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## Research Article

# Primary Testicular Non-Hodgkin Lymphoma: A Retrospective Single Centre Experience of 26 Cases with Long Follow Up

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### ABSTRACT

**Introduction:** Primary testicular lymphoma is a rare and aggressive malignancy representing 1% to 2% of all non-Hodgkin lymphomas (NHL) and accounts for approximately 5% of all testicular tumors. The aim of this study was to analyse clinical characteristics, therapy and survival outcomes of patients with primary testicular lymphoma diagnosed at our hospital from 1998 to 2017, and to compare differences in survival based on Ann Arbor Stages.

**Methods:** A retrospective patient chart review was done to analyse the patient clinical characteristics, therapy and survival outcomes. Survival was calculated using Kaplan-Meier survival analysis.

**Results:** Twenty-six patients were included; the mean age was  $85 \pm 6.7$  years. All patients presented with testicular tumor. Of the 26 patients, 17 patients were stage I, one stage III, and 8 stage IV. Orchiectomy was performed in all patients. 8 patients received no further treatment. Of the remaining 18 patients, overall, 18 received systemic chemotherapy and 5 radiation therapy. Six patients received intrathecal chemotherapy prophylaxis. Seventeen patients achieved complete remission. Four patients achieved partial remission; one patient had no response. Eleven patients died. Median survival was 144 months and was statistically significantly different between early versus advanced stage (stage I/II: 144 months; stage III-IV: 73 months,  $p=0.006$ ).

**Conclusion:** Primary testicular lymphomas are a rare and aggressive malignancy of extranodal lymphomas. Survival was different in early stages I/II versus advanced stages III- IV. Randomized, multi-center prospective studies could help to establish better prognostic and multi-modal therapy strategies.

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## Introduction

Primary testicular lymphoma (PTL) is a rare and aggressive form of extranodal lymphoma, which accounts for 1% to 2% of all non-Hodgkin lymphomas and approximately 5% of all testicular tumors. It is predominantly a disease of the elderly and is the most common testicular tumor in men over the age of 60 [1-3]. Approximately 80-98% of primary testicular lymphomas are diffuse large B-cell [4, 5]. Moreover, there is a small number of cases of primary testicular lymphoma, and prospective trials are sparse [4]. Treatment modalities are as follows orchiectomy, various protocols of chemotherapy and/or radiation therapy, and/or intrathecal chemotherapy [2, 3, 6-14]. Primary testicular lymphomas show propensity towards systemic dissemination and can

relapse years after complete response to therapy. Extranodal and central nervous system relapse is common [14-16]. Primary testicular lymphoma requires chemotherapy containing anthracycline. The most used protocol is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) at 21-day intervals. Prophylaxis with contralateral scrotal radiation and intrathecal chemotherapy is recommended because contralateral testis and central nervous system (CNS) are the most common relapse regions.

Few studies of primary testicular lymphoma (PTL) were reported, particularly in our country [17]. We retrospectively reviewed the clinical data of 26 patients and analysed the clinical features and overall survival of PTL at our hospital.

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**Methods**

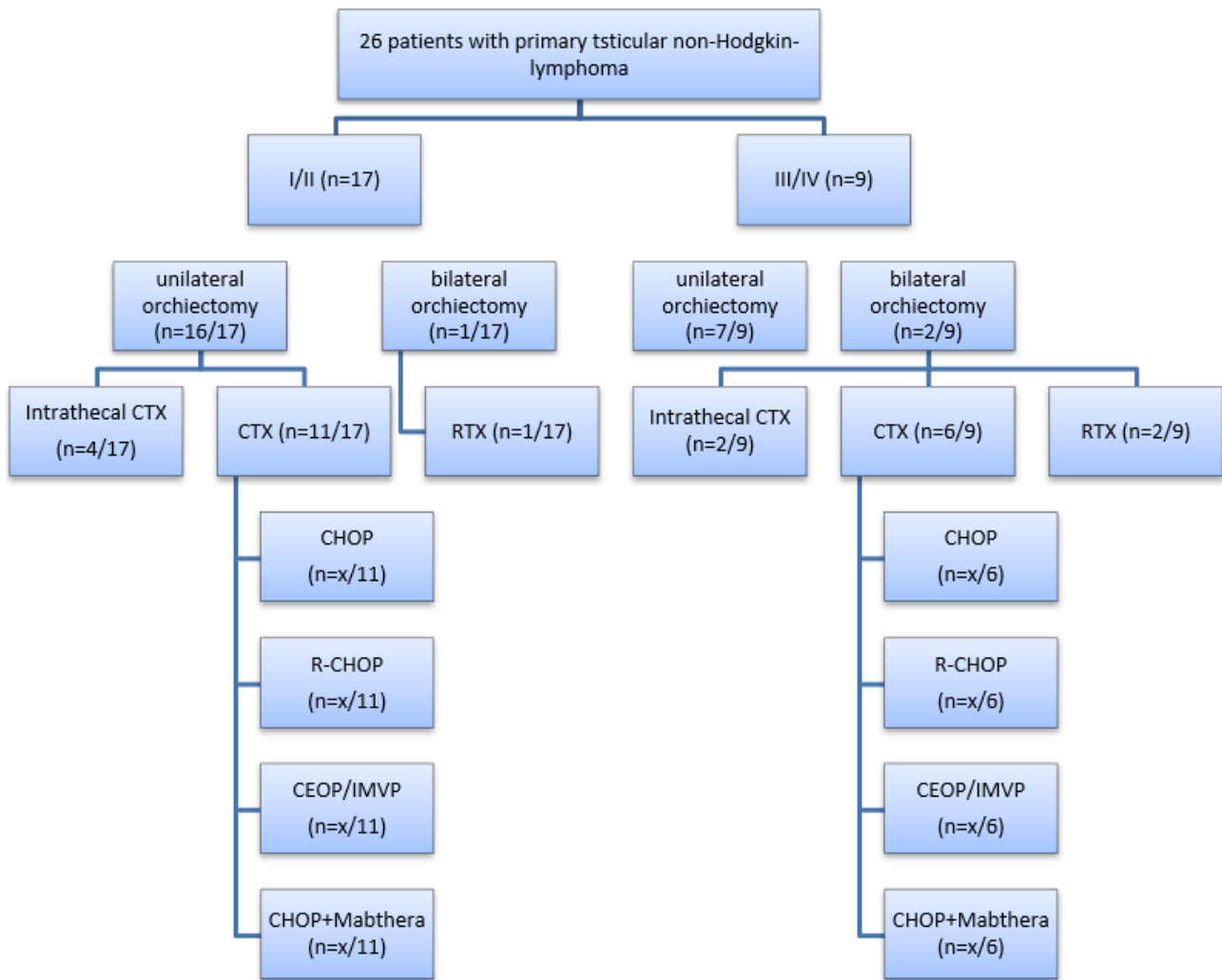
After getting the approval from our hospital research ethics committee, we included 26 patients with testicular lymphoma diagnosed at our hospital into this retrospective analysis. Cases diagnosed between 5.01.1998 and 31.5 2017 were identified. Demographic information, clinical characteristics, investigations, stage of disease, treatment and outcome including response rate, relapse site, relapse treatment and overall survival were recorded. Progression free survival was measured from the time of diagnosis to that of disease progression. The Kaplan-Meier method was used to calculate progression free survival (PFS) and overall survival (OS). The Log-rank test was used to compare survival between groups. Values of p below 0.05 were considered to indicate statistical significance. The software SPSS version 17 (IBM Inc., Chicago, IL, USA) was used for analysis.

Staging was done according to the Ann Arbor Staging system [18]. Survival was assessed according to Kaplan-Meier method. We defined complete remission (CR) as absence of disease for a minimum of 1 month following treatment. Partial remission (PR) was defined as >50%

reduction in disease burden or progression of disease with treatment. Overall survival (OS) and progression free survival (PFS) were calculated from the date of diagnosis to death and progression or date of last follow-up.

**Results**

Between January 1998 and May 2017, 26 patients were included. These patients had no prior diagnosis of hematologic malignancy. The mean age at diagnosis was  $85 \pm 6.7$ , with a median of 89 years (range 71 to 91). Table 1 shows patients of the study and their clinical characteristics, (Figure 1) shows a flow chart of patients and their outcomes. The most common presenting symptom was unilateral testicular/scrotal swelling or mass. Staging was done with thoracic, abdominal and pelvic computed tomography scan in all patients, bone marrow biopsy in 3 patients. Seventeen patients had stage I disease, 1 had stage III disease, and 8 had stage IV disease. The lactate dehydrogenase (LDH) level was elevated in 11 patients, and normal in 15 patients, LDH mean level was  $317.2 \pm 558$  (IU/L), with a median of 200.



**Figure 1:** Flow chart of patients and their characteristics and outcomes.

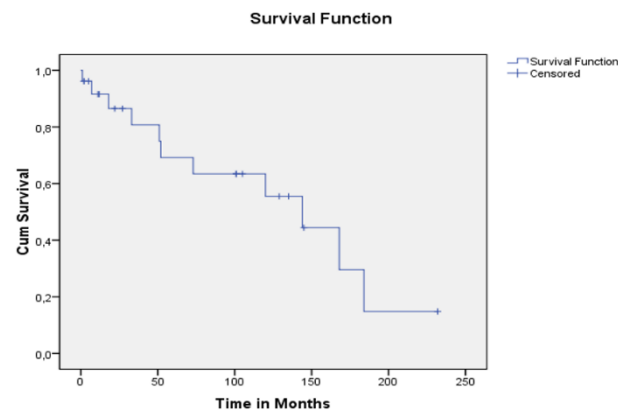
According to the World Health Organization (WHO) classification system, one was mantle cell lymphoma, 23 pathologies were B-cell lymphomas: 16 of the 23 cases were diffuse large B-cell lymphoma (DLBCL), 1 of which was anaplastic. The remaining case was lymphoblastic lymphoma. Site of initial failure was in 21 cases unilateral

testis, in 3 cases bilateral testis, and in 2 cases cerebral. Ultrasound findings were consistent with either focal or diffusely decreased echogenicity within the testicle. Doppler ultrasound showed diffuse increased flow within the mass. Most of the affected testicles were enlarged.

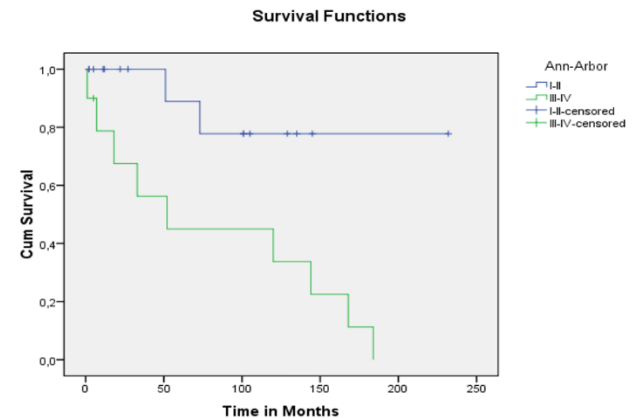
**Table 1:** Shows age, lactate dehydrogenase (LDH), duration of follow-up and death outcome according to Ann Arbor stage.

	Ann Arbor stage	N	mean
Age	III / IV	9	87.3
	I / II	17	83.5
Duration of follow up In months	III / IV	9	59.2
	I / II	17	72
Lactate dehydrogenase (LDH)	III / IV	9	490.6
	I / II	17	208.8
Death outcome according to Ann Arbor stage	yes (n=)		no (n=)
	III / IV	8	1
Progression free survival	I / II	3	14
	III / IV	5	4
Partial response	I / II	11	6
	III / IV	0	9
No response	I / II	5	12
	III / IV	9	0
	I / II	1	16

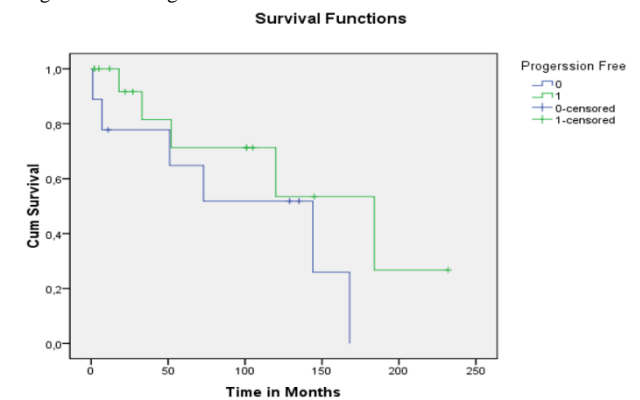
All patients underwent orchiectomy, which was bilateral in 3 cases. 8 had orchiectomy alone. 12 patients received orchiectomy and systemic chemotherapy. One patient had orchiectomy and radiation. Four patients had orchiectomy, chemotherapy and radiation. Overall, 18 patients received chemotherapy (69.2%). Five received CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), six received RCHOP (rituximab plus CHOP). Prophylaxis with intrathecal methotrexate was given in 6 cases. Radiation was given to 5 patients overall (30 Gy, fractioned in 2 Gy, 5 times /weekly for every patient). Seventeen patients (65.3%) had complete remission. Four patients (15.3%) achieved partial remission. Patients with relapse following CR showed relapse involving the CNS (n = 2), abdominal/retroperitoneal lymph nodes (n = 4) and lungs (n = 2). Out of the 26 patients, 11 died and 15 lived until the end of follow up. The median survival for all patients was 144 months (p<0.001) (Figure 2).



**Figure 2:** Kaplan-Meier estimate of overall survival in all patients.



**Figure 3:** Kaplan-Meier estimates of overall survival by Ann-Arbor stages I-II and stages III-IV.



**Figure 4:** Kaplan-Meier estimates of progression free survival by Ann-Arbor stages I-II and stages III-IV.

By stage, for all patients included in the study, the median survival was 144 months (range 52 to 184 months) for stage I/II (n = 17) and 73 months for stage III/ IV (n =9) (Figure 3). Log-rank test showed a statistically significant survival difference between patients grouped by Ann Arbor Stage I/II versus III/IV for overall survival (p = 0.006). Relapse or disease progression was seen in 8 patients, partial remission was reached in 6 patients, and in 1 case no response was seen. In 17 patients, progression free disease was reached (median 101 months, Figure 4).

## Discussion

Our study confirmed that advanced Ann-Arbor stages (III/IV) are markers of poor prognosis for primary testicular lymphoma in our country. Patients in our study had higher age at presentation, longer follow up time (19 years, 233 months), and a longer median overall survival, in comparison to other Austrian studies and other studies Abbadi *et al.* [17, 19]. Primary testicular mantle cell lymphoma is a rare event in our study, which is in line with Kemmerling *et al.* [17]. Survival analysis using age-adjusted Kaplan-Meier method showed no significant difference, which is in agreement with Kemmerling *et al.* [17].

Primary testicular lymphoma is a rare disease, which accounts for approximately 1-2% of all NHL and about 5% of testicular tumors and is primarily a disease of the elderly; this is in agreement with our results. The median age in our study was 89 years (range 71 to 91 years), which is comparable to other reports. [7, 11, 12, 14]. In our study, most patients presented with testicular swelling, which is the most common presenting symptom for testicular lymphoma. Over half of patients had stage I disease, 1 had stage III disease and 8 had stage IV disease. Primary testicular lymphoma has a poor prognosis compared to other NHL and extranodal lymphomas [8, 15]. A prolonged course of chemotherapy may be required, compared to other extranodal lymphomas stage and pathologic grading are the most important predictive factors for outcome [20, 21].

The first diagnostic and therapeutic procedure performed in testicular lymphoma cases is orchiectomy, which was performed in all cases in our study [11]. Further optimal treatment is unclear because of the rarity of this disease, and because there are very few prospective studies and no randomized studies [2, 8]. Testicular lymphoma is a disease of the elderly, which may affect the choices of further therapies, such as multi-agent systemic chemotherapy. In this study, 8 patients did not receive chemotherapy because they were either unfit or declined further treatment due in part to their health status and poor prognosis. Treatment following orchiectomy included multi-agent chemotherapy in 18 patients (5 CHOP, 4 RCHOP, 2 CHOP MABTHERA, 2 [cyclophosphamide, epirubicin, vincristine, and prednisolone/ifosfamide, etoposide (VP-16), methotrexate (CEOP/IMVP)]. Five patients received radiation; six patients received CNS prophylaxis with intrathecal chemotherapy. Because of the differences between early and advanced stages of testicular lymphoma, a complete lymphoma workup should be performed, including bone marrow biopsy and computer tomography (CT) scan of the abdomen and pelvis. Treatment regimens vary widely, since many studies on testicular lymphoma were performed retrospectively, including our study [4, 9, 15]. Connors *et al.* advocates a phased-management approach for

testicular lymphoma with all patients receiving multi-agent chemotherapy (doxorubicin, cyclophosphamide, vincristine and a corticosteroid) [22]. According to Connors, patients with early-stage disease I/II should receive brief chemotherapy with field radiation including the contralateral testis; those with B symptoms (Fever >38°C, Drenching sweats, especially at night, unintentional weight loss of >10% of normal body weight over a period of 6 months or less), bulky nodal disease (>10 cm), or stage III/IV should receive more extensive chemotherapy with radiotherapy (RT), and stage III/IV should also receive intrathecal chemotherapy.

A more recent study advocates a more extensive course of chemotherapy in early-stage disease, which may not be feasible in an elderly patient. The treatment regimen advocated by Connors addresses 2 characteristics of this disease: the propensity to relapse in the opposite testicle and in the CNS. The risk of testicular relapse without prophylactic contralateral radiation is at least 25%; this risk is essentially eliminated with radiation treatment [3, 15, 16]. Most cases of testicular lymphoma are diffuse large B-cell, which are CD20+ [21]. The chimeric monoclonal anti-CD20 antibody, rituximab, showed to give improvement in progression free and overall survival in cases of DLBCL [2, 6, 7]. It is not known if the addition of rituximab would improve survival in cases of DLBCL of the testis [23]. In the present study, the median survival for all patients was 144 months. Log-rank test showed a significant difference in survival between early-stage (I/II) versus advanced stage IV disease (p = 0.006). Median survival in stage I/II cases was 144 months versus 73 months in stage III/IV. Limitations of our study are the retrospective nature of the study, the single center experience, and the small number of patients.

## Conclusion

Primary testicular lymphoma is an uncommon malignancy. Inguinal orchiectomy, anthracycline-based chemotherapy, intrathecal chemotherapy prophylaxis, and scrotal radiotherapy are the recommended treatment. The relatively favourable outcome could be explained by the high number of patients with early-stage of the disease. Early-stage disease tends to give a better survival compared to advanced stage. Because of the rarity of PTL and the lack of prospective trials, we recommend prospective multi-center studies with large number of cases.

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