

# Primary testicular lymphoma

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## Summary

Primary testicular lymphoma (PTL) is a rare disease accounting for 1% of non-Hodgkin's lymphoma. PTL occurs more frequently in older patients and is a potentially fatal disease. In the early stages (I and II), the treatment consists of orchidectomy followed by chemotherapy (CT) and prophylactic scrotal radiotherapy (RT) with/or without iliac and/or paraaortic lymph node RT. In the advanced stages (III and IV), CT is the treatment of choice whereas the place of scrotal RT is controverted. In both early and advanced disease intrathecal CT is warranted to prevent CNS relapse. New molecular approaches and/or more aggressive treatments are being explored.

**Key words:** testis; lymphoma; treatment; radiotherapy

## Introduction

Primary extranodal lymphoma of the testis is a potentially fatal disease second only to primary brain lymphoma, median survival being between 12 and 24 months. It accounts for approximately 1% of non-Hodgkin's lymphoma, 4% of all extranodal non-Hodgkin's lymphoma and 5% of all testicular malignancies with an estimated incidence of 0.26/100 000 per year [1–4]. Primary testicular lymphoma (PTL) is essentially an intermediate or high-grade lymphoma, and the diffuse large-cell type is the most common [5]. In secondary involvement of the testis other aggressive histologies are prevalent: in particular, Burkitt's and Burkitt's-like types have been reported in 10–20% of cases, chiefly in HIV+ patients. T-cell or follicular lymphomas involving the testes have been described in rare cases [6–9]. In contrast to other testicular malignancies, PTL occurs mainly in patients aged over 50 [10]. After adequate locoregional and systemic treatment the central nervous system (CNS) remains the most frequent site of recurrence (up to 30%). Prophylactic intrathecal (IT) chemotherapy (CT)

combined with systemic treatment has therefore been introduced to improve outcome [11].

## Methods

A systematic review of randomised and retrospective trials on patients with primary testicular lymphoma was conducted. Eligible studies investigated data concerning pathology, staging, prognosis, and finally treatment options for different stages of PTL.

## Pathology, staging and prognosis

As in all situations with any suspected tumour in the testes, the primary option remains surgery, i.e., inguinal orchidectomy for diagnosis and treatment. Orchidectomy is important because it removes the tumour located in the so-called "sanctuary site" with good local control, and provides important information on grade and pathology subtype [12]. Histologically, 80–90% of primary testicular lymphomas are diffuse large-cell type with B-cell immunophenotype [13]. Complete initial staging workup is the same as for all other non-Hodgkin's lymphomas. Cerebrospinal fluid (CSF) examination for malignant cells is recommended in view of the high incidence of CNS relapse. Recently PET or PET-CT has been widely used in initial lymphoma staging, but few data are available on primary testicular lymphoma [14]. The majority of patients with PTL present stage I or II disease (Ann-Arbor staging) [15]. PTL, like other aggressive extranodal non-Hodgkin's lymphomas, shows a tendency to spread and relapse at several extranodal sites including the CNS, the contralateral testis, Waldeyer's ring, skin, pleura, lung or soft tissues [16]. The prognosis of PTL is poor even in the early stages, despite the combination of orchidectomy followed by anthracycline-based chemotherapy, radiation therapy, and CNS prophylaxis. The majority of patients fail within the first two years following treatment, mainly in the CNS [17, 18].

## Treatment options

Given the rarity of PTL, its treatment has not been standardised. No prospective trial has so far been published. Available data are reported by some single institutions and/or by international collaborative groups active in rare diseases [19, 20]. The management of PTL depends on stage, either at initial diagnosis or after relapse, following adequate initial treatment.

### Treatment of early stage I–II

The universally accepted treatment modality for stage I and II aggressive nodal lymphoma is either chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisone; CHOP) combined with rituximab, or chemotherapy (CT) followed by radiation therapy (RT) [21, 22]. However, an optimal treatment approach has not been defined for extranodal lymphomas. Nor have randomised studies been performed to evaluate the superiority of combined modality treatment to RT or CT alone, especially in testicular lymphoma where there is an increased incidence of relapse (50–80%) following orchidectomy and RT without chemotherapy [23, 24]. Table 1 summarises the available data from prospective and retrospective studies. Regarding these results and the patterns of failure, the use of systemic CT combined with prophylactic intrathecal CT has become an important part of the management of early disease. Connors et al. [25], in their study including 15 patients with stage IE and IIE testicular lymphoma, administered (following orchidectomy) a doxorubicin-based CT with testicular RT, and observed 93% actuarial relapse-free survival. However, in a retrospective study by Fonseca et al. [16] including 62 patients, no beneficial effect of combined treatment compared to single modality was observed. In their study only 10 patients, including 3 with stage I disease, received combined modality treatment. Moreover, only 4 patients received intrathecal CT and 2 of these already had leptomeningeal involvement at diagnosis. Hence it is difficult to draw a conclusion regarding the inefficacy of combined treatment. Zouhair et al. evaluated the outcome of a series of 36 patients in a multicentre *Rare Cancer Network* study [19]. The majority of patients (80%) received CHOP-CT combined with intrathecal-CT in 17 (47%). Testicular RT was delivered to the scrotum alone in 12 patients, or also to the iliac and para-aortic lymph nodes in 8. No relapse was observed in the irradiated volumes. The majority of relapses (12 out of 14) were observed at extranodal sites. Eight patients (22%) had CNS relapse. The 5-year overall lymphoma-specific and disease-free survival rates were 47%, 66%, and 43% respectively. In a series of 34 patients with localised disease registered in the *British National Lymphoma Investigation*, Crellin et al. [17] found that CHOP-CT was insufficient to prevent CNS relapse. In a Danish trial 24 out of 39 early stage patients managed by orchidectomy and doxorubicin-based CT had a relapse rate of 15.4%, while for patients not treated with adjuvant CT the relapse rate was 63.6% [13]. The median relapse-free (28 vs 14 months) and overall (43 vs 17% at 2 and 5 years) survival favoured adjuvant CT. Data from MD Anderson Cancer Center have shown that despite doxorubicin-based adjuvant CT in 22 patients, CNS and/or contralateral testes were involved in all relapsing patients. These patients did not receive prophylactic intrathecal chemotherapy [15]. Tondini et al. [11] reported the treatment in 16 out of 29 patients with localised disease with the same CT regimen as in the MD Anderson study, but supplemented with prophylactic RT to regional lymph nodes in 85% of patients. After a median follow-up of seven years one-third of patients are alive. In a retrospective study from several French cancer centres, patients were divided into three groups (orchidectomy alone, orchidectomy + RT, and orchidectomy +

RT + CT) without CNS prophylaxis [18]. Thirty-two out of 84 patients relapsed, chiefly in the CNS. There was no significant difference in terms of overall, disease-specific or disease-free survival between the three groups. Zucca et al. [20] reported a large retrospective international survey in 373 patients with PTL mainly at stage I–II. The median age at diagnosis was 66 years. Anthracycline-based CT was administered to 68% of patients, and prophylactic intrathecal CT was given to 18%. Prophylactic scrotal RT was administered in 36% of the patients. Median overall survival was 4.8 years, and median progression-free survival 4 years. The survival curves showed no clear evidence of a substantial proportion of cured patients. Combination of CT with an anthracycline-based regimen improved the outcome, particularly if six cycles or more were given. Prophylactic scrotal RT was a statistical factor for higher overall survival in multivariate analysis. Delivering at least 30 Gy locoregional RT also resulted in significantly longer overall survival. Darby et al., from the UK, reported the outcome of 30 early stage PTL patients [26]. Eleven (37%) had orchidectomy alone, 12 (40%) orchidectomy + adjuvant CT, and 4 patients orchidectomy + CT + RT. Complete remission was observed in 84%. Twelve patients (40%) relapsed after a median follow-up of 73 months, the majority of relapses occurring in the lymph nodes (58%). One relapse in CNS; one in bone, one in skin, and two in the contralateral testis were observed. The authors suggested that a combined modality approach is more effective (orchidectomy + CT + RT). A prospective trial conducted by the *Groupe Ouest Est d'Etude des Leucémies Aiguës et Maladies du Sang* (GOELAMS) of 494 patients in stage I–IIE primary non-Hodgkin's lymphoma analysed the outcome in a subgroup of 16 patients with PTL [27]. All patients completed three cycles of anthracycline-based CT followed by regional RT on inguinal, iliac, and paraaortic lymph nodes. Prophylactic intrathecal CT was given in all patients. Relapses occurred in extranodal sites in four patients, in abdominal lymph nodes in one, in CNS in one, and in the contralateral testis in another. After a median follow-up of 73.5 months the probability of disease-free and overall survival was 70% and 65% respectively. They concluded that their good results were attributable to the use of regional RT and CNS prophylaxis.

In conclusion, patients with stage IE primary testicular lymphoma should be managed with anthracycline-based chemotherapy and scrotal RT. Furthermore, some authors propose extending radiation fields to encompass paraortic and/or pelvic lymph nodes in Stage IIE patients [28]. CNS prophylaxis with intrathecal CT is warranted to prevent the high incidence of CNS relapse.

### Treatment of advanced stages III–IV

The treatment of choice for advanced disease in PTL is standard anthracycline-based chemotherapy plus rituximab. Despite a higher rate of relapse in the contralateral testis (up to 50% of patients), prophylactic scrotal irradiation is recommended by some authors [15], while others propose RT only for symptomatic patients or in the case of bulky disease [6]. Prophylactic intrathecal CT to prevent CNS relapse, which occurs in approximately 50% of patients, is also considered in patients achieving complete

<b>Table 1</b> Literature review of treatment in intermediate- or high-grade NHL.					
<b>First author</b>	<b>Study design</b>	<b>Population</b>	<b>Overall survival</b>	<b>Event-free survival</b>	<b>Comment</b>
Miller et al. (1995) [21]	Prospective randomised trial Arm 1: CHT alone (8xCHOP) (n = 201) Arm 2: CHT (3xCHOP) + RT (n = 200)	Intermediate- or high-grade NHL Stages I, E, II, IIE	5-year Arm 1: 72% Arm 2: 82% (p <0.02)	5-year* Arm 1: 64% Arm 2: 77% (p <0.03)	CHOP+RT better than CHOP alone
Reyes et al. (2005) [22]	Prospective randomised trial Arm 1: CHT (3xCHOP) + RT (n = 321) Arm 2: CHT alone (3xACVBP) (n = 309)	Stage I or II aggressive lymphoma (diffuse large B-cell)	5-year Arm 1: 81% Arm 2: 90% (p <0.001)	5-year Arm 1: 74% Arm 2: 82% (p <0.001)	ACVBP better than CHOP+RT
Connors et al. (1988) [25]	Retrospective trial (n = 29) Arm 1: Orchidectomy + RT Arm 2: Orchidectomy + CHT + RT	Stage I or II testicular lymphoma	4-year Arm 1: 50% Arm 2: 93% (p <0.02)		Orchidectomy + CHT RT is superior to orchidectomy + RT alone
Fonseca et al. (1999) [16]	Retrospective trial (n = 62) Orchidectomy: 79% OP alone: 10% IF-RT: 37% CHT: 37% Intrathecal CHT: 6% Prophylactic RT of the contralateral testis: 8%	Primary testicular Lymphoma Ann Arbor Stages I-IV	Whole group: 2.7 years Stage I: 3.3 years Stages II-IV: 1.8 years (p <0.33) CHT alone: 1.7 years CHT + RT or RT alone 5.3 years (p <0.033)	Whole group: 2.7 years	Relapse after CR: 80% Median time to recurrence: 0.8 years No difference among stages After doxorubicin-containing CHT All patients: 72% Stage I: 71% CNS: 32% Contralateral testis: 13% After RT: 0%
Zouhair et al. (2002) [19]	Retrospective trial (n = 36) Orchidectomy: 100% CHT + IF-RT: 56% CHT (CHOP): 80% CHT + Intrathecal CHT: 47%	Primary testicular Lymphoma Ann Arbor Stages I-IV	5-years whole group: 47%	5-years whole group: 43%	Relapse in the whole group: 39% CNS: 22% After IT-CHT: 11% (p = NS) After RT: No testicular, iliac or para-aortic relapse
Crellin et al. (1993) [17]	Retrospective trial (n = 34)	Primary testicular lymphoma Stages I-IV	5 years: Stages I/II: 39% Stages III/IV: 9 month	5 years: Stages I/II: 33%	CNS relapse: 21% Bilateral testicular involvement: 18%
Moller et al. (1994) [13]	Retrospective trial (n = 39)	Primary testicular lymphoma Stages I-IV	All stages 2 years: 43% 5 years: 17%		Relapse in stages I/II After orchidectomy & CHT: 15.4% Median-relapse free survival: 28 months After orchidectomy +/- RT 63.6% (p <0.05) Median relapse-free survival: 14 months
Lagrange et al. (2001) [18]	Retrospective trial (n = 84) Treatment: orchidectomy and RT and/or CHT	Primary testicular lymphoma Stages I-IV	All patients: 32 months Stage I: 52 months No difference between orchidectomy + CHT or orchidectomy ± RT Stage II: 32 months Stage III-IV: 12 months (P <0.0001)		Relapse: 38% CNS relapse: most frequent
Zucca et al. (2003) [20]	Retrospective trial (n = 373) Anthracycline-based CHT: 68% Prophylactic IT-CHT: 18% Prophylactic scrotal RT: 36%	Primary testicular lymphoma chiefly Stages I-II	Median OAS: 4.8 years	Median PFS: 4 years	Median follow-up: 7.6 years Relapse rate in all patients: 52% CNS relapse: 15% continuous risk of recurrence in the contralateral testis -> patients not receiving scrotal RT
Darby et al. (2005) [26]	Retrospective trial (n = 30) Orchidectomy alone: 37% Orchidectomy + RT: 13% Orchidectomy + CHT: 40% Orchidectomy + CHT + RT: 10%	Primary testicular Lymphoma chiefly Stages I-II			Relapse after CR: 40% Median time of relapse 9 months CNS: 1; Bone: 2; Skin: 1 Contralateral testis: 2 Lymph nodes: 58%

Linassier et al. (2002) [27]	Retrospective trial (n = 16) Treatment strategy: 3 cycles anthracycline-based CHT Regional RT on inguinal, iliac, and para-aortic lymph nodes CNS-prophylaxis by IT-CHT & RT	Stage I/II aggressive primary testicular involvement	6 year: 65%	6 year: 70%	Relapse in abdominal lymph nodes: 4 CNS relapse: 1 Contralateral testis: 1
CHOP = cyclophosphamide, doxorubicin, vincristine, prednisone ACVBP = doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone CHT = chemotherapy, RT = radiotherapy, IT = intrathecal therapy, NHL = non-Hodgkin lymphoma * Event-free survival					

remission [13, 29]. The International Extra-nodal Lymphoma Study Group is currently evaluating CNS prophylaxis with intrathecal liposomal cytarabine and systemic intermediate-dose methotrexate in a prospective trial. Many authors reported that intrathecal CT did not appear to alter the CNS relapse pattern [15, 16, 19]. A median survival of less than six months is reported, confirming the dismal outcome of this entity. High-dose CT supported by autologous or allogeneic stem-cell rescue remains an investigational option.

#### Treatment of relapse or refractory disease

Treatment of relapse or refractory disease after initial treatment is unknown [6]. No prospective trial results are available in the literature. The decision to treat depends on many factors (age, performance status, previous treatment, etc). PTL is predominantly a disease of older men with multiple co-morbidities and short life expectancy. Rituximab alone or palliative supportive care should be given in these situations [30]. However, young patients can be managed by more aggressive approaches.

#### Perspectives

The combination of cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), has been the standard chemotherapy regimen for aggressive lymphoma for more than 30 years [31, 32]. The French group (*Groupe de l'Etude des Lymphomes de l'Adulte*; GELA) added the monoclonal anti-CD20 antibody rituximab to eight cycles of CHOP (CHOP-21) [33]. The German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL) shortened intervals between six cycles of treatment with CHOP from 3 to 2 weeks (CHOP-14) [34]. Both approaches have been shown to improve the outcome of elderly patients without relevant additional toxicity. In 2008, Pfreundschuh et al. published data from the RECOVER-60 trial showing that adding rituximab to the dose-dense CHOP-14 regimen showed a significant improvement in event-free, progression-free, and overall survival in elderly patients [35]. To confirm these findings, further investigation in primary testicular lymphoma using the dose-dense six cycles R-CHOP-14 approach is warranted.

#### Conclusion

Given the lack of randomised data in this rare disease, treatment options are based only on data available from retrospective studies, few of which, however, include large numbers of patients. The prognosis remains very poor despite combined CT and RT following orchidectomy. The

current diagnostic and therapeutic algorithms used in our department are presented in table 2. Treatment of relapses at extranodal sites, contralateral testis, and/or CNS needs to be further investigated using new molecular approaches and/or more aggressive management.

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<b>Table 2</b> <b>Diagnostic and therapeutic algorithms in patients with primary testicular lymphoma (PTL).</b>	
Clinical features	Median age: 6th decade Unilateral painless scrotal swelling, sometimes with sharp scrotal pain B-symptoms (advanced stage)
Pathological diagnosis	Orchidectomy
Staging	Physical examination Complete haematological and biochemical exams Total-body computerised tomography Bone marrow aspiration and biopsy Brain magnetic resonance imaging Cerebrospinal fluid examination Screening ultrasound of the contralateral testis PET-CT (few data available for PTL)
Limited disease – Stages I and II	Orchidectomy Systemic chemotherapy: – R-CHOP (cyclophosphamide, doxorubicin, vincristin, prednisone and rituximab) CNS prophylaxis (high dose IT methotrexate) Radiotherapy: – Stage I: Scrotal 25–30 Gy – Stage II: Scrotal, para-aortic lymph nodes, and bilateral pelvic lymph nodes After CR: 30–35 Gy After PR: 35–45 Gy
Advanced disease – Stages III and IV	Systemic chemotherapy: – R-CHOP Prophylactic scrotal RT CNS prophylaxis (high dose IT methotrexate)