Original Article

Ocular adnexal lymphoma – A single-center observational study of survival outcomes

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Purpose: This study aims to comprehensively characterize the clinical, demographic, and histopathological features of ocular adnexal lymphoma (OAL) and assess their impact on patients' survival outcomes. **Methods:** A total of 123 patients were included in the study; of these, 93 patients were selected for survival analysis. Survival data were analyzed using the Kaplan-Meier test, and correlation was assessed through the log-rank test and Cox regression analysis. **Results:** The median age at presentation was 56 years. Furthermore, 98% of patients had primary OAL. The orbit was the most common site of involvement. The majority of patients were of B-cell origin (98%), and only 2% of patients had T-cell lymphoma. In addition, 83% of patients were treated with chemotherapy, and with a median follow-up of 38 months, complete remission was achieved in 48% of patients. The median progression-free survival was 26.4 months. The presence of disseminated disease was strongly linked to an unfavorable prognosis ($P < 0.001$) and reduced survival ($P = 0.037$). **Conclusion:** The 5-year overall survival of the entire study cohort was 81%. The prognosis for OAL is found to be favorable, but the presence of dissemination serves as a notable predictor for poor prognosis.

Key words: B-cell lymphoma, disease-specific survival, ocular adnexal lymphoma, orbital malignancy, overall survival, progression-free survival

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The orbit is affected by a spectrum of malignancies, ranging from indolent to aggressive, which significantly contribute to a high global mortality rate.[1] Ocular adnexal lymphoma (OAL), the most frequent orbital neoplasm, is found in 8%–10% of all extranodal lymphomas and 1% of all non-Hodgkin's lymphoma (NHL) cases.[2,3] It displays diverse clinical manifestations with a chronic progression that necessitates early diagnosis and treatment.[4,5] OAL can localize in adnexal structures, including the conjunctiva, eyelids, orbital tissues, and lacrimal apparatus (extranodal regions). It can arise within these adnexal structures as a primary lymphoma or present concurrently with secondary sites.[6,7] The majority of OAL cases are NHL-B-cell type, and it commonly affects adults and the elderly population.[8-10] External beam radiotherapy (EBRT), chemotherapy, immunotherapy, or a combination of these modalities are currently employed for treating OAL patients, depending upon the histological features, extension of the tumor, and metastatic status.[11] The prognosis of OAL greatly relies on histologic typing as each exhibits a unique clinical pattern and response.[12] The major subtypes of OAL include extranodal marginal zone lymphoma (EMZL) followed by diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and mantle-cell lymphoma (MCL). It is generally acknowledged that low-grade lymphomas (EMZL and FL) tend to have a better prognosis than high grades (MCL and DLBCL), which were reported to have aggressive clinical behavior.[13,14] To date, limited reports have described the significant association of clinical features such as presenting symptoms, age of presentation, anatomical location, tumor staging, and histological grade with survival.[6,15-18] Therefore, the present study aimed to review the clinical-pathological characteristics and their effect on survival outcomes in OAL patients who presented at a tertiary eye hospital in South India.

Methods

Study population

This was a hospital-based, retrospective observational study that included patients presented with OAL from January 1, 2012 to December 31, 2020. We included tumors involving the orbit (lacrimal gland, extraocular muscles, connective tissues), eyelid, and conjunctiva. The complete medical records of OAL patients were reviewed and followed up until the study

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period (December 31, 2022). This work was done with approval from the institutional ethics committee (IRB2018014BAS) and followed the tenets of the Declaration of Helsinki.

Clinical data

Demographic details, such as age, gender, laterality, and clinical features (e.g., the first sign and disease course), were collected. The lymphoma diagnosis was confirmed by ophthalmic examination; histopathology-immunohistochemistry; and systemic investigations, including computed tomography, magnetic resonance imaging (MRI), ultra-sonogram, and bone marrow aspiration. For histopathological examination, tumor sections were stained with Hematoxylin-Eosin. Immunohistochemistry analysis was performed with leukocyte common antigen (LCA), B-cell marker (CD20), and T-cell marker (CD3). The classification of lymphoma was made based on the Working Formulation for Clinical Usage as low-grade, intermediate, and high-grade.[19] Response evaluation was based on radiological imaging and ophthalmic examinations.[20] Depending on the response, patients were grouped as follows: complete remission – no evidence of disease; residual – partial response to treatment, not a progressive lesion; relapse – increase in the size of the lesion during treatment; recurrence – any new lesion nodal or extranodal. Information about patients lost to follow-up, leading to either recurrence or death, was also obtained. Primary lymphoma referred to lymphoma involving ocular structures with no prior history of the disease and no evidence of concomitant systemic lymphoma at diagnosis. Secondary lymphoma encompassed patients with prior history of the disease or evidence of concomitant systemic lymphoma at diagnosis.

Statistical analysis

Survival analyses were performed as defined previously.[3,8,21] Overall survival (OS) was computed from the diagnosis date to death from any cause or to the date of last contact. Progression-free survival (PFS) was determined from diagnosis to first relapse or progression after the initial treatment, death from any cause, or to the date of last contact (whichever is earlier). Disease-specific survival (DSS) was calculated in intervals between the date of diagnosis to the date of death from lymphoma or the date of last contact. Patients who failed to follow up were censored at the date of the last contact.

All the clinical and histopathological findings, type of treatment, relapse, and recurrence were taken for comparable risk variables. The association between the risk factors was evaluated by the Chi-square test. Patient survivals were generated using Kaplan–Maier plots. Univariate analysis was performed using a log-rank test with predicted risk factors. Multivariate analysis was performed by Cox regression analysis with factors studied in univariate analysis. A P value of < 0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Package, version 23 (IBM Corporation, Armonk, New York, USA).

Table 1: Clinical and histological characteristics of OAL patients

Clinicopathological Features	Total Patients n=123 (%)
Gender	
Male	75 (61)
Female	48 (39)
Age at presentation	
>55 years	60 (53)
≤55 years	52 (47)
Laterality	
Unilateral	111 (90)
Bilateral	12 (10)
Symptom*	
Proptosis	58 (47)
Swelling	56 (46)
Ptosis	10 (8)
Redness	6 (5)
Pain	15 (12)
Watering	5 (4)
Defective vision	8 (7)
Irritation	7 (6)
Mass	7 (6)
lagophthalmos	1 (1)
Disease Presentation	
Primary OAL	120 (98)
Secondary OAL	3 (2)
Tumor Location (n=120)†	
Orbit	101 (84.2)
Eyelid	10 (8.3)
Conjunctiva	3 (2.5)
Orbit, Eyelid and Conjunctiva	6 (5)
Histopathology	
B-cell	120 (98)
T-cell	3 (2)
Histology Grading	
Low	57 (46)
Intermediate	35 (29)
High	31 (25)
Treatment (n=93)‡	
Chemotherapy	77 (83)
Chemo and EBRT	4 (4)
EBRT	2 (2)
Not Taken	10 (11)
Treatment Outcome (n=93)‡	
Complete Remission	45 (48)
Alive with disease	33 (36)
Death due to lymphoma	5 (5)
Death due to other cause	10 (11)

*Total can exceed 100% because patients may exhibit one or more presenting symptoms. †Tumor location details were not accessible for 3 OAL patients. ‡Treatment outcome details were accessible for only 93 patients. EBRT: External Beam Radiation Therapy; OAL: Ocular Adnexal Lymphoma

Results

Clinical and histopathological features

A total of 123 patients with OAL were included in the study. Table 1 shows the demographic, clinical, and histopathological features of OAL [Fig. 1]. The median age of presentation was 56 years (range: 30–86 years), with 28 patients (22.7%) less than 45 years. In this cohort, 61% of patients were male and 39% were female. Most of the patients had primary lymphoma (98%) and presented with unilateral manifestation (90%). Proptosis (47%) and swelling (46%) were the most common clinical symptoms reported at diagnosis. Other symptoms such as ptosis, redness, defective vision, pain, or irritation were reported in 48% of the total study cohort. The median duration of symptoms at

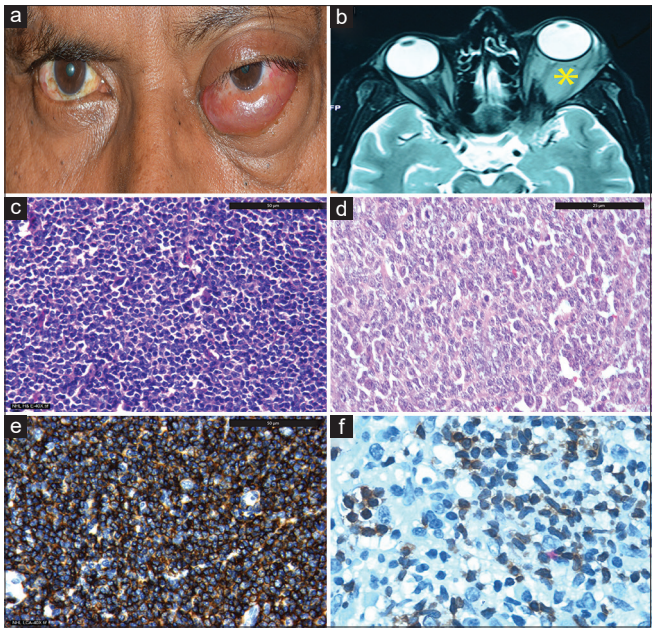


Figure 1: Representative clinical and histopathologic features in ocular adnexal lymphoma patients: (a) Axial proptosis in a 57-year-old OAL patient; (b) *MRI image revealed an isointense mass lesion in intra and extraconal compartment of left orbit with encasement of optic nerve sheath complex and extrinsic proptosis; (c) Hematoxylin-Eosin (H and E) staining shows small-sized monomorphic atypical lymphoid cells; (d) H and E staining shows of large B-cell type OAL (e, f) Tumor cells expressing CD20 (B-cell marker) and CD3 (T-cell marker: scattered positivity) exhibit typical characteristics consistent with non-Hodgkin's B-cell lymphoma

presentation was observed to be 4 months (±6.1 months). The orbit (84.2%) was the most frequently involved anatomical structure, followed by the eyelid (8.3%), more than one adnexal structure (orbital, eyelid, and conjunctiva) (5%), and conjunctiva (2.5%). In our study cohort, we did not observe any cases of intraocular involvement associated with OAL. The histological analysis revealed that the majority of patients had B-cell NHL (98%), with some cases exhibiting anaplastic and plasmablastic variants, while only 2% of patients had T-cell lymphoma. Of the 123 patients, 3.3% (n = 4) had bone marrow infiltration and 6.5% (n = 8) had lymph node infiltration on diagnosis (one regional lymph node: n = 2; more than one regional lymph node: n = 6). Two (1.6%) of the patients had a human immunodeficiency virus-associated lymphoma, one case was diagnosed as Burkitt lymphoma (BL), and another case presented as plasmablastic differentiation.

Treatment outcome

Treatment outcome and survival data, including the progression details, were accessible in 75.6% of patients (n = 93). Furthermore, 83% of the OAL patients were primarily treated with chemotherapy (CHOP: cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone). EBRT was given as mono (2%) and/or combined (4%) to patients who had presented with adverse clinical features, including secondary lymphoma (n = 1), diffused lesion involving more than one adnexal site, and lymph node (n = 5). The median dose of EBRT ranged from 20 to 40 Gy. In addition, 11% of patients underwent complete surgical excision as their primary treatment.

The median follow-up time was 38 months (range: 2–112 months). Complete remission was observed in 48% of patients at the last follow-up. Disease recurrence was observed in nine patients (9.6%), with a median recurrence time of 37 months (range : 11 –60 months). Among these, six patients presented with local recurrence, while three developed OAL with involvement in nodal sites . Re-biopsy details available for five patients confirmed recurrence of B-cell -NHL. Out of nine patients, eight were treated with extended cycles of chemotherapy and one received a combination of chemotherapy and EBRT, of which four showed complete remission. Relapse was observed in 20 patients (21.5%). Among them, three patients had lymph node involvement, one had bone marrow infiltration, one had secondary lymphoma and four had metastatic tumors (tonsil, CNS (n=2), orbital fullness). These patients treated with mono (n = 18) or combinatorial therapy (n = 2) showed median OS up to 53 months. Of relapsed patients, 20% showed complete remission. The probability of relapse is largely associated with disease dissemination (Chi-square test: P = 0.007, 95%CI: 1.38–12.29) and tumors involved in more than one adnexal site (Chi-square test: P = 0.042, 95%CI: 0.08–0.95). Disease dissemination was observed in 13% (n = 12) of patients showing 53 months as a median OS. Dissemination was highly associated with the patient presenting with diffused lesions in adnexal sites (P < 0.001, 95%CI: 0.16–0.52). These patients were treated with a CHOP regimen (n = 9), and EBRT (n = 3) showed complete remission in two cases only. We did not find any correlation between gender, laterality, and treatment groups with prognosis in OAL.

Clinical features and survival outcome

The 3-year and 5-year OS were 85% and 81% and DSS were 95% and 93%, respectively. The median progression-free survival was 26.4 months. When comparing all OAL patients, there was a prominent PFS in patients without dissemination (P = <0.001), relapse (P = <0.001), and recurrence (P = 0.001) [Table 2]. Similarly, DSS was substantially better for the patient with primary lymphoma (P = 0.007), B-cell NHL (P = 0.018), and without dissemination (P = 0.037) [Fig. 2]. OS was significantly favorable in patients who presented with primary lymphoma (P = 0.006), B-cell lymphoma (P = 0.004), were under 55 years of age (P = 0.004), and without disease dissemination (P = 0.046) [Supplementary Table 1]. Multivariate analysis through Cox regression demonstrated significant inferior DSS in patients with secondary OAL (P = 0.027) [Supplementary Table 2].

Discussion

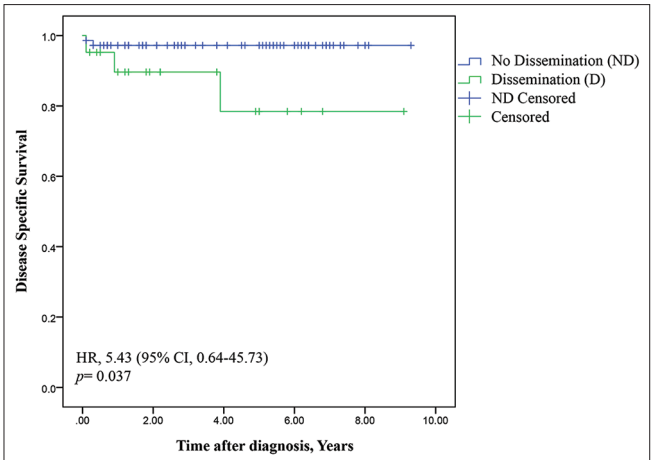
This single-center study provides a detailed clinical-pathological characteristic picture and survival outcomes of OAL. To our knowledge, this is the largest clinical report of OAL from a tertiary eye care center in South India. The median age of presentation in our study cohort was 56 years; over 23% of patients presented below 45 years of age. Previous studies have substantiated the occurrence of OAL in individuals under the age of fifty.[13] The OS rate of patients above 55 years of age was comparatively lower than that of patients below 55 years of age (P = 0.004). Similarly, studies have demonstrated that patients above 60 years of age exhibited poor outcomes.[22] As previously reported, most of the study population was B-cell derivations, whereas T-cell and BL were found to have a lower

Table 2: Univariate analyses for disease-specific survival and progression-free survival

Risk Factors	Total Patients (*n*=93)	DSS Univariate		PFS Univariate	
		Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Gender					
Male	53				
Female	40	0.17 (0.02–1.020)	0.072	1.28 (0.60–2.74)	0.523
Age					
>55 years	47				
≤55 years	46	4.25 (0.73–24.58)	0.157	1.36 (0.65–2.84)	0.396
Tumor site*					
Tumor involving one site (Orbit/Conjunctiva/Eyelid)	81				
Tumor involving multiple sites (Orbit, Eyelid and Conjunctiva)	11	-	0.428	0.37 (0.10–1.33)	0.023*
Laterality					
Unilateral	81				
Bilateral	12	-	0.373	0.78 (0.27–2.23)	0.617
Presentation					
Primary OAL	90				
Secondary OAL	3	0.09 (0.00–33.70)	0.007**	0.63 (0.05–6.98)	0.713
Histology					
B-cell	90				
T-cell	3	0.11 (0.00–24.10)	0.018*	0.78 (0.08–7.22)	0.828
Histology Grading					
Low	37				
Intermediate	28				
High	28	-	0.835	-	0.034*
Treatment†					
Mono-therapy Chemotherapy/EBRT	79				
Combined therapy	4	0.16 (0.00–13.26)	0.080	0.35 (0.06–1.82)	0.213
Dissemination					
Yes	21				
No	72	5.43 (0.64–45.73)	0.037*	4.41 (1.53–12.68)	<0.001***
Recurrence					
Yes	9				
No	84	1.81 (0.12–26.52)	0.587	3.33 (1.08–10.2)	0.001**
Relapse					
Yes	20				
No	73	0.81 (0.10–6.48)	0.857	11.5 (4.29–31.04)	<0.001***

*Tumor location details were not accessible for 1 OAL patients. †Only 83 patients were taken treatment. CI: Confidence Interval; DSS: Disease-Specific Survival; PFS: Progression-Free Survival

incidence.[21,23,24] In addition, OAL has also been reported with diverse histology.[25] It is generally acknowledged that high-grade pathological findings are clinically aggressive.[2] In a multicenter cohort study of orbital lymphoma, it was found that patients with EMZL and FL had notably better 10-year DSS rates (92% and 71%, respectively) compared to those with DLBCL (41%) and MCL (32%).[3] Similarly, another extensive study on OAL observed significantly lower DSS rates in high-grade subtypes such as DLBCL (38%) and MCL (31%) in contrast to low-grade subtypes such as EMZL (89%) and FL (56%).[4] Furthermore, independent investigations across various OAL subtypes indicated that the overall 5-year survival rates were 36% and 34% for high-grade lymphomas (DLBCL and MCL, respectively), whereas low-grade lymphomas exhibited considerably higher survival rates, with EMZL at 83% and FL at 60% for 10 years.[5-8] This study showed slight male predominance (61%). Nevertheless, the association between gender and prognosis had been previously noted to differ according to the subtype.[13] In our cohort, we did not find any correlation between gender and prognosis. The majority of the patients presented as unilateral lesions, which is consistent with other studies.[21] Recent studies have reported that most of the primary unilateral OALs are indolent, with a better prognosis for survival and relapse-free progression.[26] No statistical significance in survival was observed in our group between the laterality groups, even though some of the studies reported a poor outcome in bilateral OAL patients.[27,28] This non-significance could be owing to a smaller group of patients that presented with bilateral disease.



Dissemination status, interval, Years	0	3	5	8
Dissemination (n=21)				
Patients at risk, nos	21	9	6	1
Events, no.	2	1	0	0
Without dissemination (n=72)				
Patients at risk, nos	72	36	29	3
Events, no.	2	0	0	0

Figure 2: Disease-specific survival is associated with disease dissemination in ocular adnexal lymphoma. Patients without dissemination showed more favorable disease-specific survival than the disseminated OAL ($P = 0.037$)

A large retrospective study proved that anatomical location plays an inevitable role in disease prognosis and also highlighted the role of secondary tumors and relapse being associated with worse prognosis.[21,29] We noted the superolateral quadrant of the orbit to be the most common site of the region of the lesion. This is in agreement with Priego *et al*.,[30] who observed a majority of cases to have similarly infiltrated structures in OAL. Involvement of diffuse lesions with adjacent structures (involving more than one site) profoundly affected the clinical course ($P = 0.042$).

OAL can present as a localized indolent disease and become aggressive when it involves a secondary site, which was found to be a predictor of a poorer outcome.[14,27,31,32] A study by Holm *et al*.[22] reported disease dissemination to be more frequent in OAL, and they further emphasized that recurring lymphomas significantly show a worse prognosis. OS of disseminated lymphoma was relatively low compared to the non-disseminated group ($P = 0.046$). Notably, patients with central nervous system (CNS) spread or secondary lymphoma originating from CNS (n = 3) showed low survival when compared to other predicted risk factors. CNS involvement in orbital lymphoma worsens the prognosis, thus affecting the survival of the patients.[33] Additionally, studies have reported that the association of lymphadenopathy and viral agents are associated with poor prognosis.[34,35] We report the involvement of lymph nodes in most of the disseminated cases where OS is profoundly affected. In our series, we noted that only two cases were viral-associated lymphoma. Moreover, viral association is reported to be extremely rare in orbital lymphomas and does not play a major role in disease pathogenesis.[22]

In OAL localized radiotherapy is the most common treatment modality prescribed, whereas systemic chemotherapy is considered for advanced disease conditions.[36,37] Rasmussen *et al*.[38] reported that patients with ocular adnexal follicular lymphoma primarily treated with EBRT had a more favorable long-term disease-specific survival. Rituximab, an anti-CD20 agent, is considered an alternative treatment for localized CD20-positive OAL to improve response rates and survival.[39] In particular, combined chemotherapy with rituximab has been demonstrated to enhance the DSS in patients with Stage IIIE/IVE EMZL.[27] A study by Olsen *et al*.[21] concluded that rituximab combined with CHOP appears to be the preferred treatment option for high-grade DLBCL and MCL. In our study cohort, OAL was frequently treated with COP or CHOP regimen, and 48% showed complete remission. When comparing treatment modalities, we found no significant difference between EBRT and chemotherapy as chemotherapy was the primary mode of treatment.

In the current study, 3-year and 5-year OS were 85% and 81% and DSS were 95% and 93%, respectively. The survival outcomes of our study cohort are in line with the previous literature.[21,22] Our data suggest that patients with secondary lymphoma and disseminated disease are at a higher risk of disease relapse, subsequently increasing the rate of lymphoma-related death. Moreover, other major risk factors such as older age of presentation, disease relapse, and lesions involving more than one site are observed to be associated with poor prognosis. Despite their lower prevalence, both secondary lymphoma and T-cell lymphoma demonstrated a poor prognosis.

As a retrospective study, we had certain limitations. Currently, the study samples were marked by LCA, CD20, and CD3 alone. Studying additional subtyping markers in the future will enhance the overall prognosis of diseases. In addition, most of the patients defaulted after their curative treatment, and information on subsequent relapse and treatment was not available for a few patients. With a median follow-up time of 38 months, there might not have been enough time to detect significant outcome variables. Nonetheless, the strength of our study is focused on the clinical characteristics and their effect on the outcome and survival of OAL patients, which is rarely explored.

Conclusion

The present study delved into the clinicopathological features as prognostic indicators and their association with survival outcomes of OAL. Overall, OAL patients exhibited significantly better prognosis and survival. Nevertheless, dissemination was closely linked with deteriorated prognosis. Furthermore, our findings emphasize the importance of long-term follow-up given the enduring risk of disease recurrence and the potential for aggressive transformation over time.

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Author contributions

Conception or design of the work: UK, AV, VM; Acquisition, analysis, or interpretation of data: KKS, PS, RS; Drafting of the manuscript: KKS, PS; Critical revision of the manuscript for important intellectual content: UK, AV, RS, VM. All the authors approved the final version of the manuscript.

Ethical approval

This work was done with approval from the Institutional Ethics Committee (IRB2018014BAS) and followed the tenets of the Declaration of Helsinki.

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Supplementary Table 1: Univariate analyses for overall survival in OAL

Risk Factors		OS Univariate	
		Hazard Ratio (95% CI)	*P*
Gender	Male		
	Female	0.38 (0.135 to 1.10)	0.055
Age	>55		
	≤55	4.95 (1.791 to 13.72)	0.004**
Tumor site	Tumor involving one site (Orbit/Conjunctiva/Eyelid)		
	Tumor involving multiple sites (Orbit, Eyelid and Conjunctiva)	-	0.444
Laterality	Unilateral		
	Bilateral	-	0.132
Presentation	Primary OAL		
	Secondary OAL	0.162 (0.006 to 4.32)	0.006**
Histology	B cell		
	T cell	0.006 (0.00 to 0.19)	0.004**
Histology Grading	Low		
	Intermediate		
	High	-	0.017*
Treatment	Mono-therapy Chemotherapy/EBRT		
	Combined therapy	-	0.910
Dissemination	Yes		
	No	2.71 (0.760 to 9.68)	0.046*
Recurrence	Yes		
	No	0.55 (0.112 to 2.72)	0.558
Relapse	Yes		
	No	0.87 (0.25 to 2.95)	0.834

CI - Confidence Interval; OS - Overall Survival

Supplementary Table 2: Multivariate analyses for disease specific survival in OAL

Risk Factors		DSS Multivariate	
		CI-95%	*P*
Gender	Male		
	Female	0.005 to 1.730	0.112
Age	>55		
	≤55	0.921 to 1.078	0.072
Presentation	Primary OAL		
	Secondary OAL	1.50 to 886.4	0.027*
Histology	B cell		
	T cell	0.24 to 2.875	0.275
Dissemination	Yes		
	No	0.754 to 32.81	0.095

CI - Confidence Interval; DSS - Disease Specific Survival