Primary Breast Lymphoma: Analysis of 55 Cases of the Spanish Lymphoma Oncology Group

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Abstract

We reviewed 55 patients diagnosed with primary breast lymphoma, stages IE and IIE, in 16 Spanish institutions. Of the 55 cases, 96.4% corresponded to non-Hodgkin lymphoma. Results of 5-year progression-free and overall survival were 73% and 76%, respectively. Current treatments achieve good control of the disease, with an overall survival of 5 years in 80% of the patients.

Introduction: Primary breast lymphoma is a rare form of localized extranodal lymphoma, which affects the mammary glands unilaterally or bilaterally, and can also affect the regional lymph nodes. **Materials and Methods:** We reviewed 55 patients, with disease stages IE and IIE, diagnosed in 16 Spanish institutions between 1989 and 2016. A serial of clinical variables and treatment were collected, and overall survival (OS) and progression-free survival (PFS) were calculated. **Results:** Of the 55 patients, 96.4% were women with an average age of 69 years. A total of 53 patients corresponded to non-Hodgkin lymphoma (NHL), of whom 36.3% had lymph node involvement upon diagnosis. Of the patients, 58.2% were stage IE, and 41.8% were stage IIE. Treatments received included radiotherapy (36.3%), chemotherapy (85.5%), and rituximab (in 38 of the 45 patients with NHL treated with chemotherapy). In all, 82.2% of complete responses were achieved. OS and progression-free survival at 5 years in NHL patients was 76% and 73%, respectively. **Conclusion:** Current treatments (chemotherapy, immunotherapy, and radiotherapy) achieve good control of the disease, with an OS of 5 years in 80% of the patients, although there is no consensus in treatment, given the scarce incidence of these lymphomas.

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Introduction

Primary breast lymphoma (PBL) is a rare form of presentation of extranodal lymphoid neoplasm. It represents approximately 0.5% of all primary malignant neoplasms of the breast and between 1.7% and 2.2% of extranodal lymphomas.[1-5] It was first described in 1972 by Wiseman and Liao,[6] in a group of 31 patients diagnosed between 1951 and 1970, defining it as the infiltration of breast tissue by lymphoma with or without regional lymph node in patients without a history of prior nodal or extranodal lymphoma and systemic disease at the time of diagnosis. These criteria were reviewed in 1990 by Hugh et al.[7] More than 96% of the cases of PBL affect women, and the average age of presentation is between 60 and 70 years old, without clear clinical or demographic differences.[1-5,8-10] Clinically, it is presented as a palpable mass, unpainful, without clear radiologic differences from carcinomas, and can be associated to ipsilateral axillary lymph nodes.[1-5,10,11] Approximately 11% of the cases of PBL show bilateral involvement. More than 95% of the cases correspond to B-type non-Hodgkin lymphoma (NHL), of which 60% to 85% are diffuse large B-cell lymphoma. Much less common are the follicular lymphomas, mucosa-associated lymphoid tissue, or marginal zone lymphomas.[1-12] Isolated cases of very aggressive lymphomas, such as Burkitt lymphoma, particularly in patients with immunosuppression treatment, have been published. Moreover, T lymphomas, which include anaplastic large cell lymphoma and Hodgkin lymphoma (HL), represent a small fraction of PBL, hardly reaching 5% and 1%, respectively.[12-16] Current treatments (chemotherapy, immunotherapy, and radiotherapy) achieve good control of the disease, with an overall survival (OS) of 5 years in 80% of the patients, although there is no consensus in treatment, given the scarce incidence of these lymphomas.[1-10,17-24]

Material and Methods

From March 1989 to January 2016, a total of 55 patients with PBL were diagnosed and treated in the Medical Oncology Department of 16 Spanish hospitals, all members of GOTEL, the Spanish Lymphoma Oncology Group. Only patients with stages IE to IIE were included, and patients with bilateral affectation were considered IIE. Clinical data were analyzed according to the modified criteria of Wiseman and Liao, and the histologic classification of the World Health Organization, 2008.[1,6,7,25]

The collected data include the age at diagnosis, the affected breast, stage, type of treatment (surgery, chemotherapy, radiotherapy, and chemo-immunotherapy), type of response, pattern of relapse, relapse, OS, and progression free survival. All analyses were performed using Stata v14.1 (StataCorp, 2015, College Station, TX). Survival analysis at 3, 5, and 10 years was calculated using the non-parametric estimator of Kaplan-Meier, and the comparisons of survival with the log-rank test. A P-value $< .05$ was considered statistically significant, and an analysis was performed in order to analyze the potential clinical impact of the age, types of treatments and analysis of control of the disease, and the PFS and OS rates.

Results

A total of 55 patients were analyzed, 53 of whom were women with an average age of 69 years (range, 29-86 years). A total of 53 patients were diagnosed with NHL, and only 2 patients with HL; one of them nodular sclerosing type and the other rich in lymphocytes type (Table 1). Of the patients, 36.4% presented with lymph node involvement, 52.7% presented with right breast affectation, and 7.27% presented with bilateral affectation; 58.2% of the patients presented with stage IE and 41.8% with stage IIE. Of the whole cohort, only 2 patients presented B symptoms at diagnosis. The clinical features of patients with NHL are detailed in Table 2, of which 70% correspond to aggressive lymphomas and 30% to indolent lymphomas.

Surgery, radiation, and chemotherapy, alone or combined, have been used according to each case, and a single patient with indolent lymphoma (follicular lymphoma) remains under observation with stable disease (Table 3). A total of 21 patients (38.2%) underwent surgery, lumpectomy being the procedure most performed (60%), followed by simple mastectomy (25%), and replacement of prosthesis and/or capsulectomy in 3 cases (15%). These last 3 cases correspond to patients with a diagnosis of breast implant-associated anaplastic large cell lymphoma, of which only 1 patient received subsequent chemotherapy with a CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) scheme, with subsequent relapse and death from the disease. A total of 36.4% of patients were treated with radiotherapy alone or in combination with other treatments. Specifically, only 2 patients were treated with radiotherapy alone, both with radiologic complete response and without relapse. Of the 55 patients, 85.4% were treated with chemotherapy (45 NHL and 2 HL), and of these, 19 were treated with chemotherapy alone. Of 45 patients with NHL treated with chemotherapy, 38 of them received rituximab, and the 7 remaining cases were pre-rituximab or T lymphomas. Of these 45 patients, 77.5% received anthracyclines as part of the scheme of chemotherapy. All chemotherapy schemes used are detailed in Table 4.

In terms of response to the initial treatment, 86.7% were complete responses, 5.4% were partial responses, 3.7% were disease stabilization, and 3.7% were disease progression (2 cases, 1 corresponding to a diffuse large B-cell lymphoma and 1 to breast implant-associated anaplastic large cell lymphoma), thereby demonstrating a higher rate of complete responses in patients with aggressive lymphoma compared with indolent lymphomas.

Toward the end of the study, 10 patients had relapsed and were treated with second-line treatments, reaching full response in 50% of the cases, partial response in 10% of the cases, and progression of disease in 40% of the cases. These progressions correspond to

Table 1 Histologic Type of Lymphoma (55 Patients)

Histologic Type	N	%
DLBCL	33	60
Marginal zone/MALT	8	14.5
Follicular lymphoma	3	5.45
BIA-ALCL	3	5.45
SLL	2	3.63
ALCL CD30 +	2	3.63
B-lymphoplastic lymphoma.	2	3.63
Hodgkin lymphoma	2	3.63

Abbreviations: ALCL CD30+ = anaplastic large-cell lymphoma CD30+; BIA-ALCL = breast implant-associated anaplastic large cell lymphoma; DLBCL = diffuse large B-cell lymphoma; MALT = mucosa-associated lymphoid tissue; SLL = small lymphocytic lymphoma.

Table 2 Clinical Characteristics of the Cohort of Patients With NHL

Characteristics	Total Cases N (%)	Indolent N (%)	Aggressive N (%)
Total	53 (100)	16 (30)	37 (70)
Age			
<40 years	9 (17)	2 (12.5)	7 (18.9)
40-60 years	19 (35.8)	6 (37.5)	13 (35)
>60 years	25 (47)	8 (50)	17 (45.9)
Gender			
Female	52 (98.1)	16 (100)	36 (97.2)
Male	1 (1.88)	0 (0)	1 (2.7)
Node involvement	24 (45.28)	8 (50)	16 (43.24)
Laterality of tumor			
Right	28 (52.8)	9 (56.25)	18 (48.6)
Left	21 (39.6)	5 (31.25)	17 (46)
Bilateral	4 (7.5)	2 (12.5)	2 (5.4)
Stage			
IE	33 (62.2)	8 (50)	25 (67.5)
IIE	20 (37.7)	8 (50)	12 (32.4)
B-symptoms			
Yes	2 (3.7)	0 (0)	2 (5.4)
No	51 (96.2)	16 (100)	35 (94.6)

Abbreviation: NHL = non-Hodgkin lymphoma.

high-grade lymphomas, which were the main cause of death in all of these cases. Of note, 2 of these progressions relapsed at the central nervous system level, both with diffuse large B-cell lymphoma.

Patients with NHL had a median follow-up of 4.7 years, and 80% of them showed an OS of 3 years, 76% of 5 years, and 71% of 10 years, whereas the PFS was 78%, 73%, and 64%, respectively (Figures 1 and 2). According to the treatment received, patients with NHL treated with anthracyclines presented better OS rates than the patients who received schemes without anthracyclines (3-year OS, 81.7% vs. 61.18% and 5-year OS, 76.59% vs. 61%); no statistically significant differences were observed ($P = .23$). Similarly, PFS varied depending on whether patients received anthracyclines or not (3-year PFS, 81.7% vs. 61.1% and 5-year PFS, 76.6% vs. 61%), reaching statistical significance ($P = .05$).

Table 3 Type of Treatment Received

Treatment Type	Total N (%)	Indolent N (%)	Aggressive N (%)
Total	53 (100)	16 (30.18)	37 (69.8)
Observation	1 (1.8)	1 (6.25)	0 (0)
Surgery only	5 (9.43)	4 (25)	1 (2.7)
RT only	2 (3.77)	2 (12.5)	0 (0)
Chemotherapy only	17 (32)	4 (25)	13 (35.1)
Surgery/chemotherapy	9 (17)	2 (12.5)	7 (19)
Chemotherapy/RT	12 (22.6)	1 (6.25)	11 (29.7)
Surgery/chemotherapy/RT	6 (11.3)	1 (6.25)	5 (13.5)
Rituximab (NHL)	39 (73.6)	8 (50)	31 (83.8)

Abbreviations: NHL = non-Hodgkin lymphoma; RT = radiotherapy.

Table 4 Chemotherapy Regimens

Chemotherapy Regimens	N	%
R-CHOP	29	61.70
CHOP	5	10.63
R-CVP	4	8.51
CVP	2	4.25
Rituximab only	2	4.25
ABVD	2	4.25
R-COMP	1	2.12
R-MVP	1	2.12
M-BACOP	1	2.12

Abbreviations: ABVD = Doxorubicin, bleomicyn, vinblastine, dacarbazine; CHOP = cyclophosphamide, doxorubicin, vincristine, prednisolone; COMP = cyclophosphamide, non-pegylated liposome-encapsulated doxorubicin, vincristine and prednisone; CVP = cyclophosphamide, vincristine, prednisolone; M-BACOP = mabtera, bleomycin, epidoxorubicin, cyclophosphamide, vincristine and prednisone; MVP = mitomycin, vinblastine, and cisplatin; R = rituximab.

In the case of immunotherapy, no significant differences were observed in OS and PFS, as most of the patients were treated with rituximab. OS at 3 years was observed in 81.6% of the rituximab-treated patients versus 62.5% in non−rituximab-treated patients ($P = .98$), whereas the PFS at 3 years was 81.6% in rituximab-treated patients versus 62.5% in non−rituximab-treated patients; and the PFS at 5 years was 74.8% versus 62.5% ($P = .83$).

With regard to the stage of the disease, no significant differences were observed in OS and PFS, most likely owing to the small sample size as shown in Table 5.

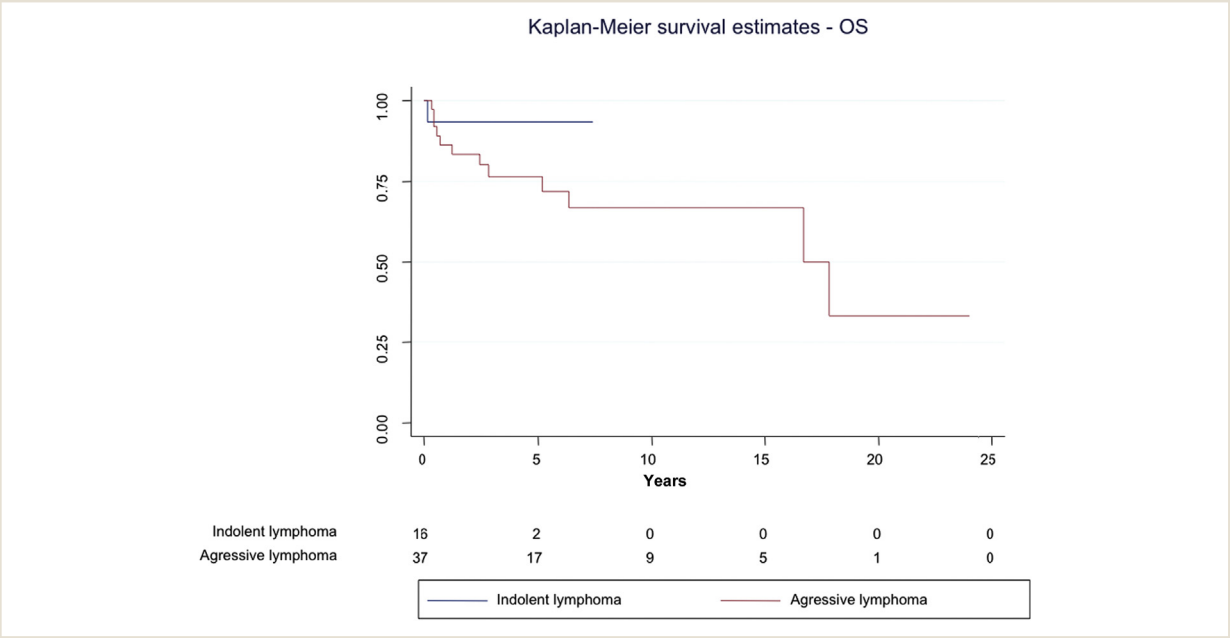
Also, no significant differences were observed in the analysis of survival according to age groups affected by the disease, with the survival at 5 years 76.5% in patients younger than 40 years old, 82.7% in patients between 40 and 60 years old, and 72.1% in patients over 60 years ($P = .81$), with a PFS of 76.5%, 82.7%, and 68.7%, respectively ($P = .54$).

The survival analysis based on the aggressiveness of the tumor shows no significant differences, with a 5-year global survival of 93% in the group of indolent lymphomas and 76.5% in the group of aggressive tumors ($P = .38$), whereas the PFS was 83.7% and 71.7%, respectively ($P = .65$).

Discussion

PBL is a rare form of extranodal lymphoma, which almost exclusively affects women.[1-10] Its low incidence makes recruitment difficult, and therefore, published studies are mostly retrospective and descriptive, both from a clinical and histologic point of view. Our series of patients brings together a total of 55 cases of PBL, strictly according to the definition of Wiseman and Liao from 1972 and reviewed in 1990 by Hugh et al,[6,7] which constitute one of the few pure studies of PBL, longer than many of the publications that exist to date, which include patients with stages IIIE and IVE disease.[1,11,15,22-24,26-28] Our results are consistent with previous publications, in which the largest number of cases correspond to large B-cell lymphoma (60%), followed by B marginal zone lymphoma (14.5%) and follicular lymphoma (5.45%),

Figure 1 Overall Survival (OS) for Indolent and Aggressive Primary Breast Lymphoma (PBL)



with a small percentage representing rare histologies, including HL, of which 2 cases were diagnosed.[1-12]

Generally, PBL is presented as a palpable mass in the breast that may or may not be accompanied by axillary lymph nodes, which makes it clinically difficult to differentiate from a breast carcinoma. Despite some studies trying to identify x ray patterns suggestive of this entity, no specific radiologic or imaging patterns characteristic of this disease have been determined.[29-34]

Thick needle biopsy is the most common technique used for reaching a histologic diagnosis of PBL. However, in many cases, the tissue available for immunohistochemical study is insufficient, so there are still a significant percentage of patients who need to undergo surgery in order to ensure the definitive diagnosis.[26,35-37]

Figure 2 Progression-Free Survival (PFS) for Indolent and Aggressive Primary Breast Lymphoma (PBL)

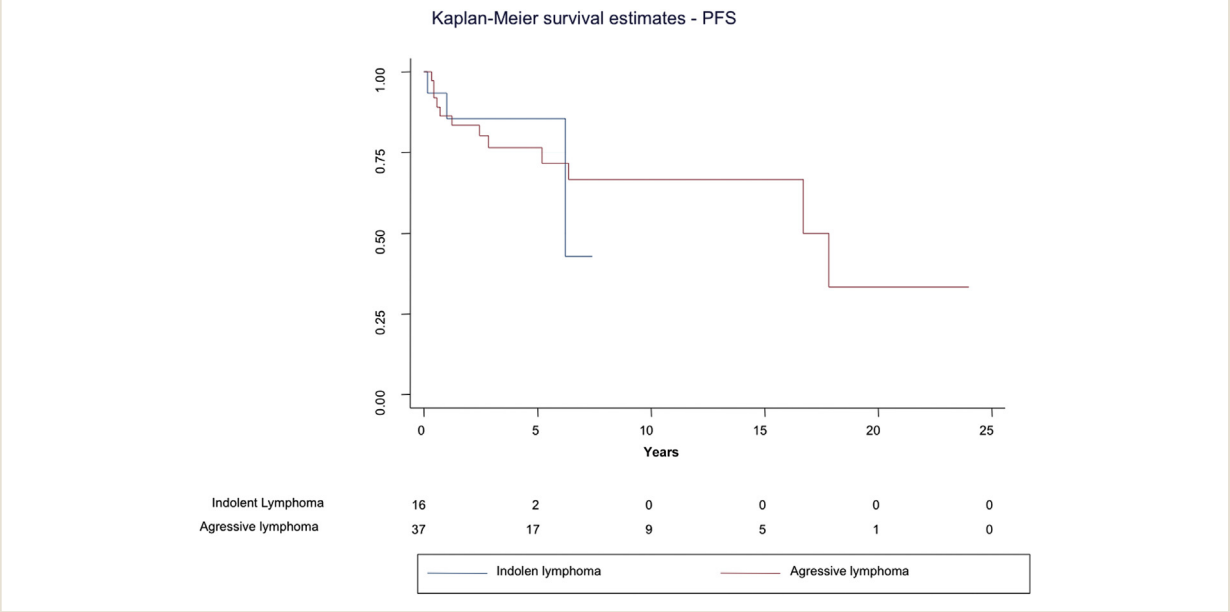


Table 5 Survival of Different Stages

	OS ($P = .39$) %			PFS ($P = .14$) %		
	3 years	5 years	10 years	3 years	5 years	10 years
Stage IE	85	78	78	80	78	78
Stage IIE	73.5	73.5	57.2	68.5	68.5	41.6

Abbreviations: OS = overall survival; PFS = progression-free survival.

Currently, there is not a well-established recommendation for treatment, given that PBL is a rare entity, and no prospective studies have been performed. Since the beginning of the 1990s, it has been well-known that surgery does not improve survival. This was confirmed by Jennings et al in a retrospective study of 465 patients, where they evaluated the role of mastectomy in PBL.[38] A particular case is the anaplastic large-cell lymphoma, which is associated with breast prostheses, in which case the surgical treatment, depending on etiology of disease, is the capsulectomy, the definitive replacement, or the removal of the prosthesis as a causal agent, offering important possibilities for the control of the disease.[39-41] As a matter of fact, this was the treatment performed in 3 patients of our series with anaplastic large-cell lymphoma associated with prosthesis. Only 2 of our patients with non-aggressive lymphomas (mucosa-associated lymphoid tissue) underwent surgery and subsequently relapsed locally with a 15- and 21-month disease-free interval, respectively. Consequently, the first case was treated with surgery and the second with radiotherapy, both with complete response.

Systemic treatment with chemotherapy remains the basis of management of PBL, with the schemes generally used being R-CHOP or similar, where the use of anthracyclines and rituximab have demonstrated to have a beneficial effect on PFS and OS.[1-5,9,10,15] The retrospective series of cases published so far include patients from both the rituximab and the pre-rituximab era, and demonstrate the main role of immunotherapy in these patients.[1-5,9,10,17,23,24] This approach was not possible in our series, as only 8% of our patients were treated in the pre-rituximab era; therefore, a comparison between the 2 groups was not possible. The same occurs with anthracyclines, as most patients received this treatment.

Moreover, radiotherapy still plays an important role in the treatment of patients with resected disease, and specially in patients with non-aggressive tumors.[1-5,9,10,21,22] Of note, in our series, 2 patients were treated exclusively with radiotherapy, 1 B marginal zone lymphoma and 1 small lymphocytic lymphoma, reaching full radiologic response and with no evidence of relapse during the follow-up, and thus demonstrating the effectiveness of this therapy. In our series, 3 of the 10 relapses were indolent lymphomas that had only been treated with radiation, reaching complete response. Therefore, we consider that it is likely, in selected cases of indolent lymphomas, that radiotherapy alone can be considered an effective treatment with significant rates of complete response.[1-5,9,10,19,21,22,42]

Overall, the published series report 5-year survival rates of 80% and 5-year PFS of 77%.[11,21,22,24,26-28] In our cohort, the 5-year OS was 76%, and the 5-year PFS was 73%, with no statistically significant differences observed in the analysis by subgroups of treatment and histology, as well as by age groups. However, there is a trend toward improvement of survival rates for patients who have received anthracyclines and rituximab, but the reduced sample size disabled obtaining statistical differences in our results.

Despite these results, the analysis of similar studies support the use of combined chemotherapy, if possible, with anthracyclines associated with rituximab, in the management of aggressive lymphomas, with subsequent assessment of consolidation of radiotherapy treatment. Several retrospective studies show rates of relapse in the central nervous system (CNS) of 5% to 15%. Aviv et al analyzed the published series, and the overall rate of CNS relapse was 8%. CNS prophylaxis is controversial and should only be considered in high-risk patients, namely patients with stage IIE, tumors > 5 cm, and aggressive histology.[1-5,8-11,15,42-46] Exclusive radiotherapy treatment can be recommended in patients with indolent histology and without bulky disease and has demonstrated a significant impact on both OS and PFS rates. On the other hand, surgery has been demonstrated to have no impact on PFS or OS,[20,38,43,47] and therefore, its use should be relegated to patients where biopsies are negative or not conclusive.

With regard to the small percentage of patients with HL PBL, they must follow the recommended ABVD (doxorubicin, bleomicyn, vinblastine, dacarbazine) scheme and assess the consolidation radiotherapy treatment, according to stages I or II, and whether or not they reached complete remission after chemotherapy. Two of our patients with HL (1 nodular sclerosing type and the other rich in lymphocytes) were treated with ABVD with complete response and were relapse-free after 2 years of follow-up.

Conclusion

The diffuse large B-cell lymphoma, in our series, remains the most frequent histologic subtype of PBL. Although there is a lack of a standard treatment of PBL, our results suggest that the optimal treatment may be chemotherapy combined with adjuvant radiotherapy. Some indolent lymphomas could be treated with exclusive radiotherapy, reaching an adequate control of the disease, low morbidity, and with a significant impact on survival rates.

Clinical Practice Points

- PBL is a rare form of presentation of extranodal lymphoid neoplasm.
- The management of primary breast NHL is generally determined by the histologic subtype and extent of disease.
- Systemic treatment with chemotherapy remains the basis of management of PBL; however, radiotherapy treatment still plays an important role in the management of patients with resected disease, and even in patients with nonaggressive tumors.
- Indolent lymphomas can be treated with exclusive radiotherapy, reaching an adequate control of the disease.

Disclosure

The authors have stated that they have no conflicts of interest.

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