Long-term outcome of primary endocrine non-Hodgkin lymphomas: does the site make the difference?

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Summary

Aim: Primary lymphomas of endocrine glands are extremely rare. Our study adds more data to the few published series regarding the incidence, clinical characteristics, management and overall survival (OS) by comparing the various diffuse large B-cell endocrine lymphomas. Moreover, it contributes to a better understanding of these neoplasms and provides concepts for future research.

Methods: We retrospectively evaluated the clinical profile and the patterns of outcome among patients who were treated in our center with the diagnosis of aggressive, B-cell, primary endocrine lymphoma.

Results: Between May 1980 and December 2011, 450 patients were diagnosed as primary extranodal non-Hodgkin lymphomas. Among them, 18 cases (4%) were primary testicular lymphoma (PTL), 8 cases (2%) were primary thyroid lymphoma (PTHL) and 4 cases (1%) were primary adrenal lymphoma (PAL). The therapeutic approaches employed were variable, including mainly chemotherapy in combination with radiotherapy and surgery. The median OS for the patients with PTL and PAL was 27 and 6 months, respectively. Better outcome was observed in patients with PTHL for whom the median OS has not been reached yet, whereas the PAL group had the worst prognosis.

Conclusions: The discrepancies in the outcome among endocrine lymphomas could be partly attributed to their biologic variability, which might be determined by the initial site involved. We conclude that treatment decisions should be made according to a multi-disciplinary approach to avoid unnecessary surgery. Existing treatment strategies for PTL and PAL fail to provide long-term survival, rendering the application of novel therapeutic approaches essential.
Introduction

Primary endocrine lymphomas represent only 3% of extranodal lymphomas and usually involve the thyroid gland and the testis. They exhibit distinct natural history and outcome, which mainly depends on the initial site involved. Most endocrine lymphomas are non-Hodgkin lymphomas (NHLs) of B-cell lineage. However, T-cell endocrine lymphomas and Hodgkin’s lymphomas have rarely been reported. Patients typically present with a rapidly growing mass that causes symptoms. As they should be distinguished from other malignancies, their differential diagnosis is often problematic.

Primary testicular lymphoma (PTL), representing 5% of all tumors of the testis and 1–2% of all NHLs, has an estimated incidence of 0.3/100,000 per year. Most cases are of diffuse large B-cell histology (DLBCL). Orchiectomy is both diagnostic and therapeutic, but not curative. Indeed, PTL has been recognized as a highly lethal disease, with 5-year overall survival (OS) ranging from 16 to 50%. Relapses frequently occur in the central nervous system (CNS). Intrathecal prophylactic chemotherapy, as long as irradiation, in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-based chemotherapy have been proposed and used as treatment strategies.

The female genital tract constitutes another rare site of primary lymphomas. Interestingly, the respective female counterpart (ovary) is very uncommonly affected by lymphoma compared with testis. Primary NHL of the thyroid is more common in women under 60 years old. Primary thyroid lymphoma (PTHL) comprises 1–5% of thyroid malignancies and <2% of extranodal lymphomas. Most of the patients present with a rapidly enlarging thyroid mass, causing pressure symptoms. Treatment of PTHL depends on the histological subtype and includes chemotherapy, radiotherapy and rarely surgery.

Primary adrenal lymphoma (PAL) is an extremely rare entity, with ~120 cases reported worldwide. Patients are usually in the sixth or seventh decade of life and present with B symptoms or adrenal insufficiency in case of bilateral involvement.

Another endocrine gland affected infrequently by lymphomas is the pituitary. More than half of the cases are of DLBCL type. Clinically, the patients may appear with symptoms and signs of hypopituitarism, diabetes insipidus and mass effect. Radiological differential diagnosis from other non-functioning sellar lesions is difficult to be made.

Primary pancreatic lymphomas have also been described comprising an extremely rare anatomical location of extranodal lymphomas. So far, data obtained from case reports have shown the poor prognosis of these neoplasms, further challenging our understanding about endocrine lymphomas.

The aim of this study is to compare the clinical characteristics, the treatment results and the OS among the patients who were treated in our center over a 30-year interval with the rare diagnosis of aggressive, B-cell origin, endocrine lymphoma, including the testis, thyroid and adrenal glands.

Materials and methods

We retrospectively analyzed data of patients who were treated in our center with histologically proven NHL of the endocrine glands between May 1980 and December 2011. Only patients with lymphoma primarily involving the endocrine glands were included. Hence, patients who had a late secondary involvement of the endocrine system were excluded. Information on patients’ demographic and clinical characteristics, staging examinations, treatment parameters and outcome was obtained from their medical records. This study was conducted according to the declaration of Helsinki.

All patients were staged according to the Ann Arbor criteria, including physical examination, chest and abdomen computed tomography (CT) scan and bone marrow biopsy. The International Prognostic Index (IPI) score was calculated for all patients either retrospectively or at diagnosis based on the published criteria. Response to treatment was defined according to the criteria proposed by the International Workshop to Standardize Response Criteria for NHLs. Relapse was defined after the first treatment as the time from the achievement of any type of remission [complete response (CR), partial response (PR)] until disease progression and/or the initiation of disease-related symptoms.

Follow-up for each subgroup of patients was measured from the time of diagnosis to the time of death from any cause or the last visit. Disease-free survival (DFS) was measured from the time of CR to the time of first relapse.

Statistical analysis

Survival curves were produced, using the Kaplan–Meier method and compared using the log-rank test. P-value <0.05 was considered statistically significant. The chi-square test was used to detect statistically significant differences in categorical variables. The Cox proportional hazards model was used to compare the survival times for groups
of patients differing in terms of clinical and laboratory parameters and the log-rank test to compare survival rates between groups of patients. SPSS version 13.0 software was used.

Results

Patients

Between May 1980 and December 2011, 450 patients with primary extranodal NHL were seen in our center. Among them, 30 cases (7%) were classified as primary endocrine lymphomas. Eighteen patients (4%) had PTL, eight patients (2%) had PTHL and four patients (1%) had PAL. Their baseline laboratory features are summarized in Table 1, while the detailed demographic data are presented in Table 2.

Clinical profile

Primary testicular NHL

Eighteen males with PTL were included in the study. The diagnosis was made after surgical resection and histological examination of a testicular mass. Sixteen patients with PTL had the histology of DLBCL. The remaining two patients were diagnosed with a high-grade lymphoma of B-cell origin non-otherwise specified. In some cases, a high Ki-67 index was found (4/18).

Early stage disease (I and II) was observed in 50% of patients. Among nine patients with advanced disease (stage III and IV) at diagnosis, five presented with disseminated disease involving contiguous and other extranodal sites. In particular, simultaneous infiltration of the urinary bladder was noted in one case, while two patients presented with pleural effusion. Finally, in one case, infiltration of the adrenals co-existed, whereas another patient had concomitant involvement of the iliopsoas muscle and the adrenals. B symptoms were described in one case. Sixty-one percent of the patients were at high risk (IPI score $\geq 2$).

Primary thyroid NHL

Eight patients were diagnosed with primary NHL of the thyroid (PTHL). Six had the histology of DLBCL, whereas the remaining two was classified as a high-grade lymphoma of B-cell origin. Four patients had Hashimoto thyroiditis. Moreover, four cases were stage IV at diagnosis. Infiltration of other sites, apart from the thyroid, co-existed: the first patient had dissemination of the disease to the lung and the bones, the second to the lung and the kidneys, the third to the bones and the fourth to the spleen. Sixty-three percent of the patients were at high risk (IPI score $\geq 2$).

Primary adrenal NHL

Four patients with PAL of DLBCL subtype were studied. Two of them underwent adrenalectomy, while in the other two diagnosis was made by CT-guided biopsy. No signs and symptoms of adrenal

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Table 1  Laboratory data of the patients

<table>
<thead>
<tr>
<th></th>
<th>Testis N=18/30 (60%)</th>
<th>Thyroid N=8/30 (27%)</th>
<th>Adrenals N=4/30 (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>69 (29–78)</td>
<td>52 (24–74)</td>
<td>65 (60–76)</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: 13.5–17.5</td>
<td>12.7 (10.4–15.4)</td>
<td>13.1 (12.2–15.4)</td>
<td>11.3 (10.9–13.2)</td>
</tr>
<tr>
<td>Female: 12–16</td>
<td>6.9 (1.9–11.9)</td>
<td>7.5 (3.9–14.6)</td>
<td>7.7 (3.8–8.6)</td>
</tr>
<tr>
<td>WBCs ($\times 10^3$ per $\mu l$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR: 4–11</td>
<td>270 (180–357)</td>
<td>228 (158–393)</td>
<td>245 (229–261)</td>
</tr>
<tr>
<td>PLTs ($\times 10^3$ per mm$^3$)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR: 150–450</td>
<td>460 (235–635)</td>
<td>500 (330–925)</td>
<td>2048 (266–2339)</td>
</tr>
<tr>
<td>LDH (IU/l)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR: 150–460</td>
<td>3.9 (2.8–4.7)</td>
<td>4.0 (3.7–4.6)</td>
<td>3.2 (3.2–3.4)</td>
</tr>
<tr>
<td>Alb (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male: 3.5–5</td>
<td>2.6 (1.5–8.3)</td>
<td>2.5 (1.7–4.5)</td>
<td>NA</td>
</tr>
<tr>
<td>Female: 0.7–1.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NR: &lt;5</td>
<td>8.4 (0.9–70.1)</td>
<td>5.8 (3.2–13.4)</td>
<td>NA</td>
</tr>
</tbody>
</table>

$N$, number of patients; NA, not available data; NR, normal range; Hb, hemoglobin; WBCs, white blood cells; PLTs, platelets; Alb, albumin; $\beta_2$M, $\beta_2$-microglobulin; CRP, C-reactive protein. Values represent median (range).
insufficiency were detected. Notably, all the patients had elevated levels of lactate dehydrogenase (LDH).

**Treatment outcome**

**Response rate and relapse**

Orchiectomy was the initial standard approach for all the patients with PTL. Half of them (9/18) were treated with chemotherapy alone (five CHOP and four R-CHOP) while in the remaining nine cases, the aforementioned therapeutic strategy was enhanced with radiotherapy (Table 3). Four patients who received radiotherapy were stage II\(_A\), two patients stage I\(_A\), and the remaining three stage IV\(_A\). Twelve of the PTL patients (67%) achieved CR, 2 (11%) had PR and 3 (17%) had NR. Response data were unavailable for one patient. Five patients (28%), with stage I and IV disease (3 and 2, respectively), relapsed within a median time of 21 months (4–52) from CR.

Among the eight patients with PTHL, three underwent thyroidectomy, mostly for diagnostic purposes. Five patients were treated with chemotherapy alone (CHOP ± rituximab); two received chemotherapy (R-CHOP) in combination with radiotherapy; while in one case after thyroidectomy, radiotherapy was only applied (Table 3). The two patients who received radiotherapy were stage II\(_A\), whereas the remaining patient was stage I\(_A\). All patients with PTHL obtained CR after front-line therapy. Relapse was observed, in the only one male patient, 35 months after CR. He received salvage chemotherapy but died under treatment, because of resistant disease.

Patients with PAL were treated with chemotherapy (CHOP ± rituximab). Two of them underwent surgery. One patient achieved unconfirmed CR, two had PR and one had NR. The responders relapsed shortly after treatment in a median time of 2.5 months.

**Survival analysis**

The median follow-up for the patients with PTHL was 102 months (range 42–278) compared with 28 (range 3–176) and 7 months (range 6–8) for PTL and PAL, respectively. Our results indicate a significant difference regarding the OS among PTHL, PTL and PAL patients with the latter having inferior outcome (log-rank test = 0.002). The median OS is 27 months for PTL patients, whereas only 6 months for PAL patients. Five of the patients with PTL (28%) are still alive, while the remaining 13 have died (72%). Our results yield a significant superior OS for the patients with PTHL in comparison to those with PTL (log-rank test = 0.008) and those with PAL (log-rank test = 0.0001; Figure 1).

**Table 2** Demographic and clinical characteristics of the patients

<table>
<thead>
<tr>
<th>Testis N=18/30 (60%)</th>
<th>Thyroid N=8/30 (27%)</th>
<th>Adrenals N=4/30 (13%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (100)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Female</td>
<td>0 (0)</td>
<td>7 (88)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>4 (22)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>14 (78)</td>
<td>3 (37)</td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I and II</td>
<td>9 (50)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>III and IV</td>
<td>9 (50)</td>
<td>4 (50)</td>
</tr>
<tr>
<td>LDH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>12 (67)</td>
<td>5 (63)</td>
</tr>
<tr>
<td>Elevated</td>
<td>6 (33)</td>
<td>3 (37)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0, 1</td>
<td>14 (78)</td>
<td>7 (88)</td>
</tr>
<tr>
<td>≥2</td>
<td>4 (22)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Extranodal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>12 (67)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>6 (33)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>IPI group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk (IPI 0–1)</td>
<td>7 (39)</td>
<td>3 (37)</td>
</tr>
<tr>
<td>High risk (IPI ≥2)</td>
<td>11 (61)</td>
<td>5 (63)</td>
</tr>
</tbody>
</table>

N\(_0\), number of patients; PS, performance status. Values represent number (%).

**Table 3** Therapeutic approaches applied in patients with primary endocrine NHL

<table>
<thead>
<tr>
<th>Primary endocrine NHL</th>
<th>Surgery N (%)</th>
<th>Chemotherapy alone N</th>
<th>Chemotherapy + radiotherapy N</th>
<th>Radiotherapy alone N</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTL (18)</td>
<td>18 (100%)</td>
<td>9</td>
<td>9</td>
<td>None</td>
</tr>
<tr>
<td>PTHL (8)</td>
<td>3 (27%)</td>
<td>5</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>PAL (4)</td>
<td>2 (50%)</td>
<td>4</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

Surgery indicates orchiectomy, thyroidectomy and adrenalectomy for patients with PTL, PTHL and PAL, respectively.
In the PTHL group, the median OS has not been reached yet, as 75% (6/8) of the patients are still alive. The two deaths were attributed to septicemia during treatment and CNS relapse, respectively. The relative death risk was higher for patients with testicular lymphoma, in comparison to those with thyroid lymphoma ($P < 0.05$).

In contrast, all the PAL patients died due to their disease. One of them developed lymphoma-related hemophagocytic syndrome and another one brain metastasis, shortly after the completion of their treatment. Patients with PTL seem to have increased probability for better survival, in comparison to those with PAL (median OS 27 vs. 6 months, respectively; Figure 1). However, no significant differences were noted in the OS between PTL and PAL ($P = 0.083$). The median DFS was 12, 96.5 and 2 months for patients with PTL, PTHL and PAL, respectively. We also analyzed the impact of rituximab in OS in patients with PTL (R-CHOP vs. CHOP). However, no significant difference was noted between the patients who received it compared with those who did not ($P > 0.05$).

**Discussion**

Primary endocrine lymphomas are rare and peculiar entities, with elements differing from their nodal counterparts. As a result, limited data exist on the incidence, natural course, optimal management and treatment outcome. Despite recent advances in diagnostic procedures and novel therapeutics, endocrine lymphomas are hard to accurately diagnose and treat.

Over a 30-year interval, 7% of our cohort (among 450 cases of extranodal NHLs) was diagnosed as primary aggressive endocrine lymphomas. This overall incidence is slightly higher than the reported one from literature (7 vs. 3%),$^1$ particularly in PTLs (4 vs. 1–2%).$^2$ Minor variations also exist for the adrenals (1 vs. 3%),$^9$ while for the thyroid there is accordance (2%).$^8,18$ These discrepancies can be partly attributed to controversies in the definition of primary extranodal lymphomas, particularly in the presence of both nodal and extranodal disease.

A female predominance was noted among the patients with PTHL (7/8 patients). The majority of the patients with PTL (14/18 patients) or PAL (3/4 patients) were more than 60 years at diagnosis, whereas the patients with PTHL were younger at diagnosis (5/8 <60 years).

No significant differences were found among the patients with testicular and thyroid lymphomas, regarding disease stage, LDH, Eastern Cooperative Oncology Group (ECOG), extranodal involvement or IPI score. However, PAL patients presented with more aggressive disease, as indicated by the following: higher risk (IPI $\geq 2$), ECOG $\geq 2$ and elevated LDH.

The thyroid lymphomas have better outcome in comparison with the testicular and the adrenal ones as highlighted in the Kaplan–Meier curves. Our findings regarding the OS among the three distinct sites...
of endocrine lymphomas are in line with the published series.\textsuperscript{2,5,7–9}

Since the PTHL has a much favorable prognosis, early diagnosis and treatment is important. Fine needle aspiration cytology is the first-line diagnostic technique in any patient with a thyroid mass. However, very often, it is non-diagnostic despite raising suspicion for lymphoma. Therefore, definitive diagnosis usually requires either core or open biopsy. In this study, 38\% of our patients had either partial or total thyroidectomy, which was not necessary in all cases. The latter reflects the diversity of the referring hospitals or inadequacies in current diagnostic pathways. Interestingly, an increased proportion of women with PTHL (50\%) presented with Hashimoto thyroiditis, which has been linked with NHL and often precedes thyroid lymphoma.\textsuperscript{19}

The differential diagnosis of PTL is complex involving a spectrum of other neoplasms, such as germ cell and gonadal stromal tumors. Remarkably, testicular lymphomas are 10 times more common than the ovarian ones. There is no explanation about this. Ovaries are very uncommonly affected primarily or secondarily by lymphomas.\textsuperscript{1,6,20}

Despite the combination of surgery, immunochemotherapy and radiotherapy, the prognosis was considered dismal,\textsuperscript{4} until recently. An improved outcome (85\% 5-year OS in a series of 53 patients) has recently been reported after combined treatment with R-CHOP, intrathecal methotrexate and testicular radiotherapy, thereby changing the current landscape.\textsuperscript{5} Nevertheless, median OS for testicular lymphomas was 27 months in our series of patients. These differences may be explained by variabilities in sample size, follow-up duration, absence of prophylactic radiotherapy and lack of rituximab use or intrathecal chemotherapy, as our cohort includes patients diagnosed 20 or even 30 years ago, when recently applied strategies were not available.

Mazloom \textit{et al.} demonstrated significant improvements in 5-year OS for early and advanced stage testicular lymphomas, after the initiation of rituximab.\textsuperscript{21} However, these results did not reveal significant differences in progression-free survival hinting that the observed differences in OS may be attributed to more effective treatment modalities for relapsed disease.\textsuperscript{22} Interestingly, no improvement in disease-specific survival in patients with testicular DLBCL after the introduction of rituximab has been found.\textsuperscript{23} In line with the above, we did not observe significant differences in the OS between the PTL patients who received rituximab compared with those who did not. These discrepancies could be due to differences in biology of testicular lymphomas, insufficient numbers of studied cases or inconsistent application of additional radiotherapy.

Although PALs represent only 3\% of extranodal lymphomas, adrenal involvement appears in up to 25\% of NHLs.\textsuperscript{9} Histological examination is essential for the differential diagnosis between PALs and other conditions.\textsuperscript{24} In our cases, adrenalectomy was performed in two patients, whereas in the other two patients, biopsy under CT guidance provided the diagnosis. Surgical resection of a suspected PAL should only be chosen when the biopsy is impossible or when the histological material is insufficient for diagnosis.\textsuperscript{24,25}

The prognosis of PALs is poor. Chemotherapy alone (CHOP±R) does not seem to be effective for these highly aggressive neoplasms. Our patients had refractory disease or relapsed in short intervals after treatment and the median OS was just 8 months. Furthermore, metastasis even to distant anatomical sites, such as CNS, was observed. Interestingly, PAL with better outcome has rarely been reported. However, in these reports, the follow-up is short.\textsuperscript{9} In the view of the above, a more intensive therapeutic approach including high-dose therapy plus hematopoietic stem cell transplantation should be considered in younger patients.

It should be underlined that treatment regimens applied in our series, were heterogeneous, differing mainly in the necessity of surgery for testicular lymphomas. Surgical excisions were performed in several cases, mainly for diagnostic and not for treatment purposes. However, excision or radiotherapy was not necessary for thyroid or adrenal lymphomas. The optimal therapeutic approach for high-grade thyroid lymphoma is chemotherapy. Radiotherapy can be added as consolidation in special cases, such as testicular lymphomas based upon recent data. Surgery should be used just as a diagnostic tool, as it gives no extra treatment benefit.

To define the pathogenesis of extranodal lymphomas, it has been hypothesized that lymphoid cells migrate from the bone marrow to the sites of the formation of extranodal lymphomas, where they should not be normally encountered, initially away from the anatomical stereotype of the lymph node. They show predilection and tropism for some organs, maybe because of adhesion molecules or antigenic stimulation.\textsuperscript{26,27} In these organs, they reside and may interact with the microenvironment receiving the adequate neoplastic or antigenic stimulation, thereby forming groups of transformed neoplastic lymphoid cells.\textsuperscript{26–28} Moreover, an immune dysfunction could be one of the main predisposing factors.\textsuperscript{29}

The different anatomical sites of the human body where the testis, the thyroid and the adrenals are located, might justify the different outcomes
among the three subtypes of endocrine lymphomas. Moreover, the distinct embryological origin and the hormonal environment of the thyroid gland, the adrenals and the testis might also be responsible for the discrepancies noted regarding OS and prognosis among these sites.\textsuperscript{30–33} The testis is formed by the mesoderm,\textsuperscript{30,31} the thyroid gland by the endoderm\textsuperscript{32} and the adrenal medulla by the neural crest and the adrenal cortex by the mesoderm.\textsuperscript{33} It could be postulated, that due to the different embryogenic origin of the three germ layers, the action of diverse transcription factors, signaling pathways and endocrine signals, the degree of neoplastic stimulation varies among the three sites. Furthermore, the discrepancies in the outcome among the three types of endocrine lymphomas could be partly attributed to their distinct biologic variability, which might be determined by the initial site involved. The variable hormonal microenvironment, which supports and triggers the tumor might also be responsible. The high rate of the observed extranodal relapses and the unique predilection for sanctuary sites could be due to the expression of adhesion molecules. However, these are speculations without certain evidence.

In conclusion, early diagnosis for primary endocrine NHLs is essential and crucial, before treatment decisions are made. Surgery has neither favorable effect in prognosis nor a definitive role in the management of these lymphomas. We therefore emphasize that lymphomas represent a systematic disease, requiring effective immunochemotherapeutic approaches. As such, novel clinical trials and drugs must be tested, as the majority of the adrenal and testicular lymphomas are highly aggressive. The therapy of these patients should be made according to a multi-disciplinary approach in specialized centers.

**Authorship**

E.H. designed the trial, treated patients, analyzed data and wrote the manuscript; M.D.D. analyzed data, performed the statistical analysis and wrote the manuscript; M.P. recruited and treated patients, analyzed data and wrote the manuscript; T.D. collected and analyzed data; A.C. and K.P.-P. recruited and treated patients, collected and analyzed data; N.C. recruited and treated patients, collected and analyzed data.

**Conflict of interest:** None declared.

**References**


