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# Non-Hodgkin's Lymphoma of the tonsil: clinical features, treatment response and prognosis

## *Tonsil Non-Hodgkin Lenfoması: klinik özellikler, tedaviye yanıt ve prognoz*

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**ABSTRACT**

**Aim:** Tonsillar lymphomas, specifically non-Hodgkin's lymphomas in extranodal regions, are a significant subset of malignancies in the head and neck. Understanding the clinical and radiological characteristics of these lymphomas is pivotal for augmenting current knowledge and refining treatment approaches, particularly considering the notable incidence and distinctive pathophysiology of these malignancies.

**Materials and Methods:** A retrospective study encompassing 45 patients diagnosed with tonsillar lymphoma across two university hospitals was undertaken. Comprehensive data, including demographics, symptoms, clinical and pathological findings, and treatment details, were analyzed. Various statistical tests explored factors influencing treatment responses and prognosis.

**Results:** Patients predominantly presented with dysphonia, dysphagia, and dyspnea, alongside a notable prevalence of comorbidities such as hypertension and diabetes mellitus. Diagnosis largely leaned on excisional biopsy, revealing diffuse large B-cell lymphoma as the most common subtype. Treatment was majorly initiated with R-CHOP, witnessing an encouraging initial response. A mean time to progression was 13 months, with a median progression-free survival of 10 months and median overall survival of 55.8 months. Variables such as age, Ann Arbor stage, lymphoma subtype, R-IPI scores, double expression status, and presence of objective response to first line treatment status evidently influenced progression-free survival and overall survival, albeit none was an independent factor in multivariate analysis.

**Conclusion:** The findings underscore the importance of comprehensive multi-faceted analyses in understanding tonsillar lymphomas. Although there was no independent risk factor for survival analyses, variables such as age, Ann Arbor stage, lymphoma subtype, R-IPI scores, double expression status, and presence of objective response to first line treatment were instrumental in influencing progression-free survival and overall survival, offering valuable insights for future research and potential tailoring of treatment approaches.

**Keywords:** Non-Hodgkin lymphoma, tonsillar lymphoma, prognosis.

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## ÖZ

**Amaç:** Tonsil lenfomaları, özellikle ekstranodal bölgelerdeki non-Hodgkin lenfomalar, baş ve boyun malignitelerinin önemli bir alt kümesidir. Bu lenfomaların klinik ve radyolojik özelliklerini anlamak, özellikle bu malignitelerin belirgin insidansı ve ayırt edici patofizyolojisi göz önüne alındığında, mevcut bilgiyi artırmak ve tedavi yaklaşımlarını rafine etmek için merkezi öneme sahiptir.

**Gereç ve Yöntem:** İki üniversite hastanesinde tonsil lenfoması tanısı alan 45 hastanın verileri retrospektif olarak incelendi. Demografi, semptomlar, klinik ve patolojik bulgular ve tedavi detaylarını içeren veriler analiz edildi. Çeşitli istatistiksel testlerle tedavi yanıtlarını ve prognozu etkileyen faktörler incelendi.

**Bulgular:** Hastalar genellikle disfoni, disfaji ve dispne ile başvurdu. Hipertansiyon ve diyabet mellitus en sık saptanan iki komorbidite idi. Tanı, büyük ölçüde eksizyonel biyopsiye dayanıyordu ve en yaygın alt tip diffüz büyük B-hücreli lenfoma olarak saptandı. İlk basamak tedavide, sıklıkla R-CHOP ile başlanmış ve iyi bir objektif yanıt oranına ulaşılmıştı. Ortalama progresyona kadar geçen süre 13 ay, medyan progresyonsuz sağkalım 10 ay ve medyan genel sağkalım 55.8 ay olarak hesaplandı. Yaş, Ann Arbor evresi, lenfoma alt tipi, R-IPI skorları, double ekspresyon durumu ve birinci basamak tedaviye objektif yanıt varlığı gibi değişkenlerin, PFS ve OS'ye anlamlı etkisi olmakla beraber çok değişkenli analizde bağımsız bir faktör bulunamadı.

**Sonuç:** Bulgular, tonsiller lenfomaları anlamada kapsamlı, çok yönlü analizlerin önemini vurgulamaktadır. Her ne kadar sağkalım analizleri için bağımsız bir risk faktörü olmasa da yaş, Ann Arbor evresi, lenfoma alt tipi, R-IPI skorları, double ekspresyon durumu ve birinci basamak tedaviye objektif yanıt varlığı gibi değişkenler, PFS ve OS üzerinde etkili olup, gelecekteki araştırmalar ve potansiyel tedavi yaklaşımlarının kişiye özel olarak düzenlenmesi için değerli veri sunmaktadır.

**Anahtar Sözcükler:** Non-Hodgkin lenfoma, tonsil lenfoma, prognoz.

## INTRODUCTION

In adults, 30% of Non-Hodgkin's Lymphomas (NHL) are located in extranodal areas (1). Extranodal NHL is the second most common primary malignancy in the head and neck region after squamous cell carcinoma (2, 3). Approximately 11% of NHL patients have primary lesions in the head and neck region (4). About 5-10% of NHL patients in the United States exhibit involvement in the Waldeyer ring, with the tonsils being the most frequently affected area at a rate of 51% (5-7). B-cell lymphomas are the most commonly occurring among lymphomas located in this region, with diffuse large B-cell lymphoma being the most frequent subtype (8-11). Extranodal NK/T cell lymphomas dominate among T-cell lymphomas. Hodgkin lymphoma is less frequently observed (12, 13). In our country, there are published studies on tonsillar lymphomas, mainly revealing similar patterns in cross-sectional studies (3). However, the data is typically based on case reports (14-16). We aimed to contribute to the national data by compiling the clinical and radiological features of tonsillar lymphomas diagnosed in two university hospitals.

## MATERIALS and METHODS

All patients evaluated in two university hospitals for various complaints and ultimately diagnosed with tonsillar lymphoma have been included in this retrospective study. Medical records of patients were reviewed to gather information such as demographic features (age, gender, etc.), presenting symptoms, radiological findings (tumor size, laterality, presence of cervical lymphadenopathy), laboratory findings, pathological features (histological subtype, expression patterns, grade of lymphoma, bone marrow involvement), treatment regimens, treatment responses, and prognosis (survival times, relapses). Collected data have been statistically analyzed. Categorical variables were presented as frequency and percentage, while continuous variables were expressed as mean ± standard deviation (minimum-maximum) or median (25-75 percentile). Appropriate statistical tests were employed to identify factors affecting treatment responses and prognosis. The study was conducted with the approval of Izmir Bakırçay University Ethics Committee (2023/1170).

## RESULTS

In this study encompassing 45 patients (Figure-1), the average age at the time of diagnosis was 62 years, with a notable 57.8% being over 60 years of age (Table-1). The gender distribution revealed a male predominance with a ratio of 1.6:1. Symptom-wise, dysphonia was observed in

60% of the patients, dysphagia in 51.1%, dyspnea in 40%, and B symptoms in 51.1%. A substantial number of patients had comorbid conditions; hypertension was the most common at 60%, followed by diabetes mellitus at 31.1%. Less prevalent comorbidities included coronary artery disease, hyperlipidemia, benign prostate hyperplasia, and congestive heart failure among others. We only had data of one case with chronic hepatitis B infection receiving proper prophylaxis; the rest of the patients were serologically negative for hepatitis B, hepatitis C and human immunodeficiency viruses. When evaluating the patients' performance status via the ECOG scale, the majority (62.2%) scored 1, indicating minor restrictions in physically strenuous activity. Few patients fell into the more severe categories of 3 and 4, with only 4.4% scoring 3 and none scoring 4. Tonsillar involvement was more frequent on a unilateral basis (60%) as opposed to bilateral (40%). Laboratory investigations unveiled a mean hemoglobin level of 12.6 g/dL, mean white blood cell count of 8239/$mm^3$, and lymphocyte count of 2041/$mm^3$. Inflammatory markers were elevated with a mean sedimentation rate of 42 mm/h and C-reactive protein level of 6.8 mg/L. The albumin level averaged at 41 g/L while lactate dehydrogenase (LDH) averaged at 219 U/L, with 37.8% of the patients having an increased LDH level. Hyperuricemia was observed in a minor (13.3%) of the cohort.

Diagnosis predominantly relied on excisional biopsy (60%), with histopathological evaluation revealing DLBCL as the most common subtype. Immunohistochemical analyses highlighted high expression rates for Bcl-6 (83.3%), followed by Bcl-2 (58.3%) and c-Myc (44.4%). The proliferative index, denoted by Ki-67, had a median value of 90%. Initial staging showed a remarkable 97.8% of patients with cervical lymphadenopathy. One patient did not give consent for bone marrow biopsy. Of 44 patients, bone marrow involvement was present in 20% of cases, while the distribution across Ann-Arbor stages demonstrated a larger concentration in stage II (48.9%). The cumulative percentage for stages III and IV was 51.1%, indicating a significant portion with advanced disease. The mean revised international prognostic index (R-IPI) score was 2.7, segregating 46.7% of patients into the good risk category and 53.3% into the poor risk category.

The patients received multiple treatment lines and regimens, predominantly initiating with R-CHOP as the first-line treatment, utilized by 73.3% of the cohort (Table-2). Other first-line treatments, though considerably less common, included R-CVP, R-CHOP/DHAP, etc. Three patients died of treatment related causes before initial response evaluation. So, the initial response to treatment, evaluated in 42 patients, was encouraging with a 71.4% complete response rate. However, 9.5% experienced progressive disease, and 16.7% achieved a partial response. As the treatment journey progressed to overall treatment response, assessed in 38 patients, the complete response rate slightly increased to 81.6%, with a notable objective response rate of 89.5%. At this juncture, a small subset of 6.7% underwent autologous stem cell transplant with BEAM conditioning.

Survival analysis shed light on the long-term outcomes, revealing a mean time to progression of 13 months and a median progression-free survival (PFS) of 10 months (Figure-2). The mean follow-up time stretched to 35 months. Overall mortality was observed in 35.4% of the cohort, with disease-related mortality accounting for 75% of these cases. The median overall survival (OS) was 55.8 months, with a 2-year survival rate of 77.3% and a 5-year survival rate of 49.9%. The PFS was 10.0 months. Pertaining to PFS, a powerful contrast was evident between different age demographics. The cohort aged below 60 manifested a median PFS of 8.9 months (p=0.887), while those aged above 60 exhibited a notably higher PFS of 10.3 months. Similarly, a difference was noted in relation to Ann Arbor staging, with stages 1 and 2 recording a median PFS of 6.1 months (p=0.024), while stages 3 and 4 revealed a PFS of 10.4 months. Additionally, when evaluating based on lymphoma subtype, DLBCL patients showed a PFS of 6.1 months (p=0.042) as opposed to their non-DLBCL counterparts who experienced a higher PFS of 10.4 months. There was no difference in PFS for DLBCL germinal center type and activated B-cell type (p=0.646). Double expression status also played a pivotal role, with a PFS of 10 months (p=0.025) observed in its absence, while its presence was associated with a markedly diminished PFS of 3.3 months. Furthermore, the absence of an objective response yielded a PFS of 10.3 months (p=0.286), whereas those exhibiting an objective response manifested a PFS of 10.4 months. There was no difference in PFS between the patients with and without lymphopenia at the time of diagnosis and the patients who had undergone surgery or not (p=0.867 and p=0.342, respectively).

**Table-1.** Characteristics of the patients

| Feature | | | Result |
|---|---|---|---|
| Number of patients (N) | | | 45 |
| Characteristics at the time of diagnosis | | | |
| Age (years) (mean±SD [min-max]) | | | 62±14 (18-94) |
| Age over 60 years old (n[%]) | | | 26 (57.8) |
| Sex (M:F) | | | 28:17 |
| Symptoms (n[%]) | | | |
| Dysphonia | | | 27 (60.0) |
| Dysphagia | | | 23 (51.1) |
| Dyspnea | | | 18 (40.0) |
| B symptoms | | | 23 (51.1) |
| Comorbidities (n[%]) | | | |
| Hypertension | | | 27 (60.0) |
| Diabetes mellitus | | | 14 (31.1) |
| Coronary artery disease | | | 8 (17.8) |
| Hyperlipidemia | | | 7 (15.6) |
| Benign prostate hyperplasia | | | 4 (8.9) |
| Congestive heart failure | | | 3 (6.7) |
| Others | | | 11 (24.4) |
| ECOG (n[%]) | | | |
| 0 | | | 4 (8.9) |
| 1 | | | 28 (62.2) |
| 2 | | | 11 (24.4) |
| 3 | | | 2 (4.4) |
| 4 | | | 0 (0.0) |
| ECOG 3-4 (n[%]) | | | 2 (4.4) |
| Tonsillar involvement (n[%]) | | | |
| Unilateral | | | 27 (60.0) |
| Bilateral | | | 18 (40.0) |
| Laboratory results (mean±SD [min-max]) | | | |
| Hemoglobin (g/dL) | | | 12.6±1.8 (8.0-16.2) |
| White blood cells (/mm$^3$) | | | 8239±2713 (2430-18370) |
| Lymphocytes (/mm$^3$) | | | 2041±1044 (770-5770) |
| Sedimentation (mm/h) | | | 42±20 (5-108) |
| C-reactive protein (mg/L) | | | 6.8±6,7 (0.1-28.0) |
| Albumin (g/L) | | | 41±4 (30-49) |
| Lactate dehydrogenase (LDH) (U/L) | | | 219±68 (108-428) |
| Increased LDH (n[%]) | | | 17 (37.8) |
| Hyperuricemia (n[%]) | | | 6 (13.3) |
| Characteristics of the histopathological diagnosis | | | |
| Diagnostic procedure (n[%]) | | | |
| Punch biopsy | | | 5 (11.1) |
| Incisional biospy | | | 13 (28.9) |
| Excisional biopsy | | | 27 (60.0) |
| Histopathological diagnosis (n[%]) | | | |
| DLBCL | DLBCL, GC | | 20 (44.4) |
| | DLBCL, ABC | | 12 (26.7) |
| MCL | MCL | | 5 (11.1) |
| | MCL, PV | | 1 (2.2) |
| PTCL, NOS | | | 2 (4.4) |
| ATCL | | | 2 (4.4) |
| ALCL, ALK(-) | | | 1 (2.2) |
| FL, Grade 2 | | | 1 (2.2) |
| PEL, HHV8 (+) | | | 1 (2.2) |
| Immunohistochemical analyses (n[%]) (DLBCL only) | | | |
| c-Myc (n=32) | | | 1 (46.9) |
| Bcl-2 (n=32) | | | 19 (59.4) |
| Bcl-6 (n=32) | | | 28 (87.5) |
| Double expressors (n=32) | | | |
| Ki-67 (%) (median [25th-75th percentiles]) (all cases, n=45) | | | 90,0 (60.0-95.0) |
| Characteristics of initial staging | | | |
| Presence of cervical LAP (n[%]) | | | 44 (97.8) |
| Bone marrow involvement (n[%]) (n=44) | | | 9 (20.0) |
| Ann- Arbor stages (n[%]) | | | |
| I | | | 0 (0.0) |
| II | | | 22 (48.9) |
| III | | | 12 (26.7) |
| IV | | | 11 (24.4) |
| Ann-Arbor stages III and IV (n[%]) | | | 23 (51.1) |
| R-IPI risk groups (n[%]) | | | |
| Very good | | | 0 (0,0) |
| Good | | | 21 (46.7) |
| Poor | | | 24 (53.3) |

ABC: Activated B-cell type; ABLC: Anaplastic large cell lyphoma; ALK: Anaplastic lymphoma kinase; ATCL: Angioimmunoblastic T-cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; Double expressors: c-Myc and Bcl-2 and/or Bcl-6 positivitiy; ECOG: Eastern cooperative oncology group; FL: Follicular lyphoma; GCB: Germinal center B-cell type; HHV-8: Human herpes virus-8; LAP: Lymphadenopathy; MCL: Mantle cell lymphoma; PEL: Primary effusion lymphoma; PTCL-NOS: Peripheral T-cell lymphoma, not otherwise specified; PV: Pleomorphic variant; R-IPI: The revised international prognostic index; SD: Standart deviation

**Table-2.** Characteristics of treatment lines

| Feature | Result |
|---|---|
| Number of patients (N) | 45 |
| First line treatment (n[%]) | |
| R-CHOP | 33 (73.3) |
| R-CVP | 4 (8.9) |
| R-CHOP/DHAP | 2 (4.4) |
| Mini R-CHOP | 1 (2.2) |
| CHOP | 1 (2.2) |
| CHOEP | 1 (2.2) |
| R-BENDA | 1 (2.2) |
| BREN-CHOP | 1 (2.2) |
| BREN-CHOEP | 1 (2.2) |
| Count of cycles | 6 |
| (median [25th-75th percentiles]) | (4-6) |
| Initial treatment response (n[%]) (n=42) | |
| Progressive disease | 4 (9.5) |
| Stable disease | 1 (2.4) |
| Partial response | 7 (16.7) |
| Complete response | 30 (71.4) |
| Overall treatment response (n[%]) (n=38) | |
| Progressive disease | 4 (10.5) |
| Stable disease | 0 (0.0) |
| Partial response | 3 (7.9) |
| Complete response | 31 (81.6) |
| Objective response rate (n[%]) | 34 (89.5) |
| Autologous SCT (n[%]) | 3 (6.7) |
| BEAM+ASCT | 3 (6.7) |
| Second-line treatment (n[%]) (n=14) | |
| Ibrutinib | 4 (28.5) |
| GEMOX-ICE | 3 (21.4) |
| Bortezomib-Dexamethasone | 2 (14.2) |
| Brentuximab | 1 (7.1) |
| Brentuximab-ICE | 1 (7.1) |
| ESHAP | 1 (7.1) |
| R-Benda-Ibrutinib | 1 (7.1) |
| R-Lenalidomide | 1 (7.1) |
| Treatment response (n[%]) (n=14) | |
| Progressive disease | 6 (42.9) |
| Stable disease | 2 (14.3) |
| Partial response | 3 (21.4) |
| Complete response | 3 (21.4) |
| Objective response rate (n[%]) (n=14) | 6 (42.8) |
| Survival analyses | |
| Primary progressive disease (n[%]) (n=42) | 14 (33.3) |
| Time to progression (months) (mean±SD [min-max]) | 13±11 (3-45) |
| Progression free survival (months) (median) | 10.0 |
| Median follow-up time (months) (min-max) | 32.2 (1-148) |
| Overall mortality (n[%]) | 16 (35.4) |
| Disease related mortality (n[%]) (n=16) | 12 (75.0) |
| Overall survival (months) (median) | 55.8 |
| 2-year survival rate (%) | 77.3 |
| 5-year survival rate (%) | 49.9 |

ASCT: Allogeneic stem cell transplantation; BENDA: Bendamustine; CHOEP: CHOP plus etoposide; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; DHAP: Dexamethasone, cytarabine, cisplatin; ESHAP: Etoposide, methylprednisolone, high-dose cytarabine, cisplatin; GEMOX: Gemcitabine and oxaliplatin; ICE: Ifosfamide, carboplatin, and etoposide; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-CVP: Rituximab, cyclophosphamide, vincristine, prednisone; RVD: Lenalidomide, bortezomib, dexamethasone

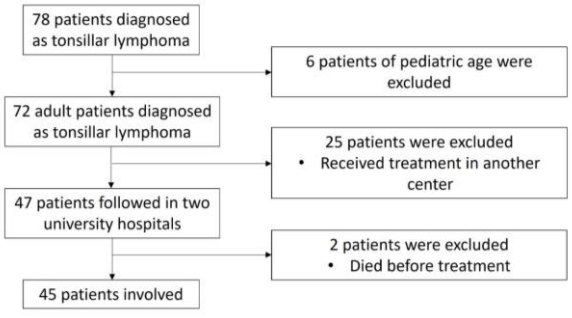
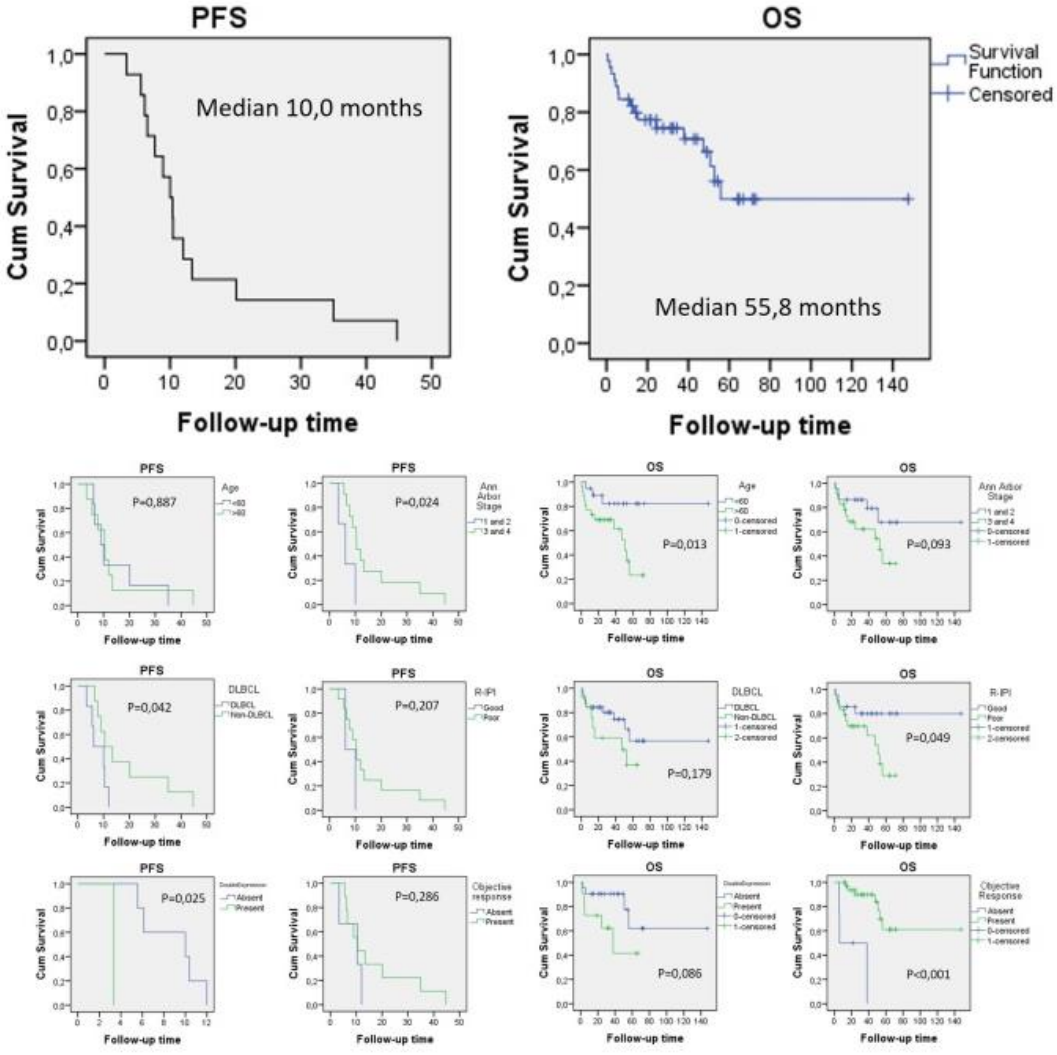



**Figure-1.** Flowchart for involved patients

Transitioning to OS, the younger age group (<60 years old) did not reach the median OS, albeit with a significant p-value (p=0.013), whilst those above 60 encountered a median OS of 50.6 months. Divergence was observed within Ann Arbor staging, with stages 1 and 2 not meeting the median OS (p=0.093) compared to the 52.8 months observed in stages 3 and 4. Distinctions were further pronounced upon lymphoma subtype exploration, where DLBCL presented an unmet median OS (p=0.179), contrasting with non-DLBCL that manifested an OS of 47.3 months. There was no difference in OS for DLBCL germinal center type and activated B-cell

type (p=0.553). Moreover, absence and presence of double expression corresponded to a median OS (p=0.087) and an OS of 37.8 months respectively. The role of objective response was again underscored, with those not achieving an objective response displaying a dramatically reduced OS of 5.9 months (p<0.001), compared to the unmet OS in their responding counterparts. There was no difference in OS between the patients with and without lymphopenia at the time of diagnosis the patients who had undergone surgery or not (p=0.322 and 0.093, respectively). In Cox regression analysis, none of these variables were found to be as an independent factor for PFS and OS.




| | | PFS (months, median) | p | OS (months, median) | p |
|---|---|---|---|---|---|
| Age | <60 years | 8,9 | 0,887 | nm | **0,013** |
| | ≥60 years | 10,3 | | 50,6 | |
| Ann Arbor Stage | Stage 1 and 2 | 6,1 | **0,024** | nm | 0,093 |
| | Stage 3 and 4 | 10,4 | | 52,8 | |
| R-IPI | Good | 6,1 | 0,207 | nm | **0,049** |
| | Poor | 10,3 | | 50,6 | |
| Histology | DLBCL | 6,1 | **0,042** | nm | 0,179 |
| | Non-DLBCL | 10,4 | | 47,3 | |
| Double expression | Absent | 10 | **0,025** | nm | 0,087 |
| | Present | 3,3 | | 37,8 | |
| Objective Response | Absent | 10,3 | 0,286 | 5,9 | **<0,001** |
| | Present | 10,4 | | nm | |

DLBCL: Diffuse large B cell lymphoma; nm: not met OS: overall survival; PFS: progression-free survival; R-IPI: The Revised International Prognostic Index

**Figure-2.** Survival analyses

## DISCUSSION

The study involved a cohort of 45 patients, with a distinct contrast between DLBCL and Non-DLBCL subgroups in terms of survival outcomes. While the OS median remained unreached for the DLBCL subgroup, indicating potentially longer survival, their PFS median was curtailed to 6.1 months. Conversely, the Non-DLBCL subgroup demonstrated a more extended median OS of 47.3 months and a median PFS of 10.4 months. Interestingly, the presence or absence of an objective response (OR) manifested a significant disparity in OS but not in PFS, with nearly identical medians of 10.4 and 10.3 months respectively. The amalgamated data revealed an overall median OS of 55.8 months and a median PFS of 10.0 months, underscoring the diverse disease characteristics and survival outcomes among these subgroups.

Primary extranodal NHL cases in the head and neck region exhibit a wide range of age and gender distribution. According to the literature, tonsillar NHL generally occurs in individuals middle-aged and above (8-11, 17-21). In comparison, our findings resonated with the established narrative to a substantial extent with the mean age at the time of diagnosis was 62. Moreover, a significant 57.8% of the cohort were aged over 60 years, further aligning with the conventional age demographic tied to this disease entity. The gender dynamics, however, unveiled a male predominance with a male to female ratio of 1.6:1. The reasons behind this gender disparity could be manifold, potentially rooted in genetic, hormonal, or environmental factors that may render males more susceptible to tonsillar NHL, or perhaps a reflection of underlying gender-based differences in immune system functionality.

The majority of patients with tonsillar NHL present with symptoms related to the primary site of involvement. The most common complaints are sore throat, dysphagia, and neck mass (14-16). However, systemic symptoms such as night sweats, fatigue, weight loss, and fever, termed as B symptoms, are less common in these patients. In one study, B symptoms were found in 27 out of 129 patients (9). In another study, B symptoms were observed in 12 out of 38 patients; symptoms such as dysphagia and hoarseness were detected in 28 patients (18). It can be said that the rate of B symptoms in this population is approximately 15% (11, 20). Our study delineated a considerably higher prevalence of B symptoms, accounting for 51.1% of the cohort. Additionally, the frequency of dysphagia, closely mirrored the literature at 51.1%, while dysphonia, not hoarseness as previously documented, was present in 60% of the patients.

The distribution of pathological subtypes of tonsillar NHLs shows similar characteristics in various studies. Without a doubt, the most common subtype is diffuse large B-cell lymphoma (8, 22). In the study conducted by Lee et al. using national data, approximately 60% of diseases affecting the Waldeyer's ring were located in the tonsils (11). Among all cases, B-cell origin NHL (281 patients, 85.6%) was dominant over T-cell origin NHL. Diffuse large B-cell lymphoma (DLBCL; 241/281 patients, 85.8%) was the most common subtype of B-cell lymphoma. Peripheral T-cell lymphoma (14 patients, 4.3%) and NK/T-cell lymphoma (14 patients, 4.3%) were the most common subtypes of T-cell origin NHL. Other subtypes included extranodal marginal zone B-cell lymphoma (11 patients, 3.4%), mantle cell lymphoma (nine patients, 2.7%), and follicular lymphoma (four patients, 1.2%). In this study, other NHL subtypes, excluding DLBCL, had a lower prevalence compared to other studies. In the study by Yan et al., 100 patients with primary extranodal NHL in the head and neck region were examined (9). Among these patients, 76 cases of B-cell lymphoma were identified: sixty cases of diffuse large B-cell lymphoma, six cases of mucosa-associated lymphoid tissue lymphoma, three cases of follicular lymphoma, three cases of Burkitt lymphoma, one case of B small lymphocytic lymphoma/chronic lymphocytic leukemia, two cases of B-lymphoblastic lymphoma, and one case of mantle cell lymphoma. DLBCL was determined as the most common subtype. Twenty-four of the cases were identified as T-cell lymphoma. Among them, twenty-one cases were extranodal NK/T-cell lymphoma, nasal type, two cases were peripheral T-cell lymphoma, and one case was anaplastic large cell lymphoma with ALK positivity. In the study by Solomides et al., among 71 lymphomas, the dominant immunologic phenotype was of B-cell origin (92%); the dominant histologic type was diffuse large B-cell lymphoma (68%). Follicular lymphomas were observed at a low frequency (4-5%). Low-grade MALT lymphomas constituted 11% of the cases in this study (10).

Our analysis unveiled DLBCL as the most prevalent subtype, harmonizing with the established narrative. However, the prevalence of other NHL subtypes, aside from DLBCL, was lower in our cohort compared to other studies. This deviation might be reflective of demographic, geographic, or methodological disparities across studies, or potentially indicative of evolving epidemiological trends.

There are various studies on prognostic factors in NHL originating from the oropharynx and Waldeyer's ring. In general, elderly patients, patients with B symptoms, tumors originating from the soft palate, and T-cell lymphomas have been significantly associated with decreased survival (8). The five-year disease-specific survival is better in MALToma and chronic lymphocytic leukemia subtypes. In multivariate analyses conducted in different studies, similarly, male gender, T-cell NHL, being 62 years and older, bone marrow involvement, and not achieving a complete response after the initial treatment have all been reported as significant poor prognostic factors for OS (9-11).

There are several data on the survival of tonsillar lymphoma. Two series with long term results were reported from Saudi Arabia and Iran followed-up at late 90's to early 2000's. Ezzat et al reported the data of 130 adult patients with localized Non-Hodgkin's Lymphoma of Waldeyer's Ring focused on identifying clinical features, management approaches, and prognosis over a median follow-up period of 49 months (20). The patient outcomes demonstrated a notable variation: 58% were alive and disease-free, 4% were alive but with disease evidence, and the remaining 38% had passed away. Although the median OS was not determined, the estimated 5-year OS was 58%. Importantly, no significant OS difference was observed between stage I and II patients. The Cox proportional hazards model pinpointed primary tonsillar site and a low-risk group, as categorized by the modified International Prognostic Index, to be correlated with a favorable OS. Similarly, favorable event-free survival was associated with a primary tonsillar site and a low-risk group as per the modified IPI. In a distinct study documenting a 10-year experience with tonsillar lymphoma, the researchers obtained complete follow-up data (21). Remarkably, until the time of documenting the study, all but one patient was alive, with the exception having succumbed to radiation-induced chondrosarcoma 90 months post-initial treatment. The follow-up durations for the subjects varied between 18 to 141 months, presenting a median of 60 and an average of 60.4 months. A noteworthy outcome was that the overall cause-specific survival rate at 5 years stood at an impressive 100%, and the median OS for the 19 patients was recorded at 60 months, with a 95% confidence interval of 18–141 months. It should be noted that these results were achieved before the era of current treatment regimens involving rituximab. One recent study from Korea, Lee et al reported a nationwide data of 328 patients with NHL originating from Waldeyer's ring (WR-NHL) (11). In the study, discernable variations were observed in OS based on factors like stage and the IPI. The treatment approaches were varied: 227 patients (69.2%) underwent chemotherapy alone, 63 patients (19.2%) received chemotherapy plus radiotherapy, 16 patients (4.9%) had radiotherapy alone, 17 patients (5.2%) were part of the surgical resection group, and 5 patients (1.5%) received supportive care. The median follow-up duration was 24.2 months, with a range from 0.2 to 106.1 months. Interestingly, the surgical resection group exhibited a marginally better disease-free survival (DFS) when compared to the chemotherapy alone group (2-year DFS rate: 100% vs. 84.6% ± 4.8%; p = 0.097) and chemotherapy plus radiotherapy group (2-year DFS rate: 100% vs. 92.1% ± 3.8%; p = 0.088). In terms of OS, the surgical resection group also displayed enhanced results compared to both the chemotherapy alone group (2-year OS rate: 100% vs. 83.1% ± 4.2%; p = 0.036) and the chemotherapy plus radiotherapy group (2-year OS rate: 100% vs. 82.9% ± 5.0%; p = 0.025). This variety in treatment outcomes provides crucial insights into the potential survival impacts of different therapeutic strategies in managing WR-NHL.

Focusing on the PFS outcomes in our study, a few unexpected trends emerge when we explore different patient factors. Interestingly, patients who are above 60 years old and those who are diagnosed at a later stage (using the Ann Arbor stages 3 and 4) show better PFS, with 10.3 and 10.4 months respectively, compared to younger and early-stage patients. Usually, we might expect PFS to decrease with age and advanced disease stage, so these surprising results ask for a closer look into other variables, like different treatments or other health conditions, that might be playing a role. Moreover, when we consider

lymphoma types and gene expression, patients with non-DLBCL and without double gene expression appear to have better PFS, posing a scientific puzzle that requires a deeper exploration into the roles of molecular and genetic factors in patient outcomes.

Moving to the OS data, some clear patterns and important differences can be observed among various patient groups. A remarkable difference appears in the age groups, where the younger patients (below 60 years old) have not reached median OS with a significant p-value (p=0.013), while the older group (above 60) shows a median OS of 50.6 months. This substantial difference between these age groups prompts questions about other factors, such as variations in treatment approaches or disease severity, that might be influencing these outcomes. This difference becomes even more noticeable when considering treatment response, with those showing an objective response not reaching median OS, while those without an objective response having an OS of just 5.9 months. This emphasizes the critical role of effective treatment in enhancing survival. Additionally, better OS in non-DLBCL patients and those without double expression highlights a need to further investigate how genetic factors and lymphoma subtypes might influence survival outcomes, suggesting a complicated network of biological, clinical, and treatment-related variables.

The limitations of the present study are manifold and include the retrospective design which inherently carries a risk of selection bias and might overlook potential confounding variables. The study was conducted in two university hospitals, which may not be representative of the broader population, potentially limiting the generalizability of our findings. The sample size of 45 patients is relatively small from the statistical point of view which may affect the power and consequently the validity of the associations observed. Also, the data lack by the means of radiological findings. Moreover, the variation in the treatment regimens and the lack of a standardized protocol could potentially introduce treatment bias. The reliance on medical records for data collection also poses a limitation as there could be inconsistencies or omissions in the documentation. Another limitation was the lack of fluorescent in-situ hybridization for gene rearrangements, we only had immunohistochemical expression profiles. Despite these limitations, the present study sheds light on the clinical features and outcomes of patients diagnosed with tonsillar lymphoma, which can serve as a foundation for future prospective studies.

## CONCLUSION

This study has been conducted on a large patient group and provides detailed case information in comparison with the literature. The findings are consistent with both national and international studies in the literature and significantly expand the current national knowledge pool. The survival analysis underscored a dichotomy in outcomes between DLBCL and Non-DLBCL cohorts. The tangible impact of an objective response on OS, albeit not on progression-free survival, was also delineated. Despite the limitations inherent to its retrospective design and relatively small cohort, this study augments the existing knowledge base, paving the way for prospective, multicentric trials to further dissect the intricacies of tonsillar lymphoma, ultimately propelling towards enhanced patient-centric management strategies.

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The initial draft is authored by the researchers themselves. Subsequently, the English manuscript undergoes refinement and polishing by OpenAI, adhering to native language standards. After using the tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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