymphoid and not histiocyte

origin and the improvements in technology allowing for differentiate of B cell neoplasms from other lymphoid cells.

In 1974 Lukes and Collins proposed the first classification based on cellular origin and lymphocyte transformation alterations. This system did not consider cellular architecture but introduced terms to describe individual cells such as small and large, cleaved and uncleaved cells.

The Kiel Classification also built on the Lukes and Collins Classification and divided neoplasms into low- and high-grade variants based on cell maturity. This classification was updated extensively in 1988 and is shown in table 2.[19]

B Cell	T Cell
Low Grade	**Low Grade**
Lymphocytic- chronic lymphocytic and hairy cell leukemia	Lymphocytic – chronic lymphocytic and prolymphocytic leukemia
Lymphoplasmacytic/cytoid	Lymphoepithelioid
Plasmacytic	Angioimmunoblastic
Centroblastic/centrocytic	T zone
Centrocytic	Pleomorphic, small cell
High Grade	**High Grade**
Centroblastic	Pleomorphic, medium and large cell
Immunoblastic	Immunoblastic
Large cell anaplastic	Large cell anaplastic
Burkitt lymphoma	Lymphoblastic
Lymphoblastic	
Rare types	Rare Types

Table 2: Updated Kiel Classification (1988)

In 1994, the International Lymphoma Study Group devised a consensus list of lymphoid neoplasms, which were published as the 'Revised European-American Classification of Lymphoid Neoplasms' (REAL). This classification utilized a

combination of morphologic, immunophenotype, genetic and clinical features to classify diseases as opposed to previous methods which insisted on just one 'gold standard' feature to guide classifications. These guidelines were thereafter modified slightly to produce the current WHO classification.[19]

Of note, since these various older classifications were based off different techniques and utilized different 'gold standards,' converting disease classifications from older case reports and databases is often not possible due to the lack of information available in those cases to reclassify the disease based on newer methods such as immunohistochemistry, genetics, and protein expression.

Disease Pathogenesis

Although lymphomas most often occur within lymph nodes, they can manifest extranodally in the conjunctiva, eyelids, lacrimal glands and the orbit. The pathogenesis of orbital lymphomas can be categorized into three main mechanisms: genetic abnormalities, autoimmune disorders and immunosuppressive disorders.

Genetic Abnormalities

MALT lymphoma of the orbit is associated with well described genetic abnormalities. At the chromosomal level, trisomy 3, 7, 12 and 18 as well as translocations t(11;18), q(21;21), t(1;14) (p22;q32), t(1;2), (p22;q12), t(14;18) (q32;q21), and t(3;14) (p14.1;q32) have been described in MALT lymphomas isolated from the ocular adnexa.[10] Most of these translocations affect cellular regulation and, in many cases, lead to the eventual activation of nuclear factor kB (NF-kB). This gene codes for a transcription

factor that is involved in immunologic signaling and is associated with numerous lymphoid malignancies. The *A20* gene is a repressor of NF-kB and is also found to be downregulated in orbital lymphomas.[10]

DLBCL is also often associated with similar mutations in genes that lead to NF-kB activation downstream. Notably, this histology is also associated with overproduction of the anti-apoptotic protein bcl2, in particular due to the mutation t(14;18) (q32,q21), which is found in up to 34% of cases. This mutation is also found in FL which may account for some FLs transforming into DLBCLs.[10] Other mutations associated with this subtype include translocations of MYC, EZH2, BCL6, and MEF2B genes, which are well known genes in tumorigenesis.

MCL is characterized by the hallmark translocation mutation of t(11;14)(q13;q32). This leads to overproduction of the cellular proliferation factor Cyclin D-1.

Other histological subtypes of orbital lymphomas also have many unique mutations, however, their role in disease pathogenesis is not fully understood and is still being actively studied.

Autoimmune Disorders

Autoimmune phenomena is commonly associated with lymphoproliferative disorders and is a complex bidirectional process of active study.[20] Many lymphomas

present with paraneoplastic autoimmune diseases in addition to many autoimmune

diseases preceding the onset of a lymphoproliferative disorder. In Non-Hodgkin's

Lymphoma (NHL), 70% of autoimmune diseases precede the onset of lymphoma. The

major theory relating the two diseases asserts that there are common underlying genetic

mutations that may drive unregulated proliferation of immune cells that are self-reactive

and/or malignant.[20] Increased risk of NHL of the orbit, especially DLBCL and MALT

lymphoma, is reported in patients suffering from Sjogren's syndrome, systemic lupus

erythematosus, rheumatoid arthritis, Hashimoto's thyroiditis, immune thrombocytopenic

purpura, and autoimmune hemolytic anemia. In one case of orbital MALT lymphoma,

treatment of the autoimmune disease with methotrexate led to resolution of the

lymphoma without any further treatment.[21]

Immunosuppressive Disorders

There is a well-established relationship between lymphomas and

immunosuppressive states. Lymphoma is the most common cancer in patients infected

with human immunodeficiency virus – in particular DLBCL manifests with a high

frequency in this patient population.[10] Furthermore, with treatment of the

immunosuppression, in particular with the introduction of highly active antiretroviral

therapy (HAART), the incidence of lymphoma has declined amongst patients with HIV.[10]

Although the mechanism underlying this association is not well known, increased viremia

amongst immunosuppressed patients, particularly with oncogenic viruses like Ebstein

Barr Virus (EBV) may play a role in pathogenesis. Orbital lymphoma has also been seen

in transplant patients as a rare manifestation of post-transplant lymphoproliferative

disorder. This form of the disease is treated with reduced immune suppression in addition to standard therapy.[22]

Clinical Features

Demographics

OL is a disease that primarily affects elderly patients. Though there are differences amongst the age distribution for various histological subtypes of the disease, 73% of patients diagnosed with OL are over the age of 50.[10] Notably, however, the age distribution of DLBCL is wider than other histological subtypes, with 20% of patients aged 40-49 years and 10% of patients aged younger than 40 years.

Although many case reports of orbital lymphoma in the past did not specify sex, in a recent multicenter retrospective study by Olsen et al, the authors noted no major difference in sex by histology with a roughly equal proportion of males and females. A notable exception to this was the MCL cohort, where men composed 73% of the cases.[11] Previous studies, although limited by their sample size, also observed a female preponderance in MALT lymphoma and FL, in addition to the male preponderance in MCL cases.

Presenting Symptoms

Patients with orbital lymphoma present with various complaints, the most common of which is proptosis. Other symptoms include swelling, ptosis, diplopia, limited extraocular movement, pain, change in vision, erythema, chemosis, and B-

symptoms (fever, weight loss, night sweats).[10] Unilateral proptosis is especially

concerning for an orbital tumor and should necessitate further imaging studies.

Duration

The duration of symptoms before formal ophthalmological consultation and

diagnosis varies widely based on the histological type of tumor. Low grade tumors tend

to present late, with MALT, FL, and CLL having a mean duration of symptoms of 6.5, 24

and 18 months respectively.[10] By contrast, DLBCL has a duration of symptoms to

consultation of weeks. However, some higher-grade lymphomas such as MCL have

longer duration of symptoms up till 9 months until consultation is sought, implying

slower growth. Sometimes, these patients may be initially treated with antibiotics for

cellulitis, further delaying the diagnosis of lymphoma.

Location

Most NHL lymphomas of the ocular adnexa present as a unilateral tumor. The

exception to this is MCL, which presents bilaterally in 43% of patients and CLL, which

presents bilaterally in 50% of cases.[10]

In terms of location within the orbit, tumors can either be extraconal or intraconal

and can involve the extraocular muscles. Some tumors can involve more than one site.

See Figure 2 for a schematic explanation of extraconal vs. intraconal. Most B cell

lymphomas are located in the extraconal space (72%) and a majority of these involve the

lacrimal glands as well (51%). 8% of tumors are in the intraconal space and 9% involve

the extraocular muscles.[10]
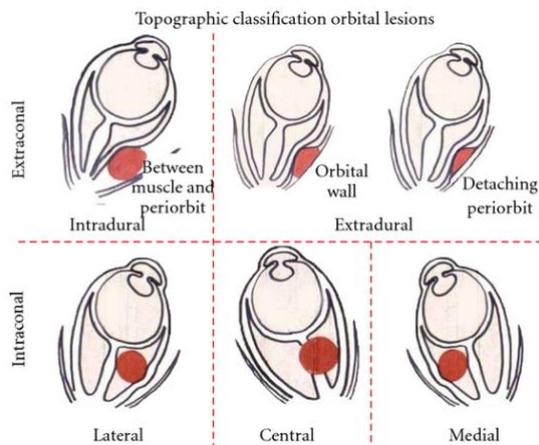
Figure 2: Extraconal versus intraconal orbital lesions. Image courtesy of Martins et al. "Microsurgery of the Orbit: The Rule of Seven." Anatomy Research International. 2011 [Creative commons license]

Tumors can be defined as primary lymphoma or secondary lymphoma. By definition, a tumor is primary if it is biopsy verified and the patient has no evidence of concurrent lymphoma in another site or any history of lymphoma. If a patient has evidence of distant neoplasms or a history of lymphoma, their OL is classified as secondary. 73% of B-cell lymphomas arise as primary tumors. MALT and FL are more likely to arise as primary tumors in the orbit whereas a large percentage of DLBCL and MCL manifest as secondary orbital tumors (42% and 41% respectively).[10] Furthermore, DLBCL has a predilection to involve the periorbital bone whereas MALT lymphoma and FL are more likely to involve the conjunctiva (40% and 38% of cases respectively).[10]

Disease Diagnosis and Workup

A full ophthalmologic evaluation alongside a complete physical examination is warranted whenever an orbital mass is suspected. If examination findings points towards an orbital tumor, imaging preferably with magnetic resonance imaging or a computed

tomography scan of the orbits is indicated. If a tumor is identified on imaging, an open biopsy is indicated for diagnostic confirmation.[10] A fine needle biopsy is recommended against, since it may not produce an adequate sample in which nodal architecture is apparent.[10]

Histopathologic examination of the biopsy sample focuses on morphology, immunohistochemical properties and protein expression studies. These are undertaken to differentiate B-cell lymphomas from other rarer neoplasms, as well as identify specific histological subtypes of the disease.[10]

Disease Staging

Although the Ann Arbor staging criteria was originally designed for Hodgkin's lymphoma, it is also very commonly used for staging NHL as well. There are 4 stages, which are determined by assessing lymph node and extra-nodal involvement (single node [or extra-nodal site] = stage I [I E], more than one node [or >1 extra-nodal site] = stage II [II E]), involvement on one or both sides of the diaphragm (if both sides involved = stage III) and disseminated metastasis (stage IV). This system is not very prognostically useful for orbital lymphomas since the orbit counts only as 1 extra-nodal site, leading to the vast majority of orbital lymphomas to be classified as stage I E, regardless of how locally aggressive the disease is.[10]

In response to this issue, in 2009 the Ophthalmic Oncology Task Force of the American Joint Committee on Cancer (AJCC) devised a new staging system for ocular

adnexal lymphomas, that was based off the TNM staging criteria and allowed for finer

delineation and better prognostication of orbit specific lymphomas. This system is

outlined in table 3.

Even though this updated staging system allowed for better prognostication and

classification of the vast majority of OL patients previously classified as Ann Arbor

Stage I E, patient disease free survival and recurrence were more closely related to the

histopathological subtype rather than the tumor size or site-specific location, as outlined

by the TNM stage.[23,24]

Primary Tumor (T)

- **TX:** lymphoma extent not specified
- **T0:** no evidence of lymphoma
- **T1:** lymphoma involving the conjunctiva alone without orbital involvement
  - **T1a:** bulbar conjunctiva alone
  - **T1b:** palpebral conjunctiva, +/- fornix, +/- caruncle
  - **T1c:** extensive conjunctival involvement
- **T2:** lymphoma with orbital involvement +/- any conjunctival involvement
  - **T2a:** anterior orbital involvement (+/- any conjunctival involvement)
  - **T2b:** anterior orbital involvement (+/- any conjunctival involvement but with lacrimal involvement)
  - **T2c:** posterior orbital involvement (+/- any conjunctival involvement, +/- anterior involvement, +/- any extraocular muscle involvement)
  - **T2d:** nasolacrimal drainage system involvement (+/- conjunctival involvement but not including nasopharynx)
- **T3:** lymphoma with preseptal eyelid involvement (infiltrates preseptal tissues such as dermis or orbicularis muscle of anterior eyelid skin) +/- orbital involvement, +/- any conjunctival involvement
- **T4:** orbital adnexal lymphoma extending beyond orbit to adjacent structures such as bone and brain
  - **T4a:** involvement of nasopharynx
  - **T4b:** osseous involvement (including periosteum)
  - **T4c:** involvement of maxillofacial, ethmoidal or frontal sinuses
  - **T4d:** intracranial spread

Regional Lymph Nodes (N)

- **NX:** involvement of lymph nodes not assessed
- **N0:** no evidence of lymph node involvement
- **N1:** involvement of ipsilateral regional lymph nodes
- **N2:** involvement of contralateral or bilateral regional lymph nodes
- **N3:** involvement of peripheral lymph nodes not draining ocular adnexal region
- **N4:** involvement of central lymph nodes

Note: regional lymph nodes include preauricular (parotid), submandibular and cervical

---

Distant Metastasis (M)

- **M0:** no evidence of involvement of other extranodal sites
- **M1a:** noncontiguous involvement of tissues or organs external to the ocular adnexa (e.g. parotid glands, submandibular gland, lung, liver, spleen, kidney, breast, etc.)
- **M1b:** lymphomatous involvement of the bone marrow
- **M1c:** both M1a and M1b involvement

Table 3: AJCC Staging Guidelines for Ocular Adnexal Lymphomas 7th Edition

Treatment

The treatment of OL is coordinated by a multidisciplinary team including an ophthalmologist, a hematologist and a radiation oncologist. Due to significant variation in

disease progression based on histology, tumor site, and patient risk factors, treatment is highly individualized for each patient.[10]

Radiation therapy (RT) is the mainstay of treatment for most localized, low-grade OLs. RT can be used to eradicate the tumor or decrease tumor site prior to surgical excision. In patients with high grade lymphomas, RT may be used in conjunction with systemic chemotherapy to control the disease. In patients with MALT lymphoma RT is used as monotherapy in 70% of cases.[10] Radiation doses vary based on various factors, but most patients are treated using a total dosage ranging between 20-54 Gy, delivered in small fractions of 2 Gy. This therapy historically received excellent local control in over 90% of patients.[10] Recently, there has been a push to decrease the total amount of radiation in indolent lymphomas to 4 Gy in 2x2 Gy fractions due to evidence indicating that excellent local control can be achieved with lower doses.[25] Ocular side effects of high dose radiation to the orbit include cataracts, cutaneous reactions, keratoconjunctivitis sicca, and retinopathy.[10]

Chemotherapy is often used for OLs when the disease is either high grade (such as in DLBCL or MCL) and/or is disseminated. Combination regimens include CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine) and CVP (cyclophosphamide, vincristine, and prednisone).[10]

Immunotherapy is an emerging modality in the treatment of OLs. The anti-CD20 antibody Rituximab is commonly used in treating B cell lymphomas by preventing cellular proliferation, activation, differentiation and signal transduction. Since its introduction in the 1990s, Rituximab has significantly improved outcomes in lymphomas – in OLs, the combination of Rituximab and chemotherapy is associated with improved outcomes in patients with FL, MCL, and DLBCL.[10]

Prognosis

Collecting accurate data on long term prognosis in OL is challenging due to the rarity of the disease and a paucity of long-term follow-up studies of patients. To date, the patient's histological subtype of OL is the most important prognostic factor. Lower grade histologies such as MALT lymphoma show excellent remission rates of 100/120 patients in a large cohort study, whereas higher grade histologies have worse remissions of 26/33 patients. Furthermore, in these patients, long term survival data was not available.[10] In the largest retrospective cohort study of OL conducted by Olsen and colleagues, 797 patients from 7 eye centers globally were included. Their analysis showed that MALT and FL lymphoma had much better long term prognosis (10 year disease specific survival of 92% and 71% respectively) compared to the more aggressive DLBCL and MCL histologies (10 year disease specific survival of 41% and 32% respectively).[11]

Statement of Purpose

The purpose of this thesis project is to elucidate prognostic factors in OL using the Surveillance, Epidemiology and End Results (SEER) database. In doing so, the aim is

to provide better prognostication data for patients suffering from this disease using the largest ever cohort of patients with orbital lymphoma studied to date in the United States.

Specifically, the three main objectives of this study are:

1. Describe the epidemiology of OLs across various histologies in the United States

2. Determine overall and disease specific survival amongst various OL histologies

3. Determine whether other factors related to patient demographics or treatment affect prognoses

We hope that our research will facilitate understanding the epidemiology and outcomes of this rare disease and can help physicians communicate disease prognoses more accurately and in an evidence-based manner to their patients depending on the subtype of disease they have.

Methods

Database and Disease Coding

We determined our study population by searching the November 2016 submission of the SEER database for all cases of Extranodal Non-Hodgkin's Lymphoma in the orbit (International Classification of Diseases 10 diagnosis code: C69.6). SEER first began collecting data on cancer cases on January 1, 1973, in Connecticut, Iowa, New Mexico,

Utah, and Hawaii and the metropolitan areas of Detroit and San Francisco-Oakland.

Since then, it has gradually increased its coverage and has included Seattle, Atlanta, Los

Angeles, Alaska, rural Georgia, Kentucky, Louisiana and New Jersey. Overall, the

geographic coverage of the database accounts for 27.8% of the overall US population.[27]

The following histologic subtypes were queried: follicular lymphoma (FL - ICD-

O-3: 9695/3, 9690/3, 9691/3, 9698/3), extranodal marginal zone lymphoma of mucosal

associated lymphoid tissue (MALT - ICD-O-3: 9699/3), diffuse large B cell lymphoma

(DLBCL - ICD-O-3: 9680/3, 9684/3), lymphoplasmacytic lymphoma (LPL - ICD-O-

3:9671/3), small lymphocytic lymphoma (SLL - ICD-O-3: 9670/3) and mantle cell

lymphoma (MCL - ICD-O-3: 9673/3). Cases were diagnosed between January 1st, 1973

and December 31st, 2014. Cases diagnosed at autopsy, or those that presented with

multiple neoplasms were excluded.

Study Variables

Data on survival, outcome, surgical procedure, radiation therapy, chemotherapy,

age at diagnosis, sex, and race were queried. Data on Ann-Arbor staging and TNM

staging was sparse in the database and thus not included. Surgical procedures were

grouped as follows: no surgery performed (SEER codes: 00), Unknown/other (SEER

codes: 90,99,27,13,10,14), or orbitotomy with biopsy (SEER codes:

20,22,23,24,25,26,27,30,41,50,60). For specifics on SEER procedure codes, see table 4.

Radiation therapy and chemotherapy was grouped into 'yes' and 'no/unknown.' Of note,

the SEER database did not provide information on the specific types, dosages or durations of chemotherapy or radiation.

SEER Code	Explanation
00	None; no surgery of primary site; autopsy ONLY
10	Local tumor destruction, NOS
11	Photodynamic therapy
12	Electrocautery
13	Cryosurgery
14	Laser
20	Local tumor excision, NOS
26	Polypectomy
27	Excisional biopsy
	Any combination of 20 or 26-27 WITH
21	Photodynamic therapy
22	Electrocautery
23	Cryosurgery
24	Laser ablation
25	Laser excision
30	Simple/partial surgical removal of primary site
40	Total surgical removal of primary site; enucleation
41	Total enucleation
50	Surgery stated to be 'de-bulking'
60	Radical surgery
90	Surgery, NOS
99	Unknown if surgery performed death certificate ONLY

Table 4: SEER surgical codes for the Eye. NOS = Not otherwise specified

Statistical Analysis

We computed patient demographic and treatment characteristics using descriptive statistics such as the ANOVA, chi-squared test and Fisher's exact test. Univariate survival analysis was conducted using Kaplan-Meier survival models and log-rank tests. A Cox proportional hazards regression was used to determine factors affecting overall survival, including age, sex, race, histology and treatment. Age was dichotomized as

above or below 60 years, per the recommendation of the International Prognostic Index model for non-Hodgkin lymphoma.[28] Analysis was conducted using RStudio version 1.0 (RStudio, Inc., Boston, MA), with cutoffs for significance defined at p<0.05.

Statement of Exemption and Compliance

This study was compliant with HIPAA, adhered to the tenets of the Declaration of Helsinki and was approved by the Yale University Institutional Review Board as being exempt from formal approval due to our work being done using a publicly accessible anonymized database.

Results

Epidemiology of Orbital Lymphomas

We identified 1504 patients across 6 lymphoma histologic subtypes (Table 5). Patients had a mean age of 66 years, which did not significantly vary amongst histologic subtypes. There were slightly more cases of females (53%) diagnosed with OL than males (800 versus 704, sex-ratio: 1.13). This trend was also observed in every histology except in the case of MCL, where males accounted for 48/74 cases (64.9%, p = 0.023, see Table 5). Race did not differ significantly amongst histological subtypes (Table 5), and 1,233 (82%) patients in the cohort were white.

Characteristic	Number of Cases (%)						P Value
	MALT	DLBCL	FL	SLL	MCL	LPL	
N	744 (49.5)	294 (19.5)	204 (13.6)	143 (9.5)	74 (4.9)	45 (3.0)	
Age, mean (SD), y	65.5 (14.8)	66.4 (17.0)	66.7 (13.7)	66.0 (13.8)	68.8 (11.7)	64.9 (15.5)	0.521
Male	344 (46.2)	140 (47.6)	83 (40.7)	67 (46.9)	48 (64.9)	22 (48.9)	0.023

Race							
White	585 (78.6)	248 (84.4)	174 (85.3)	121 (84.6)	63 (85.1)	37 (82.2)	0.052
Black	54 (7.3)	18 (6.1)	16 (7.8)	2 (1.4)	6 (8.1)	2 (4.4)	
Other	91 (12.2)	25 (8.5)	11 (5.4)	18 (12.6)	4 (5.4)	6 (13.3)	
Unknown	14 (1.9)	3 (1.0)	3 (1.5)	2 (1.4)	1 (1.4)	0 (0)	
Surgery							
Orbitotomy with Biopsy	284 (38.2)	87 (29.6)	82 (40.2)	21 (14.7)	17 (23.0)	6 (13.3)	<0.001
Unknown/ Other	41 (5.5)	72 (24.5)	41 (20.1)	87 (60.8)	22 (29.7)	26 (57.8)	
No Surgery	419 (56.3)	135 (45.9)	81 (39.7)	35 (24.4)	35 (47.3)	13 (28.9)	
Radiation	479 (64.3)	161 (54.8)	115 (56.4)	99 (30.8)	41 (55.4)	31 (31.1)	0.005
Chemotherapy	123 (16.5)	182 (61.9)	68 (33.3)	22 (15.4)	30 (40.5)	8 (17.8)	<0.001

Table 5: Baseline demographic characteristics

Treatment Choices

There were differences in the choice of surgical intervention chosen for patients with different histological subtypes (Table 5). Radiotherapy was the treatment of choice in 926 (61.6%) patients with OL. Patients with MALT lymphoma were most likely to receive radiation therapy (479/745 patients, 64.3%), whereas those with SLL were the least likely to have radiation therapy (99/143 patients, 30.8%). Chemotherapy was most commonly administered to patients with DLBCL (182/294 patients, 61.9%) and least likely given to those with SLL, the nodal form of chronic lymphocytic leukemia (22/143 patients, 15.4%).

Survival and Outcomes

Table 6 provides data on cancer specific survival probabilities amongst various histologic subtypes. MALT lymphoma conferred the best prognosis (10-year cancer specific survival [CSS] 90.2%, 95% Confidence Interval [CI] 87.4% – 93.1%) and

DLBCL conferred the worst prognosis (10-year CSS 68.6%, 95% CI 62.5% – 75.3%) (p<0.001, log-rank test). Upon pair-wise comparisons, DLBCL conferred a significantly worse overall survival compared to every other histology, except for MCL and LPL (p<0.05, log-rank test). Not only did DLBCL confer the worst cancer specific survival, but also the worst overall survival at 10 years (disease specific survival 44.6%, 95% CI 38.5%-51.7%). Figure 3 shows Kaplan Meier plots of overall and cancer specific survival amongst the histologic subtypes.

Cox proportional hazards regression showed that older age (Hazard Ratio [HR]: 3.71, 95% Confidence Interval [CI]: 2.94-4.66, p<0.001), male sex (HR: 1.22, 95% CI: 1.039-1.441, p = 0.015) and no radiation (HR: 1.72, 95% CI: 1.46-2.02, p<0.001) conferred a worse prognosis after controlling for the various histologic subtypes (Figure 4). The effects of chemotherapy and surgery on survival were not significant.

Histology	Survival Percentage (95% Confidence Interval)		
	1 year	5 year	10 year
MALT Lymphoma	98.9 (98.1 – 99.6)	94.5 (92.7 – 96.4)	90.2 (87.4 – 93.1)
Diffuse Large B Cell Lymphoma	84.5 (80.3 – 88.9)	72.7 (67.2 – 78.5)	68.6 (62.5 – 75.3)
Follicular Lymphoma	97.4 (95.2 – 99.7)	88.9 (84.2 – 94.0)	82.7 (76.1 – 89.8)
Small Lymphocytic Lymphoma	97.2 (94.5 – 99.9)	94.3 (90.5 – 98.2)	88.9 (83.5 – 94.6)
Mantle Cell Lymphoma	95.9 (91.4 – 100)	82.8 (73.9 – 92.7)	71.0 (59.5 – 84.8)
Lymphoplasmacytic Lymphoma	100 (100 – 100)	95.2 (89.0 – 100)	84.5 (72.6 – 98.3)

Table 6: Cancer specific survival probabilities by histologic subtype of OL
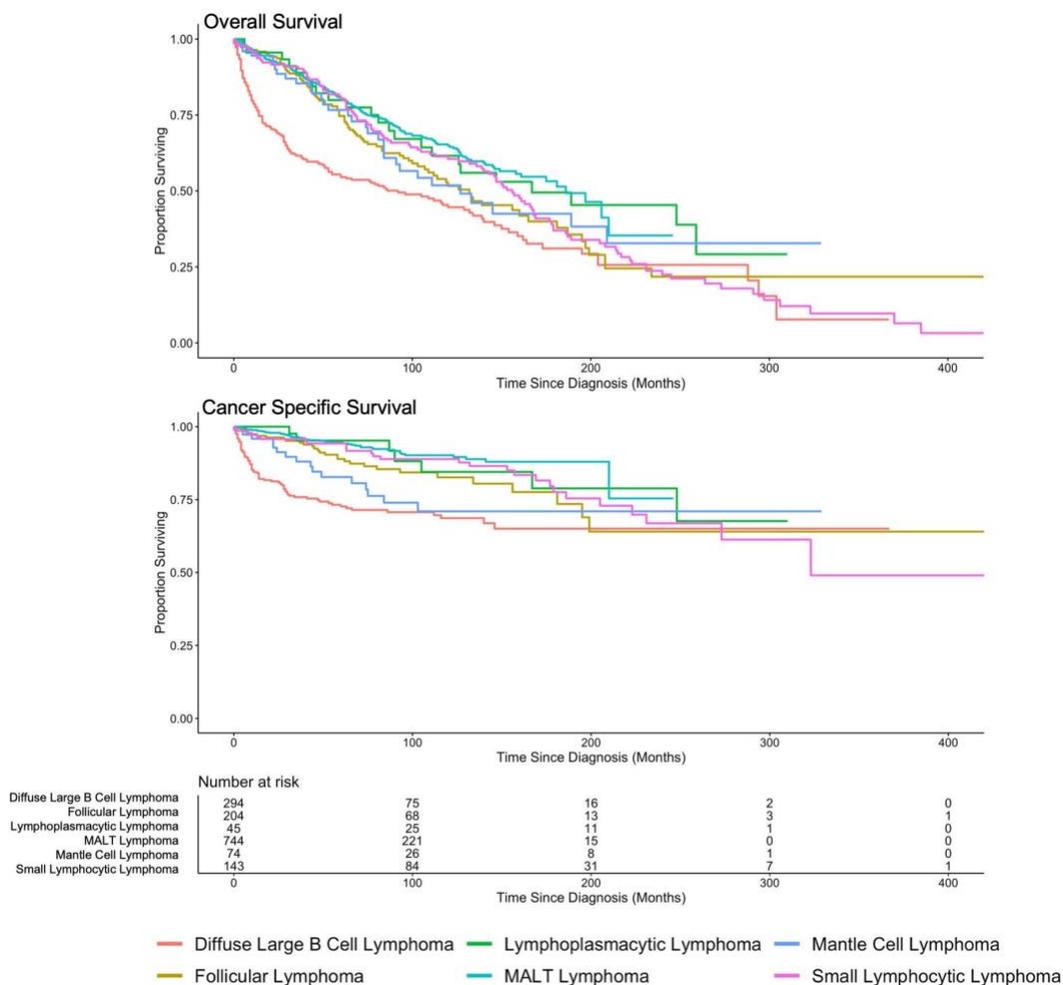
Figure 3: *Kaplan-Meier plot of overall cumulative survival and cancer specific cumulative survival for patients with differing histological subtypes*

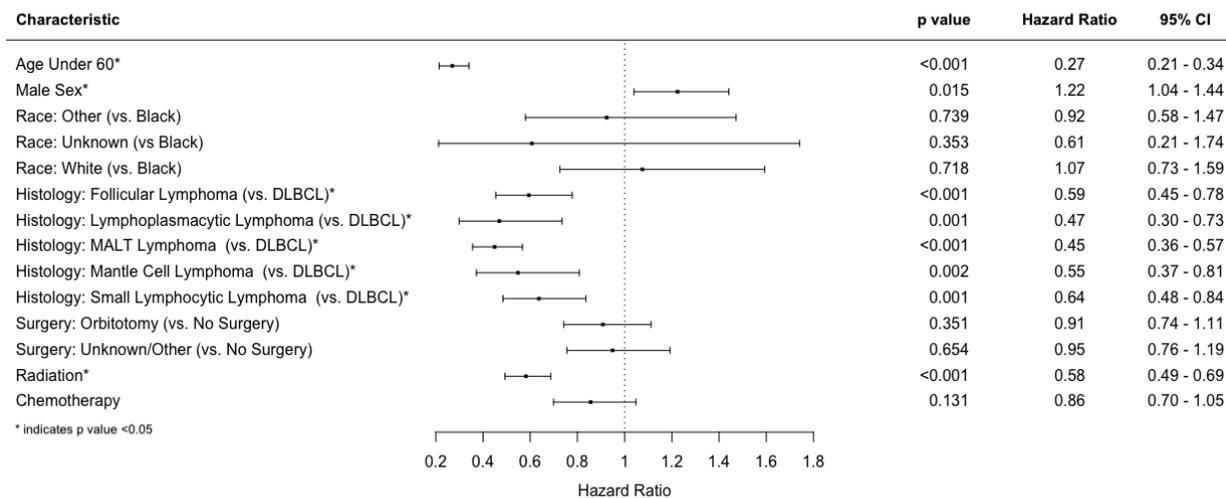| Characteristic		p value	Hazard Ratio	95% CI
Age Under 60*		<0.001	0.27	0.21 - 0.34
Male Sex*		0.015	1.22	1.04 - 1.44
Race: Other (vs. Black)		0.739	0.92	0.58 - 1.47
Race: Unknown (vs Black)		0.353	0.61	0.21 - 1.74
Race: White (vs. Black)		0.718	1.07	0.73 - 1.59
Histology: Follicular Lymphoma (vs. DLBCL)*		<0.001	0.59	0.45 - 0.78
Histology: Lymphoplasmacytic Lymphoma (vs. DLBCL)*		0.001	0.47	0.30 - 0.73
Histology: MALT Lymphoma (vs. DLBCL)*		<0.001	0.45	0.36 - 0.57
Histology: Mantle Cell Lymphoma (vs. DLBCL)*		0.002	0.55	0.37 - 0.81
Histology: Small Lymphocytic Lymphoma (vs. DLBCL)*		0.001	0.64	0.48 - 0.84
Surgery: Orbitotomy (vs. No Surgery)		0.351	0.91	0.74 - 1.11
Surgery: Unknown/Other (vs. No Surgery)		0.654	0.95	0.76 - 1.19
Radiation*		<0.001	0.58	0.49 - 0.69
Chemotherapy		0.131	0.86	0.70 - 1.05

* indicates p value <0.05

Figure 4: *Cox Proportional Hazards Model of factors associated with overall survival of patients with orbital lymphoma*

Discussion

In the largest cohort study performed on OL, our results demonstrate that histology is a significant predictor of survival.   Large analysis of histology and prognosis exist for lymphomas in other sites, including the gastrointestinal tract and thyroid, however, with the exception of the Olsen study, are lacking in the literature on orbital lymphoma.[29–31] To date, this is the first study to compare the long-term survival amongst the numerous histologic subtypes of OL in the United States. Our results confirm survival outcomes reported previously in the literature for specific histological subtypes.[10–12,32]

The Effect of Disease Histology on Survival

Our finding of the poor prognosis associated with DLBCL mirrors results reported by Olsen et al, who found DLBCL to confer a 10-year CSS of 41% in their cohort. However, we demonstrated that in the United States, DLBCL had a 10-year CSS of 68.6%. Furthermore, Olsen et al observed a 10-year CSS of only 32% for MCL, which contrasts our reported 10-year CSS of 71%. The decrease in CSS could be due to the advanced Ann Arbor Stage IV E in their cohort which included 29% DLBCL and 76% MCL. Due to inherent limitations in the SEER database, our cohort lacked staging information, thus it was not possible to directly compare survival rates. However, it should be noted that for other lower grade histologies such as MALT and FL, the vast majority of diseases documented in the literature are Ann Arbor Stage I E. Therefore, assuming that the SEER database had a similar distribution of Ann Arbor staged cases as

the general population amongst patients with low grade histological subtypes of disease,

our results are representative of what is found previously in the literature for these

subtypes of disease. Furthermore, Olsen et al have previously reported in their studies

that disease histologies have the most significant impact on prognosis, regardless of

staging using the Ann Arbor or TNM system.[10] Given this observation, our findings are

valuable even in the absence of staging data in our study.

While further prospective confirmatory studies are needed to understand the

mechanistic basis of our results, the comparative survival amongst OL with varying

histology is of clinical relevance. In addition to existing systems for staging, our results

provide additional prognostic information that can be used to guide patient expectations.

DLBCL is a high-grade aggressive malignancy, whereas MALT lymphoma is low-

grade.[29,33] In the orbit, these histologic subtypes confer the worst and best prognoses

respectively.

Epidemiological Findings

MALT lymphoma, which portends the best prognosis, presents more commonly

in women and is most commonly found in the fifth decade. These results have been

previously demonstrated in many smaller cohorts.[4,5,8,34–36]. We found that MCL of the

ocular adnexal region manifests primarily in elderly males, and our findings confirm

other published reports.[11,37]   Ahmed et al observed no difference in gender on survival in

a subgroup analysis of DLBCL.[32] Though our results demonstrated that male gender

independently confers a worse prognosis in OL, this was not a matched controlled study

and thus our results are difficult to generalize to the general population.

The Effects of Treatments on Survival

We also observed that surgery and chemotherapy did not confer any significant effect on survival. Since the SEER database did not distinguish the exact type of surgery performed, it is hard to interpret the lack of survival differences seen in our study. Since orbitotomy surgeries also included biopsies, it could be possible that the majority of surgeries performed in our study were only biopsies, which would not confer any effect on survival. Similarly, the lack of survival difference between patients receiving chemotherapy versus those who did not could be confounded by the lack of staging data: it may be possible that patients receiving chemotherapy group had more advanced disease than those who did not.

Lastly, we also observed that patients who received radiation had better outcomes compared to those whose radiation status was unknown or negative. Although radiation is a significant component of effective treatment for OL, our dataset does not provide any details on the type, extent or frequency of radiation therapy nor the lymphoma staging of the patients to whom it was administered. Since radiation therapy is typically utilized for less aggressive stages of orbital lymphoma, our results may be confounded by more patients with less aggressive lymphoma being treated with radiation.

Study Limitations

There are inherent limitations when using the SEER database. Although the SEER database is the largest national collection of data on cancers across multiple health

systems, it has restricted data and does not provide information about clinical course, lab values, or detailed radiation, type of surgery and chemotherapy information. In the current database used for this analysis, it was not possible to assess the percentage of lymphoma from the orbit with conjunctival extension, laterality, and disease recurrence, which could have been confounding variables. Furthermore, data on AJCC and Ann Arbor Staging was not available, which is important in disease prognostication. In addition, over the course of the 41-year study period, our cohort has a higher frequency of Small Lymphocytic Lymphoma cases compared to other multicenter trials. This may have occurred due to the variation in histologic classification at the time of diagnosis spanning four decades. Since histologic data was provided through the database, it is not possible to confirm the reclassification of our cases in the database according to the current World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues.[38] However, in the case of rare diseases like OL, performing large prospective studies is not possible, and hence studies are restricted to retrospective analysis of large databases or individual cases.[39]

Conclusion

This SEER database analysis confirms known prognostic information on orbital lymphoma using the largest cohort of patients to date. Specifically, we demonstrate that histology is a significant predictor of survival in OL, with DLBCL conferring the worst prognosis (OS: 44.6% at 10 years) and MALT lymphoma conferring the best prognosis (OS: 64.9% at 10 years), while fully acknowledging the limitations of the SEER database. Although age, gender, and the use of radiation treatment are associated with

differing outcomes, further studies are needed to elucidate the mechanisms governing these observations.

References

1. Shields JA, Shields CL, Scartozzi R. Survey of 1264 patients with orbital tumors and simulating lesions. Ophthalmology 2004;111(5):997–1008.

2. Margo CE, Mulla ZD. Malignant tumors of the orbit. Analysis of the Florida Cancer Registry. Ophthalmology 1998;105(1):185–90.

3. Fitzpatrick PJ, Macko S. Lymphoreticular tumors of the orbit. Int J Radiat Oncol Biol Phys 1984;10(3):333–40.

4. Martinet S, Ozsahin M, Belkacémi Y, et al. Outcome and prognostic factors in orbital lymphoma: A Rare Cancer Network study on 90 consecutive patients treated with radiotherapy. Int J Radiat Oncol Biol Phys 2003;55(4):892–8.

5. Kiesewetter B, Lukas J, Kuchar A, et al. Clinical Features, Treatment and Outcome of Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma of the Ocular Adnexa: Single Center Experience of 60 Patients. PLoS ONE 2014;9(7):e104004.

6. Karlin J, Peck T, Prenshaw K, Portell CA, Kirzhner M. Orbital mantle cell lymphoma presenting as myasthenia gravis. Orbit 2017;36(6):365–9.

7. Sriram P. A rare case of aggressive, huge primary orbital lymphoma with intracranial extension and bone invasion. Asian J Neurosurg 2016;12(4):766.

8. Eckardt AM, Lemound J, Rana M, Gellrich N-C. Orbital lymphoma: diagnostic approach and treatment outcome. World J Surg Oncol 2013;11:73.

9. Freedman K, Shenoy S. Mucosa-associated lymphoid tissue lymphoma with intraocular and orbital involvement: case presentation and review of the literature. Orbit 2017;1–5.

10. Olsen TG, Heegaard S. Orbital lymphoma. Surv Ophthalmol 2019;64(1):45–66.

11. Olsen TG, Holm F, Mikkelsen LH, et al. Orbital Lymphoma—An International Multicenter Retrospective Study. Am J Ophthalmol 2019;199:44–57.

12. Jenkins C, Rose GE, Bunce C, et al. Histological features of ocular adnexal lymphoma (REAL classification) and their association with patient morbidity and survival. Br J Ophthalmol 2000;84(8):907–13.

13. Jortay A. [A case of unilateral exophthalmos: chronic granuloma or orbital lymphoma]. Acta Chir Belg 1965;64(9):1185–94.

14. Henderson JW. Orbital Tumors [Internet]. W.B Saunders Company; 1974 [cited 2020 Oct 30]. Available from: https://pediatrics.aappublications.org/content/54/1/130

15. Jakobiec FA, Williams P, Wolff M. Reticulum cell sarcoma (histiocytic lymphoma) of the orbit. Surv Ophthalmol 1978;22(4):255–70.

16. Quintanilla-Martinez L. The 2016 updated WHO classification of lymphoid neoplasias. Hematol Oncol 2017;35(S1):37–45.

17. Caponetti G, Bagg A. Demystifying the diagnosis and classification of lymphoma: a guide to the hematopathologist's galaxy. J Community Support Oncol 2017;15:43–8.

18. Surgical Pathology Criteria - Stanford University School of Medicine [Internet]. [cited 2020 Oct 31];Available from: http://surgpathcriteria.stanford.edu/

19. Sabharwal R, Sircar K, Sengupta S, Sharma B. Update on classification of lymphomas. Dent Hypotheses 2013;4(1):4.

20. Miller EB. Autoimmunity and Lymphoma: A Brief Review. J Rheum Treat [Internet] [cited 2020 Nov 14];4(62). Available from: https://clinmedjournals.org/articles/jrdt/journal-of-rheumatic-diseases-and-treatment-jrdt-4-062.php?jid=jrdt

21. Kobayashi Y, Kimura K, Fujitsu Y, Shinkawa K, Muta H, Sonoda K-H. Methotrexate-associated orbital lymphoproliferative disorder in a patient with rheumatoid arthritis: a case report. Jpn J Ophthalmol 2016;60(3):212–8.

22. Douglas RS, Goldstein SM, Katowitz JA, et al. Orbital presentation of posttransplantation lymphoproliferative disorder: a small case series. Ophthalmology 2002;109(12):2351–5.

23. Lee S-E, Paik J-S, Cho W-K, et al. Feasibility of the TNM-based staging system of ocular adnexal extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). Am J Hematol 2011;86(3):262–6.

24. Graue GF, Finger PT, Maher E, et al. Ocular Adnexal Lymphoma Staging and Treatment: American Joint Committee on Cancer versus Ann Arbor: Eur J Ophthalmol [Internet] 2013 [cited 2020 Nov 17];Available from: https://journals.sagepub.com/doi/10.5301/ejo.5000224

25. Fasola CE, Jones JC, Huang DD, Le Q-T, Hoppe RT, Donaldson SS. Low-Dose Radiation Therapy (2 Gy × 2) in the Treatment of Orbital Lymphoma. Int J Radiat Oncol 2013;86(5):930–5.

26. Dimitrakopoulos I, Venetis G, Kaloutsi V, Sotiropoulos D, Papadimitriou C. Effect of Chemotherapy on Primary Mucosa-Associated Lymphoid Tissue Lymphoma of the Orbit. J Oral Maxillofac Surg 2008;66(1):16–20.

27. SEER*Stat Databases: November 2016 Submission [Internet]. SEER. [cited 2020 Nov 23];Available from: https://seer.cancer.gov/data-software/documentation/seerstat/nov2016/index.html

28. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. N Engl J Med 2002;329(14):987–94.

29. Gatter K, Pezzella F. Diffuse large B-cell lymphoma. Diagn Histopathol 2010;16(2):69–81.

30. Aozasa K, Ueda T, Kurata A, et al. Prognostic value of histologic and clinical factors in 56 patients with gastrointestinal lymphomas. Cancer 1988;61(2):309–15.

31. Aozasa K, Inoue A, Tajima K, Miyauchi A, Matsuzuka F, Kuma K. Malignant lymphomas of the thyroid gland: Analysis of 79 patients with emphasis on histologic prognostic factors. Cancer 1986;58(1):100–4.

32. Ahmed AH, Foster CS, Shields CL. Association of disease location and treatment with survival in diffuse large B-cell lymphoma of the eye and ocular adnexal region. JAMA Ophthalmol 2017;135(10):1062–8.

33. Cohen SM, Petryk M, Varma M, Kozuch PS, Ames ED, Grossbard ML. Non-Hodgkin's lymphoma of mucosa-associated lymphoid tissue. The oncologist 2006;11(10):1100–17.

34. Moslehi R, Coles FB, Schymura MJ. Descriptive epidemiology of ophthalmic and ocular adnexal non-Hodgkin's lymphoma. Expert Rev Ophthalmol 2011;6(2):175–80.

35. Hassan WM, Alfaar AS, Bakry MS, Ezzat S. Orbital tumors in USA: Difference in survival patterns. Cancer Epidemiol 2014;38(5):515–22.

36. Hassan WM, Bakry MS, Hassan HM, Alfaar AS. Incidence of orbital, conjunctival and lacrimal gland malignant tumors in USA from Surveillance, Epidemiology and End Results, 1973-2009. Int J Ophthalmol 2016;9(12):1808–13.

37. Rasmussen P, Sjo LD, Prause JU, Ralfkiaer E, Heegaard S. Mantle cell lymphoma in the orbital and adnexal region. Br J Ophthalmol 2009;93(8):1047–51.

38. Swerdlow SH, World Health Organization, International Agency for Research on Cancer. WHO classification of tumours of haematopoietic and lymphoid tissues.

39. Sedgwick P. Retrospective cohort studies: advantages and disadvantages. BMJ 2014;348(jan24 1):g1072–g1072.