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Survival in B-cell primary ocular lymphoma 1997–2014: a population-based study

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► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/jim-2018-000758).

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Accepted 20 May 2018

ABSTRACT

This study sought to explore the prognostic factors in a large retrospective cohort of patients with B-cell primary ocular lymphoma (POL) from the Surveillance, Epidemiology, and End Results database. There were 2778 patients with B-cell POL whose complete clinical information was listed in the Surveillance, Epidemiology, and End Results database between 1997 and 2014. The epidemiology, therapeutic measures, and clinical characteristics were listed as descriptive statistics. Survival analysis was conducted by univariate and multivariable Cox regression models. Multivariate analysis identified age, lymphoma subtype, primary lesion, and radiation status as independent prognostic factors. For indolent lymphoma, radical treatment, especially intravenous chemotherapy, should be avoided. For invasive lymphoma, chemotherapy combined with full orbital irradiation is recommended. Radiotherapy alone or in combination with chemotherapy is superior to chemotherapy alone. These differences were statistically significant ($p<0.05$). Radiation brings benefits, with tolerable neurotoxicity, to patients with invasive B-cell POL. Radical tumor treatment may not be needed for patients with indolent B-cell POL.

Significance of this study

What is already known about this subject?

► Primary ocular lymphoma is a rare type of extranodal non-Hodgkin's lymphoma and includes intraocular and ocular adnexal lymphomas. Wide acceptance for certain therapeutic regimens has not been gained as the incidence of ocular lymphoma is low. Using local resection to achieve the same favorable treatment outcomes as that of solid tumor resection is difficult. Radiotherapy may cause neurotoxicity and achieving a high intraocular drug concentration with intravenous chemotherapy is also difficult due to the blood–eye barrier.

What are the new findings?

► In this study, based on a large cohort, we found that radical treatment, especially intravenous chemotherapy, should be avoided for indolent lymphoma. For invasive lymphoma, chemotherapy combined with full orbital irradiation is recommended. Radiotherapy alone or in combination with chemotherapy is superior to chemotherapy alone.

How might these results change the focus of research or clinical practice?

► These finds may contribute to better options for treatment.

INTRODUCTION

Primary ocular lymphoma (POL) is a type of extranodal non-Hodgkin's lymphoma and includes intraocular and ocular adnexal lymphomas. Due to limited ocular lymphoid tissue, the incidence of ocular lymphoma is low, and most cases are primary.[1] POL includes many pathological types with varying degrees of malignancy and may be difficult to distinguish from other ocular diseases such as retinal choroidal reactive lymphoid hyperplasia and orbital inflammatory pseudotumor.[1–3] Primary intraocular lymphoma (PIOL) accounts for 1.86% of malignant ocular tumors; B-cell PIOL is most common, though some malignancies are derived from T cells and natural killer cells.[4] Based on the tumor site, PIOLs include vitreoretinal lymphoma, choroidal lymphoma, iris lymphoma, and ciliary body lymphoma. According to the Surveillance, Epidemiology, and End Results (SEER) program, the incidence of PIOL was approximately 0.48 per 100,000 individuals in the USA (1973–2014). The etiology of PIOL is unknown, and the optimal treatment regimens remain controversial among researchers.[5] Ocular adnexal lymphomas account for approximately 11% of all ocular tumors and most often occur in the orbit, followed by the conjunctiva. The most common subtype of ocular adnexal lymphoma is extranodal marginal zone B-cell lymphoma (60%–66%), followed by follicular lymphoma (10%–15%), diffuse large B-cell lymphoma (8%–13%), and mantle cell lymphoma (1%–5%)%). The prognosis of ocular adnexal lymphomas varies with each pathological type.[6–9]

For ocular lymphomas, the commonly used treatments are local and systemic treatments, including surgical resection, radiotherapy, and chemotherapy. Lymphomas are systemic

To cite: Liu DL, Zheng ZJ. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2018-000758

hematological malignancies and using local resection to achieve the same favorable treatment outcomes as that of solid tumor resection is difficult. Radiotherapy may cause neurotoxicity.[10–13] Because of the blood–eye barrier, achieving a high intraocular drug concentration with intravenous chemotherapy is also difficult. In recent years, targeted drug therapy has advanced rapidly. In 1997, rituximab became the first targeted drug approved by the FDA for the treatment of lymphoma. Since then, rituximab has achieved promising outcomes in patients with B-cell non-Hodgkin's lymphoma and has become the foundation of first-line therapy.[14] However, the efficacy of rituximab for the treatment of ocular lymphoma is unclear, thus contributing to the controversy among researchers regarding the optimal treatment regimens.[15 16] In this study, we used the SEER database to retrospectively analyze cases of primary ocular B-cell lymphoma diagnosed between 1997 and 2014, and investigate prognostic factors and appropriate treatments.

Materials and methods

Data source

The data source used in this study are from the SEER database (1973–2014), which was released in November 2016. The SEER program collects clinical data, such as patient demographics and tumor characteristics, annually and openly. The National Center for Health Statistics is responsible for mortality data collection and updates.[17] Data necessary for the present analysis were obtained using The National Cancer Institute's SEER*Stat software (Surveillance Research Program, National Cancer Institute SEER*Stat software, www.seer.cancer.gov/seerstat) (V.8.3.4).

Inclusion criteria

The inclusion criteria for the study were as follows: patients who were diagnosed with complete clinical manifestations between 1997 and 2014, patients who had the orbital and intraocular tissue listed as the primary disease lesion (International Classification of Diseases for Oncology, third Edition (ICD-O-3) topography codes C69.0.0–C69.9), and patients who were diagnosed as having NHL subtypes (ICD-O-3 histology codes 9591, 9670–9699, 9728, 9734, 9823). All diagnoses were histologically confirmed. All included patients were regularly followed up. Patients with insufficient clinical profiles, unknown cause of death, T-cell lymphoma diagnoses, and unknown survival times were excluded. Ultimately, a total of 2778 patients were eligible and included. This study was conducted with use of a publicly accessible database, and all methods were carried out in accordance with the Declaration of Helsinki. No experiments on humans or the use of human tissue samples were involved in this study.

Variables for the analyses

Age at diagnosis, sex, race, lymphoma subtypes, tumor primary sites, tumor laterality, therapy modality, insurance status, marital status, overall survival (OS) and cancer-specific survival (CSS) were extracted from original data and considered as primary variables. Age at diagnosis was dichotomized into less than 60 years and 60 years or older. Race was classified into African American, non-Hispanic Caucasus, and other. Lymphoma subtypes were grouped into the following four categories: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, mucosa-associated lymphoid tissue (MALT) lymphoma and other subtypes. Primary sites were dichotomized as conjunctiva and other orbital and intraocular locations (including cornea, retina, choroid, ciliary body, lacrimal gland, and orbit). Tumor laterality was described as either left—origin of primary, right— origin of primary or paired site. Therapy modalities included surgery, radiation, and chemotherapy. Insurance status was defined as either uninsured, insured, or any Medicaid or insurance status unknown. Marital status was categorized as never married, married, ever married (including divorce, separated, and widowed), or marital status unknown.

Outcome measurement

OS and CSS were the observed indicators of outcome. OS was determined by 'vital status', which represents the time from the date of diagnosis to the date of death. The time from date of diagnosis to the date of death caused by primary cancer was defined as CSS and was determined by 'SEER cause-specific survival'. Death and death attributed to primary cancer were considered as separate events. Censored observations included patients who were still alive at the time of the last follow-up or died from other causes.

Statistical analysis

All statistical analyses were calculated using Statistical Package for the Social Sciences (SPSS) software V.22. Univariate and multivariate Cox proportional hazard models were performed to estimate the association between various covariates and survival outcome. Kaplan-Meier curves and the log-rank (Mantel-Cox) test were used to compare the OS rates. Differences were considered statistically significant when p value <0.05.

RESULTS

Baseline characteristics

Patients with ages ranging from 1 year to 98 years were analyzed; patients aged ≥60 years had the most cases (59.8%). There were 1539 males and 1239 female patients included in the analysis. MALT lymphoma was the most common subtype. The primary tumor lesion was most often located in the conjunctiva. More azygous lesions were detected in patients than paired lesions. More patients underwent radiation (58.2%) as compared with surgery (39.4%) or chemotherapy (25.7%). The insurance status of most patients (52.7%) was unknown. Most patients were either ever married or never got married. Demographics and clinical characteristics are summarized in table 1.

Univariate and multivariate analysis of overall survival and cancer-specific survival

Age, race, lymphoma subtype, primary site, radiation, chemotherapy, and marital status were identified as risk factors in univariate analysis of OS. In multivariate analysis with Cox regression, the variables that were validated

Table 1 Summary of characteristics for patient population: SEER 1997–2014 (n=2778)*

Characteristic	All patients n (%) (n=2778)
Age	
<60	1118 (40.2)
≥60	1660 (59.8)
Sex	
Male	1539 (55.4)
Female	1239 (44.6)
Race	
Black	214 (7.7)
White	2181 (78.5)
Other (American Indian/AK Native, Asian/Pacific Islander)	383 (13.8)
Lymphoma subtypes	
DLBCL	359 (12.9)
Follicular lymphoma	303 (10.9)
MALT lymphoma	1557 (56.0)
Other B-cell lymphomas	559 (20.1)
Primary site	
Conjunctiva	811 (29.2)
Cornea	3 (0.1)
Retina	10 (0.4)
Choroid	15 (0.5)
Ciliary body	36 (1.3)
Lacrimal gland	356 (12.8)
Overlapping lesion of eye and adnexa	11 (0.4)
Other sites	1536 (55.3)
Laterality	
Left—origin of primary	1206 (43.4)
Right—origin of primary	1309 (47.1)
Paired site	263 (9.5)
Surgery performed	
Yes	1095 (39.4)
No	1663 (59.9)
Unknown	20 (0.7)
Radiation	
Yes	1617 (58.2)
No	1161 (41.8)
Chemotherapy	
Yes	715 (25.7)
No	2063 (74.3)
Cause of death	
Alive or dead of other cause	2504 (90.1)
Dead (attributable to lymphoma)	274 (9.9)
Vital status	
Dead	769 (27.7)
Alive	2009 (72.3)
Insurance status	
Uninsured	30 (1.1)
Insured/any Medicaid	1285 (46.3)
Insurance status unknown	1463 (52.7)
Marital status	
Never married	389 (14.0)
Married	1535 (55.3)
Ever married (divorce, separated, and widowed)	589 (21.2)
Unknown	265 (9.5)
Multiple modalities	
Nothing but conservative treatment	399 (14.4)
Surgery only	312 (11.2)
Radiation only	817 (29.4)
Chemotherapy only	279 (10.0)
Surgery and radiation	516 (18.6)
Surgery and chemotherapy	155 (5.6)
Radiation and chemotherapy	168 (6.0)
All three	112 (4.0)
Missing	20 (0.7)

*Data are presented as the number (percentage) of patients.
DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; SEER, Surveillance, Epidemiology, and End Results.

as independent prognostic factors included the following: age (age ≥60 years, HR 5.363, 95% CI 4.341 to 6.625, p<0.001), lymphoma subtype (follicular lymphoma, HR 0.601, 95% CI 0.461 to 0.784, p<0.001; MALT lymphoma, HR 0.453, 95% CI 0.364 to 0.562, p<0.001; other B-cell lymphomas, HR 0.696, 95% CI 0.556 to 0.871, p=0.002), primary site (primary lesion of non-conjunctiva, HR 1.569, 95% CI 1.304 to 1.890, p<0.001), and radiation (received radiation therapy, HR 0.674, 95% CI 0.583 to 0.780, p<0.001) (table 2). Most results for predicting CSS were the same as those for OS. Tumors located in paired site and chemotherapy were regarded as risk factors for CSS in the multivariate analysis, as shown in table 3.

Treatment selection for patients based on subtype of lymphoma

The total median OS time was 181 months. The total median CSS time was not reached, which indicated that the cancer-specific mortality is relatively low. Patients with primary orbital and intraocular B-cell lymphoma tended to die from complications. Indolent lymphomas, such as MALT lymphoma and follicular lymphoma grades 1–2, were not recommended for radical treatments, while invasive lymphomas were. The therapeutic approaches to invasive lymphomas need to be further studied. In this study, 516 patients with mantle cell lymphoma, DLBCL, Burkitt lymphoma, follicular lymphoma grades 3–4 and precursor B-lymphoblastic lymphoma were considered invasive B-cell lymphomas. The median OS time of patients with invasive lymphomas was 103 months, which was notably shorter than the observed OS for those with indolent lymphomas (the median OS time was not reached) (figure 1). As surgery impacts OS rather little, radiation and chemotherapy were the main treatments we considered. Patients who received both chemotherapy and radiation had the best OS time. The median OS time was 159 months in the chemotherapy and radiation group (10-year OS 54.7%), 93 months in the radiation-only group (10-year OS 36.8%), 103 months in the chemotherapy-only group (10-year OS 42.6%), and 60 months in the group that received neither (10-year OS 32.5%). This

Table 2 Univariate and multivariate survival analysis on OS in primary ocular B-cell lymphoma from SEER database

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	**P values**	**HR (95% CI)**	**P values**
Age (years)				
<60	Reference		Reference	
≥60	5.95 (4.838 to 7.317)	<0.001	5.363 (4.341 to 6.625)	<0.001
Race				
White	Reference		Reference	
Black	0.652 (0.474 to 0.898)	0.009	1.033 (0.748 to 1.425)	0.845
Other (American Indian/AK Native, Asian/Pacific Islander)	0.735 (0.585 to 0.922)	0.008	0.972 (0.771 to 1.224)	0.807
Gender				
Female	Reference			
Male	1.056 (0.916 to 1.217)	0.455		
Lymphoma subtypes				
DLBCL	Reference		Reference	
Follicular lymphoma	0.599 (0.465 to 0.772)	<0.001	0.601 (0.461 to 0.784)	<0.001
MALT lymphoma	0.347 (0.286 to 0.421)	<0.001	0.453 (0.364 to 0.562)	<0.001
Another B-cell lymphoma	0.595 (0.482 to 0.735)	<0.001	0.696 (0.556 to 0.871)	0.002
Primary site				
Conjunctiva	Reference		Reference	
Other sites	2.115 (1.766 to 2.532)	<0.001	1.569 (1.304 to 1.890)	<0.001
Laterality				
Left—origin of primary	Reference			
Right—origin of primary	1.059 (0.913 to 1.229)	0.448		
Paired site	1.020 (0.789 to 1.319)	0.878		
Radiation				
No	Reference		Reference	
Yes	0.596 (0.517 to 0.687)	<0.001	0.674 (0.583 to 0.780)	<0.001
Chemotherapy				
No	Reference		Reference	
Yes	1.465 (1.256 to 1.708)	<0.001	0.997 (0.836 to 1.188)	0.973
Surgery				
No	Reference			
Yes	0.955 (0.827 to 1.103)	0.532		
Unknown	0.646 (0.207 to 2.010)	0.450		
Insurance status				
Uninsured	Reference			
Insured/any Medicaid	1.063 (0.503 to 2.248)	0.872		
Insurance status unknown	1.323 (0.627 to 2.792)	0.462		
Marital status				
Never married	Reference		Reference	
Married	0.944 (0.758 to 1.176)	0.608	1.002 (0.804 to 1.248)	0.987
Ever married (divorce, separated, and widowed)	1.394 (1.100 to 1.767)	0.006	1.163 (0.917 to 1.475)	0.214
Unknown	1.080 (0.801 to 1.456)	0.615	0.826 (0.611 to 1.116)	0.213

DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; OS, overall survival; SEER, Surveillance, Epidemiology, and End Results.

difference in OS was statistically significant (p=0.003). The Kaplan-Meier-estimated OS distributions are shown in figure 2A. For patients with indolent lymphomas, radiation-based therapeutic regimens were associated with improved OS. The OS time for the radiation-only group did not reach the median (10-year OS 74.6%), which was also observed in the chemotherapy plus radiation group (10-year OS 71.3%). The chemotherapy-only group had an even shorter median overall survival time (141 months, 10-year OS 58.4%) than the group receiving neither (187 months, 10-year OS 60.3%) (figure 2B). This difference was statistically significant (p<0.001).

Treatment selection for patients based on age stratification

It came to our attention that age was a significant prognostic factor. Appropriate treatment plan based on age stratification should be taken into consideration by physicians. Elder patients were susceptible to additional risks caused

Table 3 Univariate and multivariate survival analysis on CSS in primary ocular B-cell lymphoma from SEER database

	Univariate analysis		Multivariate analysis	
Variable	**HR (95% CI)**	**P values**	**HR (95% CI)**	**P values**
Age (years)				
<60	Reference		Reference	
≥60	3.867 (2.842 to 5.262)	<0.001	3.227 (2.359 to 4.416)	<0.001
Race				
White	Reference		Reference	
Black	0.468 (0.256 to 0.857)	0.014	0.733 (0.398 to 1.350)	0.319
Other (American Indian/AK Native, Asian/Pacific Islander)	0.469 (0.297 to 0.740)	0.001	0.642 (0.405 to 1.018)	0.060
Gender				
Female	Reference			
Male	1.073 (0.846 to 1.361)	0.561		
Lymphoma subtypes				
DLBCL	Reference		Reference	
Follicular lymphoma	0.306 (0.198 to 0.472)	<0.001	0.369 (0.236 to 0.577)	<0.001
MALT lymphoma	0.168 (0.124 to 0.228)	<0.001	0.276 (0.196 to 0.388)	<0.001
Another B-cell lymphoma	0.469 (0.346 to 0.636)	<0.001	0.611 (0.442 to 0.844)	0.003
Primary site				
Conjunctiva	Reference		Reference	
Other sites	3.066 (2.167 to 4.337)	<0.001	1.930 (1.349 to 2.762)	<0.001
Laterality				
Left—origin of primary	Reference		Reference	
Right—origin of primary	1.157 (0.895 to 1.497)	0.266	1.109 (0.857 to 1.437)	0.431
Paired site	1.743 (1.206 to 2.518)	0.003	1.998 (1.379 to 2.896)	<0.001
Radiation				
No	Reference		Reference	
Yes	0.506 (0.399 to 0.642)	<0.001	0.608 (0.476 to 0.778)	<0.001
Chemotherapy				
No	Reference		Reference	
Yes	2.654 (2.092 to 3.368)	<0.001	1.440 (1.099 to 1.888)	0.008
Surgery				
No	Reference			
Yes	0.944 (0.741 to 1.202)	0.639		
Unknown	0.567 (0.079 to 4.052)	0.572		
Insurance status				
Uninsured	Reference			
Insured/any Medicaid	1.338 (0.331 to 5.412)	0.683		
Insurance status unknown	1.625 (0.403 to 6.556)	0.495		
Marital status				
Never married	Reference			
Married	1.317 (0.885 to 1.959)	0.174		
Ever married (divorce, separated, and widowed)	1.531 (0.990 to 2.367)	0.055		
Unknown	1.306 (0.769 to 2.218)	0.323		

CSS, cancer-specific survival; DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma; SEER, Surveillance, Epidemiology, and End Results.

by complications that led to elevated mortality according to CSS survival analysis. For patients older than 60 years, the chemotherapy-only group had the shortest median survival overtime (79 months, 10-year OS 36.2%). Both groups involving radiation had similar median OS time (radiation only: 138 months, 10-year OS 53.8%; radiation plus chemotherapy: 130 months, 10-year OS 52.6%). The median OS time for the group that received neither radiation or chemotherapy was 100 months (10-year OS 41.1%) (figure 3A). For younger patients, the chemotherapy-only group had a median OS time of 193 months (10-year OS 75.8%). Other groups had not reached the median OS time (figure 4). In elder patients, those with invasive lymphomas also had a relatively shorter OS time than those with indolent lymphomas (76 months vs 126 months). Elder patients with invasive lymphomas had the maximum mortality, and 353 such patients were identified. Among these patients, those in the radiation plus chemotherapy group survived the longest with the median OS time of 109 months (10-year OS 44.9%). The median OS time was 70 months in the

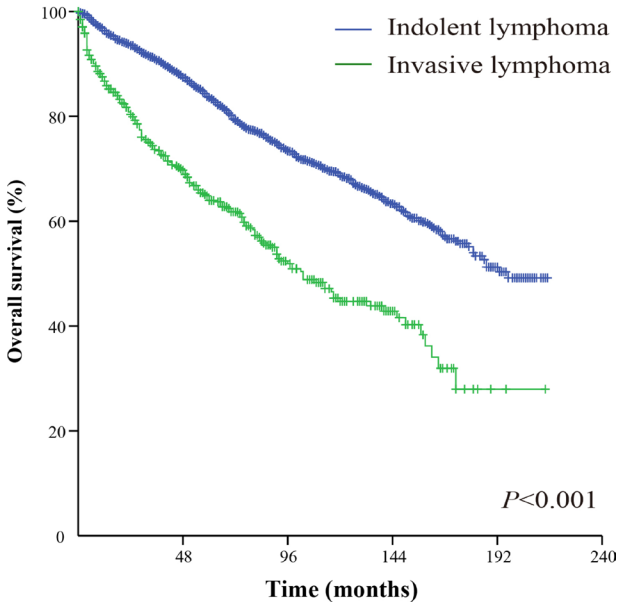

Figure 1 Kaplan-Meier survival curves of patients with invasive lymphoma and indolent lymphoma on overall survival.

radiation-only group (10-year OS 25.4%), 79 months in the chemotherapy-only group (10-year OS 31.4%), and 55 months in the group receiving neither (10-year OS 24.2%). The Kaplan-Meier-estimated OS distributions are shown in figure 6. These differences were statistically significant ($p<0.05$).

DISCUSSION

Most cases of B-cell POL are ocular adnexal lymphomas; relatively few are intraocular lymphomas. For ocular adnexal lymphomas, common subtypes include indolent lymphomas, such as MALT lymphoma and follicular lymphoma, whereas intraocular lymphomas are more aggressive. Independent risk factors for OS are age and lymphoma subtype. An age of 60 years or older and invasive lymphoma subtype significantly affect survival. In this study, the median OS was 181 months, and the median tumor-related mortality has not yet been reached. Patients with ocular B-cell lymphoma, if treated properly, have a greater chance of surviving for longer periods than patients with other B-cell lymphomas. In this study, 516 patients were diagnosed with invasive lymphoma, and the median survival was only 103 months. In contrast, the median survival has not yet been determined for patients with indolent lymphomas, suggesting that patients with invasive lymphoma, as with other B-cell lymphomas, require more aggressive treatments. Among those with invasive lymphoma, patients who received both chemotherapy and radiotherapy had the longest survival time, whereas the survival time was similar between patients who received radiotherapy alone and those who received chemotherapy alone. The survival time was shortest in patients who received neither radiotherapy nor chemotherapy. For indolent lymphomas, the survival time was shortest in patients (≥60 and <60 years old) who received chemotherapy alone. Among all patients, the patients aged 60 years or over with invasive lymphoma (n=353) had the highest mortality rate, with a median survival of only 76 months; the survival time was longer in patients who received both radiotherapy and chemotherapy.

Patients with indolent ocular B-cell lymphoma had longer survival times because indolent lymphoma progresses slowly and exhibits less invasiveness. Patients with indolent lymphoma may survive a long time even without tumor treatment. Because of the blood–eye barrier, drugs selected for intravenous chemotherapy should be those with high permeability, such as methotrexate (MTX). However, these drugs are associated with significant side effects and may

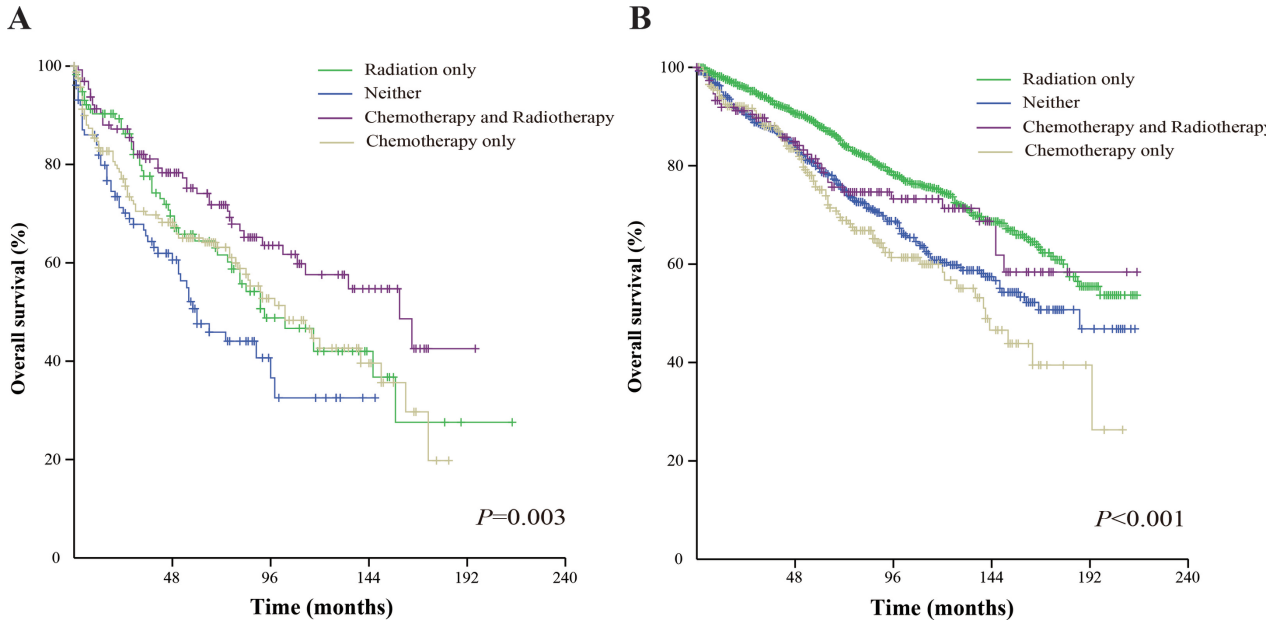

Figure 2 Kaplan-Meier survival curves of patients with invasive lymphoma (A) and indolent lymphoma (B) according to multiple treatments.

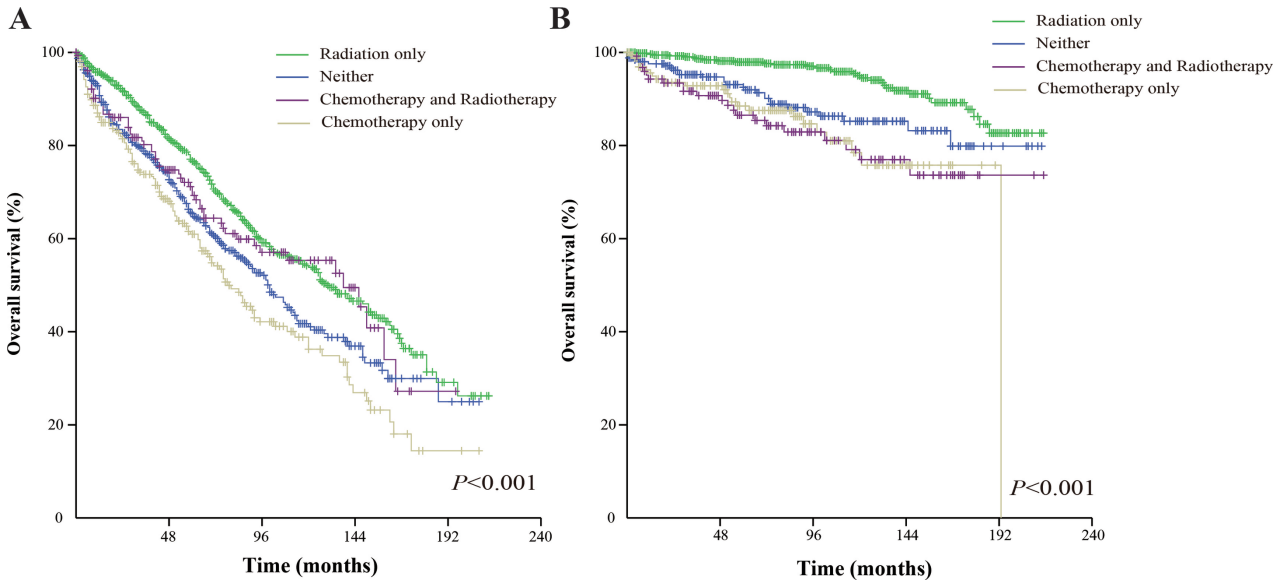

Figure 3 Kaplan-Meier survival curves of patients over 60 years (A) and under 60 years (B) according to multiple treatments.

not be suitable for elderly patients.[18 19] Patients with invasive ocular B-cell lymphoma may be treated with, and can benefit similarly from, chemotherapy regimens used with other B-cell lymphomas. For patients with ocular B-cell lymphoma, radiotherapy alone or in combination with chemotherapy is more advantageous than chemotherapy alone. In general, full orbital irradiation at 2 Gy per fraction for a total of 35 to 40 Gy is used to treat ocular lymphoma.[20] Berenbom *et al*[21] studied 12 cases of POL and found that seven patients who received radiotherapy did not relapse during the follow-up, whereas two of five patients who did not receive radiotherapy relapsed. These results indicated that radiotherapy alone resulted in good control of the ocular lesion and reduced early side effects of intravenous therapy in patients with POL, without increasing the rate of central nervous system relapse. The side effects of orbital radiotherapy included dermatitis, cataracts, dry eye, keratitis, radiation retinopathy, and macular degeneration.[12 22] Most complications were mild and tolerable. MTX is the main treatment for POL. Frenkel *et al*[19] injected MTX (up to 25 doses) in 26 patients with intraocular lymphoma and found that an average of 6.4 injections were needed to achieve clinical remission. These patients were followed for an average of 63 months, and no relapse was observed; the side effects were conjunctival hyperemia, corneal epithelial lesion, phakic cataract, and glaucoma. Smith *et al*[23] performed intraocular MTX injection in 16 patients with ocular lymphoma. Their results showed that ocular lymphoma abated after 12 injections, with a response rate of 100%. Batchelor *et al*[24] administered high-dose intravenous MTX in nine patients with POL with or without primary central nervous system lymphoma. Their results showed that the overall response rate was 78%, and the relapse rate was 86%. The above results indicate that intraocular MTX injection was superior to intravenous MTX for ocular lesion control, with less systemic side effects. Ma *et al*[25] recommended intraocular MTX combined with intravenous MTX to further improve complete remission and overall survival rates and reduce central nervous system relapse. Since 1997, rituximab has been used in clinical practice. Larkin *et al*[26] investigated intravitreal rituximab alone or in combination with MTX in 34 patients with PIOL and observed a response rate of 87.9%. Hashida *et al*[27] enrolled 13 patients who either did not respond to intravitreal MTX or could not tolerate the side effects of MTX. After intravitreal rituximab injection, the overall relapse rate was 55%; the side effects were transient high intraocular pressure and iridocyclitis. Rituximab is indicated in patients who relapse after MTX treatment or cannot tolerate the side effects of MTX. In the present study, however, an analysis of a large data set revealed that chemotherapy alone showed no significant clinical benefits in patients with invasive lymphoma; chemotherapy combined with radiotherapy showed optimal clinical benefits.

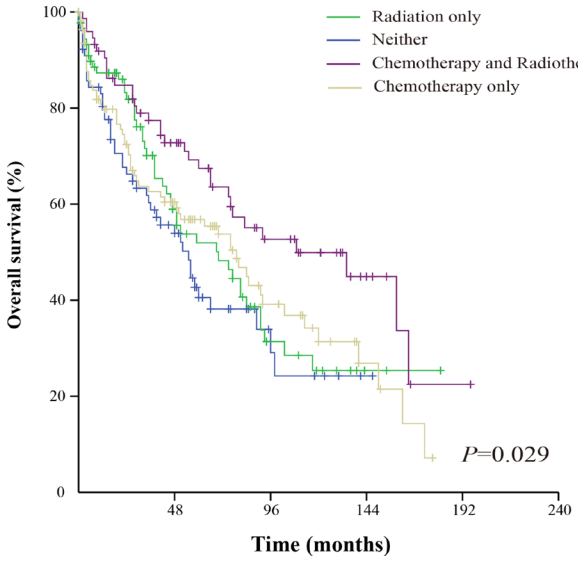

Figure 4 Kaplan-Meier survival curves of patients with invasive lymphoma over 60 years according to multiple treatments.

In summary, the advent of targeted drugs has had little impact on the available treatment options for patients with primary ocular B-cell lymphoma. For indolent lymphoma, radical treatment, especially intravenous chemotherapy, should be avoided. For invasive lymphoma, chemotherapy combined with full orbital irradiation is recommended, and rituximab may benefit patients who cannot tolerate MTX or who have relapsed after MTX treatment. Radiotherapy alone or in combination with chemotherapy is superior to chemotherapy alone, with tolerable side effects. Prospective studies with large sample sizes are required to further validate these findings.

Contributors All authors collaborated in the collection and interpretation of the data and contributed to the manuscript. DLL wrote the main manuscript text. ZJZ edited the manuscript.

Funding This work was supported by grants from Science and Technology Bureau foundation application project of Changzhou (CJ20179025).

Competing interests None declared.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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