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Clinicopathological Features, Treatment, and Prognosis in Primary Diffuse Large B Cell Lymphoma of the Breast: A Retrospective Study of 46 Patients

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Background: Primary lymphoma of the breast is rare, and primary diffuse large B cell lymphoma (DLBCL) of the breast is very rare. This study aimed to identify the clinicopathological characteristics and treatment associated with prognosis in patients with primary DLBCL of the breast.

Material/Methods: A retrospective study included the clinical and treatment data from 46 women with a histological diagnosis of primary DLBCL. Patients were staged using Ann Arbor staging criteria, overall survival (OS), progression-free survival (PFS), and the international prognostic index (IPI) scores were obtained. Laboratory finding included serum lactate dehydrogenase (LDH), and the immunohistochemistry findings were recorded.

Results: Patients (n=46), included stage I (n=18), stage II (n=18), stage III (n=3), and stage IV DLBCL (n=9). Treatment included chemotherapy with rituximab (n=16), and radiotherapy (n=12). The median follow-up time was 40.5 months, the 5-year OS rate was 36.2%, and the 5-year PFS rate was 29.1%. Univariate analysis showed that clinical stage, serum LDH, the IPI score, chemotherapy cycles >3, and Bcl-2 and Bcl-6 expression were correlated with the 5-year OS and PFS. Multivariate risk regression analysis showed that the number of chemotherapy cycles (>3) and Bcl-6 expression were independent prognostic factors in primary DLBCL of the breast (P<0.05).

Conclusions: A retrospective study of 46 patients with primary DLBCL of the breast showed that >3 cycles of chemotherapy and expression of Bcl-6 resulted in improved OS and PFS. Radiotherapy controlled local tumor recurrence but did not improve the OS and PFS. Rituximab did not improve patient survival.

MeSH Keywords: Breast • Lymphoma, Large B-Cell, Diffuse • Prognosis

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Background

Primary lymphoma of the breast is rare and is more commonly extranodal non-Hodgkin lymphoma (NHL) associated with axillary lymph node involvement [1]. Most cases of primary lymphoma of the breast are B-cell NHL, followed by T-cell NHL, with primary Hodgkin lymphoma of the breast being more rarely reported [2]. Primary lymphoma of the breast represents about 0.5% in all breast malignancies, 3% of all cases of extranodal lymphoma, and 1% of all cases of NHL [3,4]. Diffuse large B cell lymphoma (DLBCL) is the most common primary lymphoma of the breast, which accounts for about 40–70% of all cases, but other subtypes include follicular lymphoma (8.8–15.5%), marginal zone lymphoma (12.2%), and Burkitt lymphoma (10.3%) [2].

Because primary DLBCL of the breast is very rare, there have been few previous studies on outcome following treatment and because of the limited data, currently, there are no treatment guidelines. Treatments include surgery, chemotherapy, radiotherapy, and targeted therapy, but the optimal treatment remains unknown. There is no consensus on the aspects of treatment that include the requirement for surgery and radiotherapy, the appropriate number of chemotherapy cycles, the benefits for the use of rituximab, and the key prognostic factors.

Therefore, this retrospective study aimed to determine the clinicopathological characteristics and treatment associated with 5-year overall survival (OS) and progression-free survival (PFS) in 46 patients with primary DLBCL of the breast.

Material and Methods

Clinical, demographic, laboratory, and follow-up data

Clinical data were obtained from the medical records of 46 patients with primary diffuse large B cell lymphoma (DLBCL) of the breast who were diagnosed and treated at Hunan Cancer Hospital, Xiangya Hospital, and the Second Xiangya Hospital from January 2006 to December 2016. Patients were included based on the diagnostic criteria for primary lymphoma of the breast as described in 1972 by Wiseman and Liao [1], and included an adequate tissue specimen available for diagnosis, no evidence of systemic lymphoma or history of extra-mammary lymphoma, excluding ipsilateral axillary lymph node involvement.

The clinicopathological data and the follow-up data of patients were collected by telephone interview and clinic visits, with the cutoff date of October 1, 2018. All the patients had a histopathological diagnosis of primary DLBCL of the breast and had detailed and available clinical data. Survival data, details of lymphoma progression, and mortality from any cause were carefully recorded. To distinguish primary lymphoma of the breast from secondary breast lymphoma, tissue specimens were sampled by fine-needle biopsy, excision biopsy, partial mastectomy, or total mastectomy and examined by light microscopy. Data from the findings of additional laboratory tests included peripheral blood tests, biochemical tests for renal and liver function, and serum lactate dehydrogenase (LDH). Imaging findings were obtained from chest X-ray, abdominal ultrasound (US), computed tomography (CT), and positron emission tomography (PET), which were used to confirm the site of the primary lymphoma, to stage the lymphoma, and to monitor the effects of treatment.

Evaluation criteria for treatment response of diffuse large B cell lymphoma (DLBCL)

The consensus response evaluation criteria and definitions of lymphoma from the International Working Group (RECIL 2017) were used [5]. A complete response (CR) occurred when the primary lesion completely disappeared, and the long axis of the regional lymph nodes was <10 mm, there was ≥30% reduction in the sum of the longest diameters or a normal scan result using fluorodeoxyglucose positron emission tomography (FDG-PET) (Deauville score of 1–3), there was no involvement of the bone marrow, and the biopsy was negative [5]. A partial response (PR) was defined as ≥30% reduction in the sum of the long diameters of the primary lymphoma, but not a CR with positive FDG-PET (Deauville score is 4–5), a 10–30% reduction in the sum of the long diameters of the primary lymphoma, bone marrow involvement, but no new lesions [5]. Stable disease (SD) was defined as a –10% to +20% change in the sum of the long diameters of the primary lymphoma, any positive FDG-PET result, any involvement of bone marrow, and no new lesions [5]. Progressive disease (PD) was defined as >20% increase in the sum of the long diameters of the primary lymphoma, lymph nodes measuring <15 mm following treatment, an increase of at least 5 mm in the sum of the long diameters of the primary lymphoma, or > 15 mm in one diameter, any new lesion on FDG-PET, and bone marrow involvement with or without new lesions [5].

Patient survival

Overall survival (OS) was calculated from the date of the definitive diagnosis to the date of the last follow-up, or the date of death from any cause. Progression-free survival (PFS) was calculated from the date of the definitive diagnosis to the initial date of disease progression, relapse, or death. Event-free survival (EFS) was calculated to any change in clinical events, including death, disease progression, change of chemotherapy treatment, administration of any other treatment, the occurrence of severe side effects, and other events.

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Statistical analysis

The Kaplan-Meier method was used for the survival analysis and univariate analysis, and the data were compared with the log-rank test. The chi-squared (χ^2) test was performed to compare the clinical characteristics. All statistically different variables were included in the multivariate analysis and analyzed using the Cox proportional hazards model, and the differences were analyzed using the two-tailed t-test. A P-value <0.05 was considered to be statistically significant.

Results

Clinical, demographic, laboratory, and follow-up data

The 46 patients included in the study were women who were aged between 28–78 years (average age, 51 years). Two patients presented with bilateral breast involvement, 27 presented right breast lymphoma, and 17 presented left breast lymphoma. Two patients had clinical 'B' symptoms (fever, night sweats) and 44 patients had no 'B' symptoms. No patient was pregnant or breastfeeding at the time of diagnosis.

The average size of the primary breast lymphoma was 3.6 cm (range, 1.8–9.0 cm). Based on the Ann Arbor clinical staging criteria, 18 patients had stage I lymphoma, 16 patients had stage II lymphoma, three patients had stage III lymphoma, and nine patients had stage IV lymphoma. A total of 32 patients presented with involvement of adjacent organs, including 25 patients with axillary lymph node involvement, three patients had involvement of the axillary lymph nodes and chest wall, three patients had involvement of the axillary lymph nodes and skin, and one patient had nipple involvement. There were 18 patients with lymph node enlargement, of which, 12 patients had cervical lymph node enlargement, 10 patients had axillary lymph node enlargement, five patients had supraclavicular lymph node enlargement, and six patients had inguinal lymph node enlargement. Six patients presented with metastases, including three patients with spread to the bones, one patient with liver metastases, one patient with lung metastases, one patient with spread to the contralateral breast, and one patient with metastases to the right lower gingiva and right mandible. In 12 patients with recurrence and metastases, six patients had involvement of the ipsilateral breast, three patients had involvement of the contralateral breast, one patient had bilateral breast recurrence and spread, one patient had brain metastases, and one patient had both brain and liver metastases (Table 1).

Pathological characteristics

The primary breast lymphomas were typed and classified according to the 2001 classification system from the World Health Organisation (WHO). Histopathological diagnosis was performed on the tissue sections that were stained histochemically with hematoxylin-eosin (H&E). In all 26 patients, the diagnosis of primary diffuse large B cell lymphoma (DLBCL) of the breast was confirmed by immunohistochemistry. B cells were labeled with antibodies to CD20 and CD79a in all 26 patients, Bcl-2 expression was found in 16 patients, Bcl-6 expression was found in 27 patients, CD3 expression in three patients, CD5 expression in four patients, CD10 expression in seven patients, multiple myeloma oncogene 1 (MUM1) expression in 16 patients, and PAX5 expression in 13 cases. The proliferation index with Ki-67 immunostaining was 30–95% (median, 71.9%). In six cases, patients were diagnosed with germinal center B-cell like (GCBC) diffuse large B-cell lymphoma (DLBCL), and 17 patients had non-GCBC DLBCL (Table 2).

Table 1. Prevalence of distnat spread or recurrence in 19 patients with primary diffuse large B cell lymphoma (DLBCL) of the breast.

Site of spread or recurrence	Cases	Percentage
Distant spread	**7**	
Bone	3	42.8%
Liver	1	14.3%
Lung	1	14.3%
Contralateral breast	1	14.3%
Right lower gum and jaw	1	14.3%
Recurrence	**12**	
Ipsilateral breast	6	50.0%
Contralateral breast	3	25.0%
Bilateral breast	1	8.3%
Brain	1	8.3%
Brain and liver	1	8.3%

Treatment and follow-up

The follow-up time ranged from 2–149 months (median, 40.5 months) for all 46 patients. Among the 46 patients, 38 patients underwent surgery, including 28, five, three, and two patients who underwent simple lesion resection, modified radical resection, radical resection, and expanded mass resection, respectively. Eight patients did not receive surgical treatment, including seven patients who had a biopsy only, and one patient with an axillary lymph node biopsy.

There were 44/46 patients who received chemotherapy, of which, 26/44 patients received simple chemotherapy, 12/44 received chemotherapy combined with radiotherapy,

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Table 2. Immunohistochemistry in 46 patients with primary diffuse large B cell lymphoma (DLBCL) of the breast.

Immunohistochemistry	Total	Percentage
CD20 positive	46/46	100.0%
CD79 positive	46/46	100.0%
Bcl-2 positive	16/46	34.8%
Bcl-6 positive	27/46	58.7%
CD3 positive	3/46	6.5%
CD5 positive	4/46	8.7%
CD10 positive	7/46	15.2%
MUM1 positive	16/46	34.8%
PAX5 positive	13/42	31.0%
Subtype	GCBC: 6	13.0%
	Non-GCBC: 17	37.0%
	Unknown: 23	50.0%

GCBC – germinal center B-cell like; DLBCL – diffuse large B-cell lymphoma; MUM1 – multiple myeloma oncogene 1.

3/44 received intrathecal injection after chemotherapy, 1/44 received allogeneic hematopoietic stem cell transplantation after chemotherapy, 1/44 received allogeneic hematopoietic stem cell transplantation and intrathecal injection after chemotherapy, and 1/44 received cytokine-induced killer (CIK) cell immunotherapy after chemotherapy. Forty-one patients received more than three cycles of chemotherapy, while five patients received <3 cycles of chemotherapy. Sixteen patients were treated with rituximab, and 30 were not.

The following chemotherapy regimens were used. Twenty-two patients received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy; 14 patients received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R + CHOP) chemotherapy; two patients received rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (R+DA-EPOCH) chemotherapy; 11 patients received etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone (EPOCH) chemotherapy; two patients received dexamethasone, ifosfamide, cisplatin, and etoposide (DICE) chemotherapy; one patient received mesna, ifosfamide, mitoxantrone, and etoposide (MINE) chemotherapy; one patient received etoposide, methylprednisolone, cisplatin, and cytarabine (ESHAP) chemotherapy; and one patient received chemotherapy with gemcitabine and oxaliplatin (GEMOX).

Thirty-four patients were not treated with radiotherapy, and 12 patients received radiotherapy. The radiotherapy dose ranged from 20–53 Gy (median dose, 36.5 Gy). Four patients received preventive intrathecal injection, but no patient received preventive intracranial radiotherapy. Thirty-four patients did not show recurrence, and 12 patients showed disease recurrence. In the patients who underwent relapse, all patients had received chemotherapy, with CHOP/R-CHOP in four patients, GEMOX in four patients, EPOCH in two patients, cyclophosphamide, doxorubicin, etoposide, bleomycin, vincristine, methotrexate, and prednisone (ProMACE/CytaBOM) in two patients, with the other chemotherapy regimens including MINE, ESHAP, and DICE. Four patients received radiotherapy, and one patient received intrathecal chemotherapy for intracranial recurrence.

Correlation analysis of the clinical characteristics and treatment methods with 5-year progression-free survival (PFS) and overall survival (OS) rates

Univariate analysis was performed for patient age, lesion site, tumor size, tumor stage, B symptoms, surgical procedure, radiotherapy, number of chemotherapy cycles, serum levels of lactate dehydrogenase (LDH), the international prognostic index (IPI) score, treatment with rituximab, lymphoma recurrence, Bcl-2 expression level, and Bcl-6 expression level. The results showed that clinical stage, serum LDH level, the IPI score, number of chemotherapy cycles, Bcl-2 expression, and Bcl-6 expression were significantly associated with 5-year survival rates ($P < 0.05$). Patient age, site of the lymphoma, tumor size, presence or absence of 'B' symptoms, surgical procedure, radiotherapy, use of rituximab, and lymphoma recurrence were not associated with patient prognosis ($P > 0.05$) (Table 3).

In the 46 patients with primary DLBCL of the breast, the 5-year OS was 36.2%, and 5-year PFS was 29.1%. Among the 44 patients who received chemotherapy, 28 patients achieved complete remission (CR) after the first treatment with chemotherapy, with a CR rate of 63.6% (28/44), 12 patients achieved a partial response (PR) with a PR rate of 27.3% (12/44), and four patients developed progressive disease (PD) (4/44). The 5-year OS of stage IE+IIE was 40.8% (34/46), and the 5-year PFS was 34.61%. For patients with stage IIIE+IVE, the 5-year OS was 20.4% (12/46), and the 5-year PFS was 12.2% ($P < 0.05$). These findings indicated that patient prognosis in primary DLBCL of the breast was associated with stage, indicating increased survival time in low-grade malignant lymphoma than in medium-grade to high-grade malignant lymphoma (Figures 1A, 2A).

For patients with an IPI score of 0–1, the 5-year OS was 43.4% (33/46) and the 5-year PFS was 37.1%. For patients with an IPI score of 2–4, the 5-year OS and the 5-year PFS were 13.3% (13/46) and 7.5%, respectively ($P < 0.01$). Therefore, the higher the IPI score, the worse the prognosis (Figures 1B, 2B). For patients who received at least 3 cycles of chemotherapy, the 5-year OS was 40.7% (41/46), and the

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Table 3. Univariate analysis of factors affecting the 5-year overall survival and the 5-year progression-free survival (PFS) of patients with primary diffuse large B cell lymphoma (DLBCL) of the breast.

Clinico-pathological parameters	N				χ^2	P-value	5-year OS	5-year PFS
Age					0.930	0.335		
≤50	28	(60.9%)					41.8%	24.8%
>50	18	(39.1%)					39.3%	35.7%
Primary site					4.127	0.127		
Left breast	17	(37%)					55.3%	38.2%
Right breast	27	(58.7%)					22.1%	20.7%
Both breast	2	(4.3%)					50.0%	50.0%
Tumor size (cm)					3.478	0.062		
≤5	37	(80.4%)					42.1%	33.3%
>5	9	(19.6%)					10.2%	10.5%
Stage					6.661	0.010#		
IE	18	(39.1%)						
IIE	16	(34.8%)	34	(73.9%)			40.8%	34.6%
IIIE	3	(6.5%)						
IVE	9	(19.6%)	12	(26.1%)			20.4%	12.2%
B symptoms					0.001	0.995		
Yes	2	(4.3%)					50.0%	50.0%
No	44	(95.7%)					35.4%	30.8%
Radiotherapy					2.151	0.142		
Yes	12	(75.6%)					60.5%	49.6%
No	34	(58.8%)					25.4%	22.9%
LDH level					6.037	0.014#		
Normal	31	(67.4%)					18.0%	5.3%
Elevated	15	(32.6%)					43.2%	40.7%
IPI score					7.183	0.007*		
0–1	33	(71.7%)					43.4%	37.1%
2–4	13	(28.3%)					13.3%	7.5%
Rituximab					2.913	0.088		
Yes	16	(34.8%)					34.4%	29.8%
No	30	(65.2%)					35.7%	28.0%
Chemotherapy cycles					18.351	0.000*		
≥3	41	(89.1%)					40.7%	33.6%
<3	5	(10.9%)					0%	0%

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Table 3 continued. Univariate analysis of factors affecting the 5-year overall survival and the 5-year progression-free survival (PFS) of patients with primary diffuse large B cell lymphoma (DLBCL) of the breast.

Clinico-pathological parameters	N		χ^2	P-value	5-year OS	5-year PFS
Recurrence			1.072	0.300		
Yes	12	(33.3%)			38.3%	12.1%
No	34	(73.5%)			33.4%	34.8%
Intrathecal therapy			1.064	0.302		
Yes	4	(8.7%)			25.0%	25.0%
No	42	(91.3%)			39.1%	32.25%
Transplantation			0.472	0.492		
Yes	2	(4.3%)			50.0%	50.0%
No	44	(95.7%)			35.6%	28.5%
Bcl-2			5.632	0.018#		
Positive	16	(37.8%)			16.6%	10.2%
Negative	30	(65.2%)			44.3%	38.7%
Bcl-6			9.113	0.003*		
Positive	27	(58.7%)			50.2%	42.4%
Negative	19	(41.3%)			14.3%	8.1%
Surgery			0.296	0.587		
Yes	38	(82.6%)			37.4%	23.3%
No	8	(17.4%)			24.9%	23.2%

a, N – case number; LDH – lactate dehydrogenase; IPI – international prognostic index. * P<0.01 was statistically significant. # P<0.05 was statistically significant.

5-year PFS was 33.6%. For patients who had <3 cycles of chemotherapy, the 5-year OS and 5-year PFS were 10% (5/46) (P<0.01). Therefore, ≥3 cycles of chemotherapy were associated with an increased survival rate in patients with primary DLBCL of the breast (Figures 1C, 2C).

The 5-year OS of patients with a normal serum LDH was 43.2% (31/46), and the 5-year PFS was 40.7%; the 5-year OS of patients with an increased serum LDH was 18.0% (15/46), and the 5-year PFS was 5.3% (P<0.05), indicating that patients with increased serum LDH had a worse prognosis (Figures 1D, 2D).

In patients with DLBCL that was positive for Bcl-2 using immunohistochemistry, the 5-year OS was 16.6% (16/46), and the 5-year PFS was 10.2%. In patients with DLBCL that was negative for Bcl-2, the 5-year OS was 44.3% (30/46), and the 5-year PFS was 38.7% (P<0.05), indicating that Bcl-2 expression resulted in a worse prognosis (Figures 1E, 2E). In patients with DLBCL that was positive for Bcl-6 using immunohistochemistry, the 5-year OS was 50.2% (27/46) and the 5-year PFS was 42.4%. In patients with DLBCL that was negative for Bcl-6, the 5-year OS was 14.3% (19/46), and the 5-year PFS was 8.1% (P<0.01), indicating that Bcl-6 expression was associated with a better prognosis (Figures 1F, 2F). Multivariate risk regression analysis using the Cox model showed that the number of chemotherapy cycles and Bcl-6 expression were independent prognostic factors for patients with primary DLBCL of the breast (P<0.01) (Table 4).

Discussion

This retrospective study aimed to determine whether clinicopathological characteristics and treatment were associated with prognosis in 46 patients with primary diffuse large B cell lymphoma (DLBCL) of the breast. The findings showed that that >3 cycles of chemotherapy and expression of Bcl-6 by the lymphoma, detected using immunohistochemistry,

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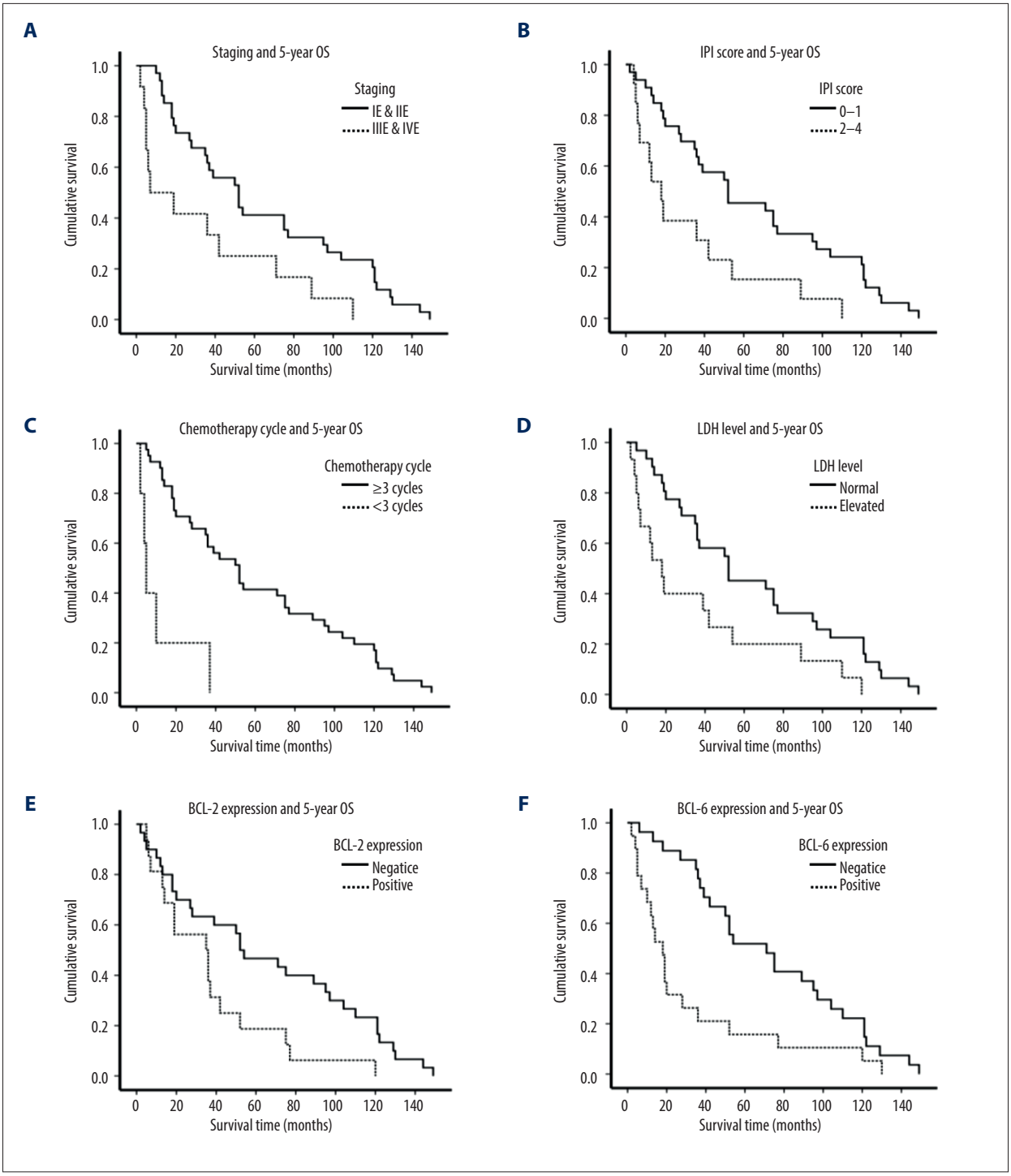

Figure 1. Correlation of the 5-year overall survival (OS) with the clinicopathological features in 46 patients with primary diffuse large B cell lymphoma (DLBCL) of the breast. (**A**) Comparison of the 5-year OS in patients with primary DLBCL of the breast according to stage. (**B**) Comparison of the 5-year OS in patients with primary DLBCL of the breast according to the international prognostic index (IPI) score. (**C**) Comparison of the 5-year OS in patients with primary DLBCL of the breast according to the chemotherapy cycles. (**D**) Comparison of the 5-year OS in patients with primary DLBCL of the breast according to the serum level of lactate dehydrogenase (LDH). (**E**) Comparison of the 5-year OS in patients with primary DLBCL of the breast according to Bcl-2 expression. (**F**) Comparison of the 5-year OS in patients with primary DLBCL of the breast according to Bcl-6 expression.

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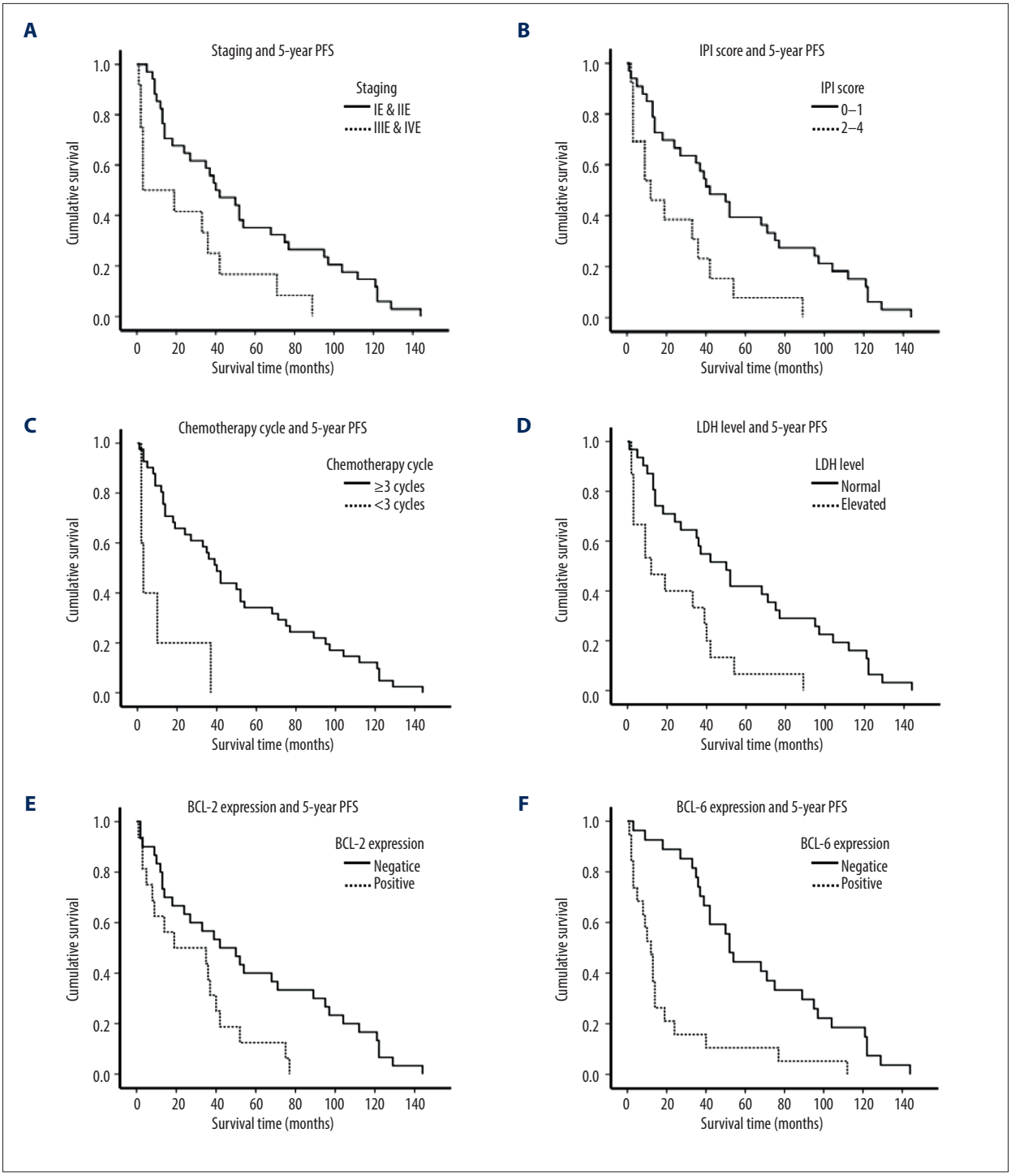

Figure 2. Correlation of the 5-year progression-free survival (PFS) with the clinicopathological features in 46 patients with primary diffuse large B cell lymphoma (DLBCL) of the breast. (**A**) Comparison of the 5-year PFS in patients with primary DLBCL of the breast according to stage. (**B**) Comparison of the 5-year PFS in patients with primary DLBCL of the breast according to the international prognostic index (IPI) score. (**C**) Comparison of the 5-year PFS in patients with primary DLBCL of the breast according to the chemotherapy cycles. (**D**) Comparison of the 5-year PFS in patients with primary DLBCL of the breast according to the serum level of lactate dehydrogenase (LDH). (**E**) Comparison of the 5-year PFS in patients with primary DLBCL of the breast according to Bcl-2 expression. (**F**) Comparison of the 5-year PFS in patients with primary DLBCL of the breast according to Bcl-6 expression.

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Table 4. Multivariate analysis and regression analysis of the Cox model for factors affecting the prognosis of patients with primary diffuse large B cell lymphoma (DLBCL) of the breast.

Clinicopathological parameters	β	SE	OR	χ^2	P-value	95% CI
Stage	–0.473	0.661	0.623	0.511	0.475	0.171–2.277
LDH	0.242	0.550	1.274	0.194	0.660	0.433–3.746
Chemotherapy cycles	2.098	0.561	8.154	14.014	0.000*	2.718–24.462
IPI	–1.023	0.820	0.359	1.558	0.212	0.072–1.793
Bcl-2	0.406	0.359	1.500	1.277	0.259	0.742–3.031
Bcl-6	–1.066	0.355	0.344	9.002	0.003*	0.172–0.691

SE – standard error; OR – odds ratio; CI – confidence interval; LDH – lactate dehydrogenase; IPI – international prognostic index.
* P<0.01 was statistically significant.

resulted in improved overall survival (OS) and progression-free survival (PFS). Radiotherapy controlled local tumor recurrence but did not improve the OS and PFS, and treatment with rituximab did not improve patient survival. In most solid tumors, including gastric cancer, lung cancer, and renal cancer, the prognosis is closely correlated with tumor size [6–8]. However, in the present study, the size of the primary lymphoma in the breast was not significantly associated with 5-year OS. In patients with tumor size >5 cm, the 5-year OS was 10.2%, and the 5-year PFS was 10.5%. In patients with a primary tumor size <5 cm, the 5-year OS was 42.1%, and the 5-year PFS was 33.3% (P>0.05). Therefore, in primary DLBCL of the breast, biological activity may play a more important role in patient prognosis, rather than the tumor size. However, Fukuhara et al. showed that the tumor size of patients with primary DLBCL of the breast was related to prognosis, as tumors with a size of 4–5 cm had a worse prognosis [9]. The difference in findings between the present study and this previous study may be due to the different sizes of the study populations.

In the present study, high serum levels of lactate dehydrogenase (LDH), high international prognostic index (IPI) scores, and advanced clinical stage were associated with poor prognosis. Previous studies showed that serum LDH levels were positively correlated with cancer cell proliferation, and poor prognosis [10]. Hosein et al. [11] showed that the 5-year OS rate of patients with an IPI score in the 0–1 range was 87% (95% CI, 25–71), and was 48% for patients with an IPI score of between 2–4, supporting that the IPI score is negatively correlated with prognosis. The findings from the present study showed that the clinical stage had a significant impact on the 2-year and 5-year OS. Patients with early-stage lymphoma had a better prognosis, which was consistent with the findings from previously published studies [12,13]. A recent study showed that the 5-year OS for patients with primary lymphoma of the breast was 75–80%, while in this study of 46 patients with primary DLBCL of the breast, the 5-year OS was 36.2% [14]. The distribution of the clinical stages might explain these differences, as patients included in the present study had more advanced clinical stage compared with previous studies [3,15,16]. More than 90% of patients in previously reported studies were stage IE to stage IIE, while this proportion was less than 74% in the present study, which might explain the different survival rates.

This study also analyzed the relationship between pathological characteristics and patient prognosis in primary DLBCL of the breast. The results showed that positive Bcl-2 expression, detected using immunohistochemistry, was associated with poor prognosis and that patients with negative Bcl-6 expression had a better prognosis. These results are consistent with the functional roles of Bcl-2 and Bcl-6. Bcl-2 is an anti-apoptotic protein, which plays an important role in the normal development and differentiation of B cells [17]. Bcl-2, encoded by the BCL-2 gene, is associated with cell proliferation in lymphoma [18]. BCL-6 is a transcription inhibitor gene that inhibits the apoptosis of tumor cells and is involved in the cell activation and proliferation [19]. Given the significant relationship between the Bcl-2 and Bcl-6 proteins in the prognosis of patients with primary DLBCL of the breast demonstrated in this study, the expression of Bcl-2 and Bcl-6 might have clinical prognostic significance.

Because primary DLBCL of the breast is relatively rare, many patients with primary breast lymphoma are often misdiagnosed as having breast cancer and undergo surgical resection [20]. In the present study, patients with complete resection of the primary lesion did not have a significantly improved prognosis. This finding may be explained by the fact that lymphoma is a hematologic malignancy, and its pathogenesis and progression will be different from that of solid tumors. Systematic treatment, especially with chemotherapy, may be more beneficial for tumor control than local surgical resection.

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For lymphoma that occurs at sites other than the breast, surgery is not the primary treatment method. Therefore, when primary DLBCL of the breast is diagnosed, systemic treatment should be given. Previous studies support this recommendation, as they have shown that mastectomy was not associated with improved outcomes in patients with primary lymphoma of the breast [21,22].

These findings highlight the need for clinicians to be aware of the diagnosis of primary lymphoma of the breast in clinical practice, to avoid misdiagnosis. Biopsy and rapid histopathology during surgery are required to confirm the diagnosis [23]. If patients with primary breast lymphoma were treated initially by mastectomy, supplementary radiotherapy, chemotherapy, and immunotherapy should be administered promptly following surgery.

In the present study, statistical analysis of patient outcome following radiation therapy for primary DLBCL of the breast showed that radiotherapy was not significantly associated with improved 5-year OS and 5-year PFS. In this study, 12 patients received local radiotherapy with a dose range of 20–53 Gy (median, 36.5 Gy). No patients received preventive brain radiotherapy. All of the 12 patients achieved complete remission (CR), four patients showed recurrence and the other eight patients showed no signs of recurrence until October 1, 2018, suggesting that radiotherapy reduced the rate of local recurrence. Due to the limited number of cases studied, no further stratification analysis was performed on the correlation of other prognostic factors, such as radiation dose and radiation field. However, these findings suggest that radiotherapy should be administered carefully to patients with primary breast lymphoma. A recently published phase III study reported there was no statistically difference in the event-free survival (EFS) rate, and the OS rate after patients with DLBCL received rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R+CHOP) chemotherapy combined with radiotherapy or non-combined radiotherapy [24], which demonstrated that radiotherapy did not improve patient prognosis. Studies have shown that the use of radiotherapy did not improve the OS in patients with primary lymphoma of the breast [25,26]. However, several studies have shown that although the use of radiotherapy did not improve the OS of patients with primary DLBCL of the breast, the use of chemotherapy combined with radiotherapy could reduce local recurrence [11,27]. Avilés et al. [28] reported the findings from a prospective study of 96 patients with stage I and II primary lymphoma of the breast and showed that the efficacy of CHOP chemotherapy combined with radiotherapy was associated with improved EFS and OS when compared with chemotherapy or radiotherapy alone. In this previous study, the 10-year EFS rates were 83%, 56%, and 50%, respectively ($P<0.01$) and the 10-year OS rates were 76%, 50%, and 50%, respectively [28]. However, whether radiotherapy has a similar effect on breast lymphomas other than primary DLBCL of the breast requires further studies.

The choice of the chemotherapy regimen in patients with lymphoma should be based on the histological subtype, and stage, and should be individualized for different patients. The CHOP regimen is the standard treatment for primary DLBCL of the breast. In the present study, 44 patients received chemotherapy, 22 patients received the CHOP regimen, 14 patients were treated with R+CHOP, two patients were treated with R+DA-EPOCH, and 11 patients received EPOCH chemotherapy. Other chemotherapy regimens included DICE, MINE, ESHAP, and GEMOX. After the initial treatment, 28 of the 44 patients achieved complete remission (CR), 12 patients achieved partial remission (PR), and four patients developed progressive disease (PD). Due to the limited number of cases in this study, prognosis following the use of different chemotherapy regimens was not compared. We analyzed the correlation between chemotherapy cycles and prognosis and found that >3 chemotherapy cycles significantly increased the OS and PFS, but >4 cycles of chemotherapy did not increase the OS further. This result suggests that excessive chemotherapy may not be beneficial for patients, and may be harmful. Previous studies have shown that adequate courses of chemotherapy are beneficial to the OS. In 2008, a study reported by the study from the International Extranodal Lymphoma Study Group (IELSG-15) showed that >3 cycles of chemotherapy increased the OS rate in extranodal B cell lymphoma (HR, 0.5; 95% CI, 0.2–0.9) [29]. In 2010, the findings from the Consortium for Improving Survival of Lymphoma (CISL) also showed that for patients who received <4 cycles of chemotherapy, the 5-year OS was 28% and the 5-year PFS was 19.3%, while for patients who received >4 cycles of chemotherapy, the 5-year OS was 58% ($P<0.001$), and the 5-year PFS was 66.2% ($P<0.0001$), indicating that the number of chemotherapy cycles affected both PFS and OS [30].

Targeted therapy is currently being investigated for the treatment for lymphoma. CD20 is highly expressed in primary DLBCL of the breast, and in the present study, all 46 patients had lymphoma that was positive for CD20. Although the expression of CD20 in primary DLBCL of the breast is present, and a chemotherapy regimen that includes rituximab might seem to be a promising treatment, in this study, treatment with rituximab did not affect the OS of patients with primary DLBCL of the breast. These findings are supported by the findings from previously reported retrospective studies that have shown that rituximab did improve the prognosis of patients with primary DLBCL of the breast [31]. In 2013, Held et al. studied patients with DLBCL and showed that combined chemotherapy regimens that included rituximab did not result in additional benefit to patients, which supports the findings of the present study [31]. A previous study has shown that rituximab combined with chemotherapy could prevent recurrence in the central nervous

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system [32]. However, recent studies have shown that rituximab has limited efficacy against recurrence in the breast and central nervous system, but significantly reduces the risk of systemic lymph node recurrence [33,34]. However, as most of the data regarding the efficacy of rituximab come from retrospective clinical studies, future controlled and large-scale multicenter studies are needed to determine the role of rituximab in primary lymphoma of the breast, and in extranodal DLBCL.

In this study, four patients were treated with intrathecal chemotherapy, including three patients who were stage IE–IIE, with an IPI score of 0–2, and one patient with staged IVE and an IPI score of 3. One patient with stage IIE DLBCL had brain involvement and bilateral breast involvement, and the other three cases did not have CNS recurrence. For the 42 patients who did not receive intrathecal injections of chemotherapy, one case had a recurrence in the brain and liver. The overall recurrence rate of CNS lymphoma was 4%. A previous study showed that patients with DLBCL patients had a total risk of between 2–5% for CNS relapse, usually within 2 years after treatment [11]. However, the role of preventive treatment for CNS recurrence remains controversial [33]. Several studies failed to show the benefits of preventative intrathecal chemotherapy [34,35]. However, in patients with primary breast lymphoma, as in patients with testicular lymphoma, there is a significant preference for recurrence to occur in the CNS [15,16]. The Spanish Lymphoma Group (SLG) have suggested that preventative CNS treatment should be recommended for patients with invasive bilateral breast lymphoma [36]. In the present study, 42 patients without intrathecal chemotherapy included only one case of CNS recurrence, while in four patients who underwent intrathecal chemotherapy, one patient with bilateral breast lymphoma had CNS recurrence. This finding supports that intrathecal chemotherapy might have a limited preventive effect for the CNS recurrence. Whether more active prophylaxis for CNS recurrence is needed remains to be determined by further controlled and large-scale prospective studies. Due to the limited number of cases in this study, the role of chemotherapy in the prevention of CNS recurrence and survival analysis in patients with primary DLBCL of the breast was not studied, but this is an important area that requires further investigation.

Conclusions

Primary diffuse large B cell lymphoma (DLBCL) of the breast is a rare primary extranodal non-Hodgkin lymphoma (NHL) with characteristic behavior and prognosis. This study aimed to investigate 46 patients with primary DLBCL of the breast to determine whether clinicopathological characteristics and treatment were associated with prognosis. Surgery may be required for the definitive diagnosis, but this study showed that it did not improve patient prognosis. As with other types of extranodal high-grade B cell NHL, patients with primary DLBCL of the breast responded to at least 3 cycles of chemotherapy, which improved overall survival (OS). Radiotherapy and a chemotherapy regimen with rituximab regimen did not improve the OS and progression-free survival (PFS) rates, even though DLBCL cells were CD20 positive. Therefore, in patients with primary DLBCL of the breast, rituximab should be administered with caution. In this study, the number of chemotherapy cycles and Bcl-6 expression were found to be independent factors that affected patient prognosis. However, due to the low incidence of this disease, currently available clinical data on primary DLBCL of the breast is limited to a few patients and retrospective studies. Further data from patient treatment and prognosis from long-term follow-up in prospective clinical studies are needed to guide the clinical management of patients with primary DLBCL of the breast.

Conflict of interest

None.

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