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ORIGINAL RESEARCH

Diffuse large B-cell lymphoma of the breast: prognostic factors and treatment outcomes

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Background: The breast is a rare site of extranodal involvement of diffuse large B-cell lymphoma (DLBCL). We aimed to assess the clinical characteristics, prognostic factors, and treatment outcomes of breast DLBCL.

Patients and methods: We retrospectively analyzed 113 patients (from our institution and the literature) between 1973 and 2014. The primary end point was overall survival (OS). Kaplan–Meier OS curves were compared with the log-rank test. Cox regression analysis was applied to determine the prognostic factors for OS, progression-free survival (PFS), local control (LC), and cause-specific survival (CSS).

Results: A total of 113 patients were included in the study: 42 cases from our hospital and 71 cases from 12 publications. The median age at diagnosis was 58 years. With a median follow-up time of 39.2 months, the estimated 5-year OS, PFS, LC, and CSS were 71.4%, 58.8%, 75.6%, and 74.9%, respectively. In multivariate analysis, more than four cycles of chemotherapy, having localized cancer, lumpectomy with or without axillary lymph node (ALN) dissection, and low to low-to-intermediate International Prognostic Index were favorable factors for OS. For PFS, significant prognostic factors were rituximab use, B symptoms, and tumor size. As for the local group, lumpectomy with or without ALN dissection and more than four cycles of chemotherapy were favorable factors for OS. Tumor size >4 cm and nonuse of rituximab were adverse factors for PFS. Twenty-one patients (18.6%) developed local relapse and 33 (29.2%) developed systemic relapse. Eight patients had central nervous system relapse (7.3%).

Conclusion: Our results reveal that local and extended staging criteria can reflect the different prognosis and treatment outcomes of breast DLBCL. Rituximab use, lumpectomy, and more than four cycles of chemotherapy are recommended as a treatment regimen. However, further study is warranted to validate our data.

Keywords: diffuse large B-cell lymphoma, breast, rituximab, surgery, chemotherapy

Introduction

Breast lymphoma is a rare form of extranodal lymphoma. It constitutes 0.5% of breast malignancies, 1% of non-Hodgkin lymphoma (NHL), and 3% of extranodal lymphoma. The predominant histopathology is diffuse large B-cell lymphoma (DLBCL).[1,2] Breast lymphoma can be subdivided into primary breast lymphoma (PBL) and secondary breast lymphoma (SBL). In PBL, the breast is the only site of lymphoma with or without regional lymph node involvement. SBL refers to the presentation of lymphoma in the lymph node region and organs other than the breast and regional lymph nodes.[3]

Currently, there is controversy about the staging of breast lymphoma as PBL or SBL. The definition of PBL was first proposed by Wiseman and Liao[3] in 1972 in a study that included just 31 patients. This is an extremely small sample from which to draw a conclusion for staging criteria. Because of the rarity of the disease, most

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of the previous studies were small retrospective analyses. There was only one prospective study.[4] There were wide variations in conclusions about the prognosis and outcome of breast lymphoma.

The treatment of breast lymphoma includes surgery, radiotherapy (RT), and chemotherapy. These have been used alone or in combinations of two or three modalities. However, no consensus has been reached for the best therapy regimen for breast lymphoma. The largest retrospective analysis found that mastectomy provides no survival benefit compared to lumpectomy or biopsy.[5] Furthermore, the one prospective study revealed that combined therapy with RT and chemotherapy was the best treatment, giving a significant improvement for event-free survival (EFS) and overall survival (OS) compared to single treatment.[4] These, however, were all studies based on old therapy regimens from the pre-rituximab era. At present, rituximab has been used widely in nodal DLBCL. The best treatment regimen for breast DLBCL in the rituximab era remains unknown.

This study aims to clarify the issue of prognosis, optimal treatment regimen, and treatment outcome for breast DLBCL now that we have rituximab as a treatment option.

Patients and methods

Study design and patient eligibility

The sample included patients with breast lymphoma recruited from our hospital and data extracted from the literature. Patients with a confirmed histopathological diagnosis of breast DLBCL were included. The exclusion criteria were as follows: 1) diagnosis of breast lymphoma other than DLBCL (eg, mucosa-associated lymphoid tissue type lymphoma or follicular lymphoma); 2) uncontrolled comorbidity (metabolic or psychiatric); 3) unrecorded survival time. Initial staging procedures included the following: a complete blood count, chemistry, mammography, breast sonography, bone marrow aspiration and biopsy, and computed tomography of the thorax, abdomen, and pelvis. Fluorodeoxyglucose-positron emission tomography and computed tomography was optional and has been performed since 2005 for staging. According to the Ann Arbor staging criteria, the patients were divided into PBL and SBL. Only bilateral breast involvement was grouped as PBL IV_E. According to the number of involved organs, the patients were divided into one extranodal disease group (OED, the only involvement of breast with or without nodal disease) and multiple extranodal disease group (MED, multiple extranodal organ involvement including breasts, regardless of nodal status).[6] According to the extent of disease, the patients were classified into local group (PBL I_E and II_E) and extended group (PBL IV_E and SBL). The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the independent ethics committees of Tianjin Medical University Cancer Institute and Hospital. Written informed consent was obtained from all patients in the study.

Literature search and data extraction

We searched Medline for patients with breast DLBCL between April 1966 and June 2015. The search terms included the word "breast" combined with "DLBCL". For the shortlisted studies, we contacted all principal researchers through email for obtaining detailed information about the patient. A flowchart of patient selection from the literature is shown in Figure 1. The included studies from literature are summarized in Table 1.

Treatment schedule

Surgical interventions consisted of biopsy, lumpectomy with or without axillary lymph node (ALN) dissection, and mastectomy with or without ALN dissection. RT was administered with conventional fields (tangent beams) or three-dimensional conformal RT for whole breast irradiation. Conventional photon and electron beams were planned for postmastectomy RT. Data were gathered about the chemotherapy agents used and number of cycles. Most of the patients (98.2%) received anthracycline-based CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)-like chemotherapy.

Measurements of outcomes and end points

The primary outcome was OS. The secondary outcomes included progression-free survival (PFS), local control (LC), and cause-specific survival (CSS). All the outcomes were calculated from the date of histopathological diagnosis to the following points: OS (to the date of death), PFS (to the date of progression), LC (to the date of local failure), and CSS (to the date of death from disease or treatment-related causes).

Statistical analysis

The categorical variables were summarized as frequencies and percentages, while median and range were calculated for continuous variables. The curves for PFS, OS, LC, and CSS were plotted using the Kaplan–Meier method, and comparisons between groups were calculated using log-rank tests.[7] Multivariate analysis was estimated using Cox proportional hazard models.[8] *P*-values of <0.05 were considered to be statistically significant. SPSS PASW Statistics Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

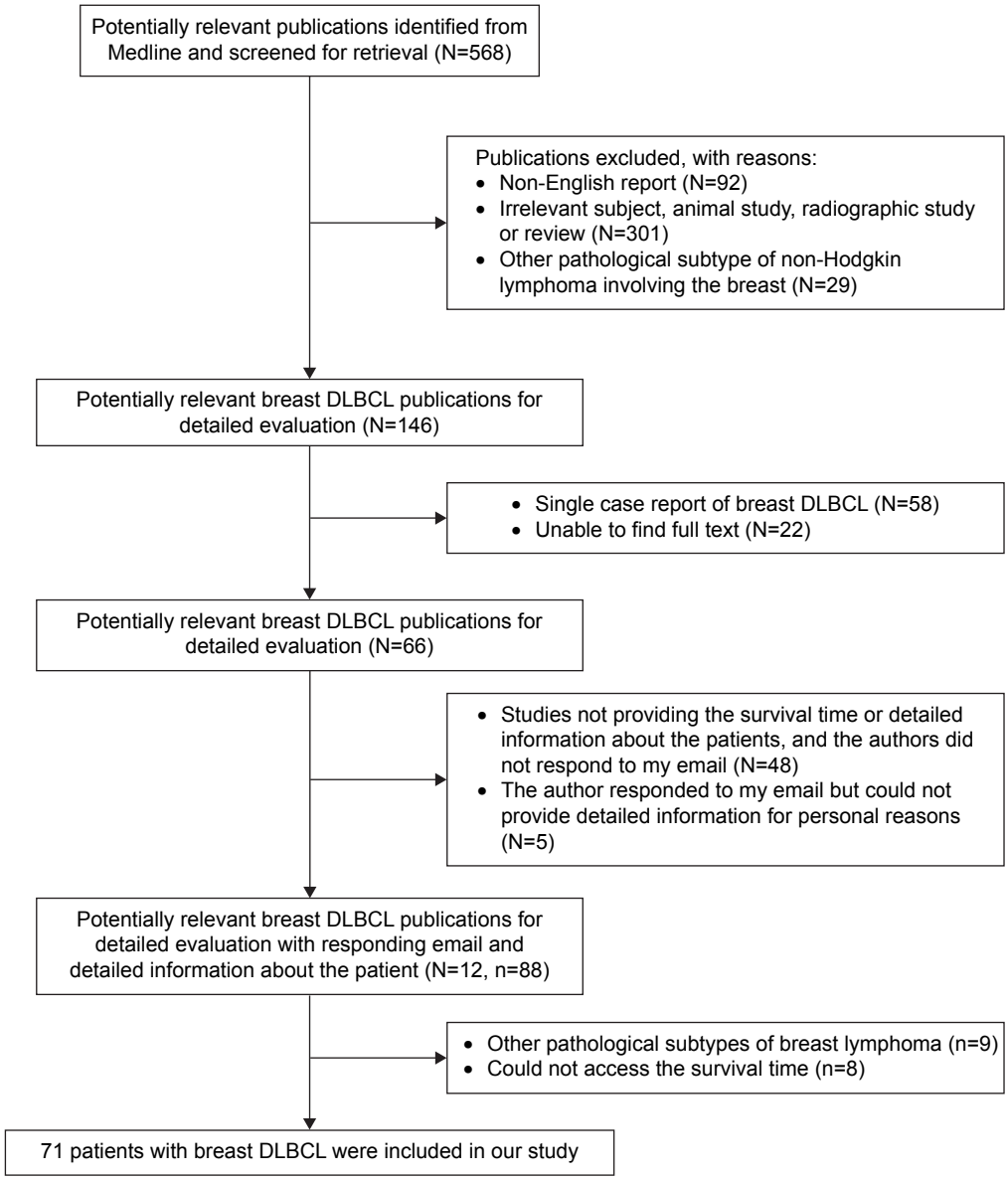

Figure 1 Flowchart of patient selection from literatures.
Abbreviations: N, number of studies; n, number of patients; DLBCL, diffuse large B-cell lymphoma.

Table 1 The included studies from literature

Study	Number of patients	Country of origin
Duan et al[31]	11	People's Republic of China
Inic et al[32]	3	Serbia
Jung et al[33]	8	Korea
Mouna et al[34]	5	Morocco
Joks et al[35]	2	Poland
Julen et al[36]	5	Switzerland
Sanguinetti et al[37]	1	Italy
Cabras et al[38]	8	Italy
Yoshida et al[39]	15	Japan
Seker et al[40]	9	Turkey
Ogawa et al[41]	3	Japan
Romero-Guadarrama et al[42]	Total 5, included 1	Mexico

Results

Patient characteristics

A total of 113 patients were included in the analysis: 42 cases (37%) from our hospital and 71 cases (63%) from 12 publications. The baseline characteristics of the patients are shown in Table 2. The median age at diagnosis was 58 years (range: 20–89 years old). Of these patients, 108 were female (95.6%) and five patients were male (4.4%). The median tumor size was 4 cm (range: 2–15 cm). Three patients were found to have breast DLBCL during pregnancy. The *Eastern Cooperative Oncology Group* (ECOG) performance status was 0 or 1 in 102 patients (90.3%). B symptoms were present in eight patients (7.1%). Both breasts were involved in

Table 2 Patient characteristics

Characteristics	N	%
Sex		
Male	5	4.4
Female	108	95.6
Age at diagnosis		
<60 years	60	53.1
≥60 years	53	46.9
Pregnancy at diagnosis		
Yes	3	2.7
No	110	97.3
ECOG performance status		
0–1	102	90.3
2–4	11	9.7
LDH		
Normal	78	69.0
Elevated	35	31.0
B symptoms		
Yes	8	7.1
No	105	92.9
Primary site		
Left	60	53.1
Right	48	42.5
Bilateral	5	4.4
Tumor size		
≤4 cm	59	52.2
>4 cm	54	47.8
IPI		
Low	83	73.5
Low intermediate	21	18.6
High intermediate	4	3.5
High	5	4.4
Ann Arbor staging		
PBL stage I_E	64	56.6
PBL stage II_E	37	32.7
PBL stage IV_E	3	2.7
SBL	9	8.0
OED/MED staging		
OED	104	92.0
MED	9	8.0
Local/extended staging		
Local	101	89.4
Extended	12	10.6

Abbreviations: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; IPI, International Prognostic Index; PBL, primary breast lymphoma; SBL, secondary breast lymphoma; OED, one extranodal disease; MED, multiple extranodal disease.

five patients (4.4%). All the patients were pathologically confirmed as having breast DLBCL. Sixty-four patients were stage PBL I_E, 37 were stage PBL II_E, three patients were stage PBL IV_E, and nine patients were stage SBL – according to the Ann Arbor staging criteria. A total of 104 patients (92.0%) were classified as having low to low-to-intermediate risk according to International Prognostic Index (IPI) scores.

Treatment and outcome

The first-line treatment is presented in Table 3. Surgery consisted of lumpectomy and mastectomy with or without axillary dissection. Biopsy was not included. Of the 113 patients, surgery was performed on 69% of the patients. Systemic chemotherapy was administered to 97.3% of the patients, and 98.2% of regimens included anthracycline. Of the patients undergoing chemotherapy, 33.6% received rituximab. RT was performed on 30.1% of the patients, and the involved breast and regional lymph node was the most common RT field. Four patients received intrathecal chemotherapy as central nervous system (CNS) prophylaxis.

Table 3 First-line therapy

Therapy	N	%
S (n=77)		
Lumpectomy ± ALN dissection	37	48.7
Mastectomy ± ALN dissection	40	51.3
CT		
Yes	110	97.3
No	3	2.7
Rituximab use		
Yes	37	33.6
No	73	66.4
CT cycles		
<4	29	25.7
≥4	81	71.7
No	78	69.9
Yes	35	30.1
RT fields (n=35)		
Involved breast and regional LN	15	42.8
Regional LN	1	2.8
Involved breast only	11	31.4
Chest wall only	1	2.8
Chest wall and regional LN	1	2.8
Unknown	6	17.4
RT dose (n=35)		
Median	48.6 Gy	
Range	30–50 Gy	
30–40 Gy	9	25.7
41–50 Gy	15	42.8
Unknown	11	31.5

Abbreviations: S, surgery; ALN, axillary lymph node; CT, chemotherapy; RT, radiotherapy; LN, lymph node.

With a median follow-up at 39.2 months (range: 0.5–198 months), the median OS was 144 months, and the estimated 5-year and 10-year OS rates were 71.4%±5.0% and 55.7%±7.6%, respectively. The median PFS was not reached at the time of analysis, and the estimated 5-year and 10-year PFS rates were 58.8%±5.6% and 51.4%±6.9%, respectively. The median CSS was also not reached, with 5-year and 10-year CSS rates being 74.9%±4.6% and 62.9%±6.8%, respectively. The 5-year and 10-year LC rates were 75.6%±4.9% and 71.6%±6.0%, respectively. There were 39 progression events and 32 deaths during the

follow-up time, with 29 deaths attributed to the disease and treatment-related toxicity.

Following treatment, 21 of 113 patients (18.6%) developed local relapse. The most common local relapse site was the contralateral breast (n=9, 42.9% of the patients with locoregional recurrence). Seven patients developed ipsilateral relapse with or without ALN metastasis within 4 years. The other local relapse sites were as follows: bilateral breast with or without ALN metastasis (n=2), regional lymph node alone (n=2), and ipsilateral chest wall (n=1). RT substantially decreased the risk of ipsilateral progression (hazard ratio [HR] of RT:no RT =0.470; *P*=0.340).

Thirty-three patients (27.4%) developed distant metastasis following first-line therapy, with eight patients having more than two metastatic sites at first progression. The distant metastatic sites were as follows: distant lymph node (n=16), CNS (n=8), bone (n=9), lung (n=3), liver and spleen (n=2 for each site), orbit, maxillary sinus, bladder and uterine cervix (n=1 for each site), and sites unknown (n=4). Eight patients had CNS relapse (7.1% of all patients). Of the four patients who received intrathecal prophylaxis, none developed CNS relapse.

Prognostic factors

Univariate analysis of factors influencing OS, PFS, LC, and CSS is presented in Table 4. In univariate analysis, primary tumor size larger than 4 cm, less than four cycles of chemotherapy, and presentation of B symptoms were adverse prognostic factors for all outcome measures. The ECOG performance status, Ann Arbor staging, IPI, lactate

Table 4 Univariate analysis (log-rank test)

Variables	n	5y OS	*P*-value	5y PFS	*P*-value	5y LC	*P*-value	5y CSS	*P*-value
All patients	113	0.714		0.588		0.756		0.749	
Sex									
Male	5	0.400	0.594	0.267	0.254	0.533	0.300	0.400	0.476
Female	108	0.730		0.603		0.767		0.767	
LDH									
Normal	78	0.756	0.016	0.657	0.007	0.802	0.107	0.810	0.012
Elevated	35	0.599		0.405		0.637		0.599	
Age, years									
<60	60	0.725	0.719	0.593	0.650	0.753	0.499	0.749	0.474
≥60	53	0.688		0.586		0.767		0.745	
ECOG performance status									
0–1	102	0.755	<0.001	0.616	0.027	0.750	0.686	0.794	<0.001
2–4	11	0.364		0.284		0.875		0.364	
B symptoms									
Yes	105	0.742	<0.001	0.610	<0.001	0.773	0.019	0.780	<0.001
No	8	0.333		0.292		0.525		0.333	
Primary site									
Left breast	60	0.680	<0.001	0.582	0.072	0.795	0.675	0.756	<0.001
Right breast	48	0.805		0.614		0.713		0.805	
Bilateral	5	0.200		0.267		0.667		0.179	
Primary tumor size									
≤4 cm	59	0.767	0.008	0.713	0.001	0.851	0.009	0.838	0.004
>4 cm	54	0.642		0.432		0.661		0.642	
IPI									
Low	83	0.750	<0.001	0.608	0.011	0.767	0.765	0.795	<0.001
Low intermediate	21	0.749		0.529		0.680		0.749	
High intermediate	4	0.500		0.750				0.500	
High	5	0.200		0.267				0.200	
Ann Arbor staging									
PBL I_E	64	0.769	<0.001	0.589	<0.001	0.776	0.482	0.805	<0.001
PBL II_E	37	0.713		0.675		0.740		0.836	
PBL IV_E	3	0		0.000		0.500		0.000	
SBL	9	0.333		0.469		0.667		0.333	
OED/MED staging									
OED	104	0.738	0.016	0.597	0.389	0.749	0.211	0.776	0.010
MED	9	0.444		0.469				0.444	

(*Continued*)

Table 4 (*Continued*)

Variables	n	5y OS	*P*-value	5y PFS	*P*-value	5y LC	*P*-value	5y CSS	*P*-value
Local/extended staging									
Local	101	0.776	<0.001	0.616	0.015	0.763	0.798	0.817	<0.001
Extended	12	0.250		0.344		0.643		0.250	
Lumpectomy ± ALN dissection									
Yes	37	0.972	0.001	0.728	0.023	0.853	0.060	0.972	0.002
No	76	0.593		0.520		0.704		0.645	
Rituximab use									
Yes	37	0.788	0.059	0.826	0.004	0.918	0.010	0.867	0.038
No	73	0.674		0.479		0.688		0.696	
Local radiotherapy									
Yes	35	0.786	0.302	0.676	0.192	0.770	0.772	0.830	0.277
No	78	0.685		0.548		0.738		0.714	
Cycles of chemotherapy									
<4 cycles	29	0.434	<0.001	0.408	0.017	0.492	0.001	0.434	<0.001
≥4 cycles	81	0.818		0.651		0.840		0.865	

Abbreviations: OS, overall survival; PFS, progression-free survival; LC, local control; CSS, cause-specific survival; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; PBL, primary breast lymphoma; SBL, secondary breast lymphoma; OED, one extranodal disease; MED, multiple extranodal disease; ALN, axillary lymph node.

dehydrogenase (LDH) level, local/extended staging criteria, and lumpectomy with or without ALN dissection were prognostic factors for OS, PFS, and CSS. Rituximab was a favorable factor for PFS, LC, and CSS. Bilaterality and multiple extranodal diseases were adverse prognostic factors for both OS and CSS.

The multivariate analysis for all the treatment outcome measurements is presented in Table 5. The prognostic factors that retained statistical significance for OS and CSS were cycles of chemotherapy and local/extended staging criteria. Lumpectomy with or without ALN dissection and low to low-to-intermediate IPI were favorable factors for OS. Tumor size >4 cm and ECOG performance status 2–4 were adverse prognostic factors for CSS. For PFS, the prognostic factors included rituximab use, B symptoms, and tumor size. For LC, fewer than four cycles of chemotherapy, tumor size >4 cm, and nonuse of rituximab were adverse prognostic factors. The factors that lost statistical significance in multivariate analysis were Ann Arbor stage, OED/MED stage, primary site, and LDH level.

The univariate analysis of local group (PBL I_E and II_E) is presented in Table 6. Fewer than four cycles of chemotherapy significantly correlated with a worse 5-year OS rate, as is shown in Figure 2A (5-year OS: 59.5% vs 84.2%; *P*=0.015). The patients who received rituximab had a significantly superior 5-year PFS compared with patients without rituximab (5-year PFS: 84.3% vs 50.6%; *P*=0.007; Figure 2B). Patients with lumpectomy with or without ALN dissection had significantly better 5-year OS compared with the patients without lumpectomy with or without ALN dissection (5-year OS: 96.3% vs 68.9%; *P*=0.003; Figure 2C). However, we found that RT was not associated with significant improvements of OS and PFS, and these findings are presented in Figure 2D. The multivariate analysis is presented in Table 7. Lumpectomy with or without ALN dissection and more than four cycles of chemotherapy were favorable factors for OS. Tumor size >4 cm and nonuse of rituximab were adverse factors for PFS.

Discussion

Breast lymphoma is a distinct clinicopathological entity of NHL, with DLBCL being the most common subtype. The recommended treatment regimen based on many retrospective studies included limited surgery, anthracycline-based chemotherapy, and local RT for PBL. Despite the aggressive treatments being employed, the prognosis for PBL is poor, with 5-year OS rates only between 50% and 75%.[1,9] In our study, even though patients with PBL IV_E and SBL were included, the 5-year OS was 71.4%, which is not less than that for nodal DLBCL.[10,11] The better outcome may be attributed to the fact that the IPI scores of most our patients (92%) were <2, and 37 patients received rituximab in addition to the standard chemotherapy.

Because of the rarity of breast lymphoma, most of the studies have been retrospective, and there has been only one controlled randomized prospective study.[4] The retrospective studies of breast lymphoma, involving more than 100 patients, were from the International Extranodal Lymphoma Study Group (IELSG) (204 cases),[5] Japan (380 cases), and Oklahoma College of Medicine

Table 5 Multivariate analysis of prognostic factors for OS, PFS, LC, and CSS

Variables	Hazard ratio	95% CI	*P*-value
OS			
Local/extended staging			
Local	1		
Extended	3.919	1.462–10.499	0.007
Cycles of chemotherapy			
<4 cycles	1		
≥4 cycles	0.359	0.166–0.788	0.009
IPI			
Low to low intermediate	1		
High intermediate to high	1.674	1.077–2.601	0.022
Lumpectomy ± ALN dissection			
No	1		
Yes	0.183	0.053–0.631	0.007
PFS			
Tumor size			
≤4 cm	1		
>4 cm	2.664	1.310–5.418	0.007
B symptoms			
No	1		
Yes	5.274	1.805–15.410	0.002
Rituximab use			
Yes	1		
No	4.355	1.698–11.173	0.002
LC			
Cycles of chemotherapy			
<4 cycles	1		
≥4 cycles	0.325	0.131–0.805	0.015
Tumor size			
≤4 cm	1		
>4 cm	2.904	1.094–7.710	0.032
Rituximab use			
Yes	1		
No	4.593	1.059–19.930	0.042
CSS			
Tumor size			
≤4 cm	1		
>4 cm	3.194	1.265–8.065	0.014
ECOG performance status			
0–1	1		
2–4	3.228	1.273–8.187	0.014
Local/extended staging			
Local	1		
Extended	6.117	2.263–16.532	<0.001
Cycles of chemotherapy			
<4 cycles	1		
≥4 cycles	0.377	0.164–0.865	0.021

Abbreviations: OS, overall survival; PFS, progression-free survival; CI, confidence interval; IPI, International Prognostic Index; ALN, axillary lymph node; LC, local control; CSS, cause-specific survival; ECOG, Eastern Cooperative Oncology Group.

(465 cases),[12,13] all of which comprised multiple pathological subtypes in the prerituximab era. The conclusions were contradictory, and different treatments were recommended. Our study is a retrospective study but focuses solely on breast DLBCL.

Breast lymphoma is categorized as PBL or SBL. The definition of PBL was first proposed by Wiseman and Liao[3] in 1972, and it only included patients with lymphoma involvement of the breast with or without regional lymph node (ipsilateral axillary and supraclavicular lymph node region). Patients who did not fit this definition were considered stage SBL. This definition criterion has many limitations because it was developed from a retrospective study of just 31 patients, and only 16 of these were PBL. Yhim et al[6] attempted to divide breast lymphoma into OED and MED according to the number of extranodal organs involved. The study showed that instead of Ann Arbor traditional staging criteria, OED/MED criteria were an independent prognostic factor in multivariate analysis. Staging of bilateral extranodal disease is challenging for Ann Arbor staging criteria. One can group it into I_E (biclonal with bilateral disease), IV_E (monoclonal with hematogenous dissemination), or II_E (bilateral disease located on the same side of the diaphragm). In retrospective studies, the bilateral extranodal disease of paired organs such as adrenals and eyes always had a poor prognosis,[14,15] whereas the testes, lungs, and salivary glands had a relatively good prognosis.[16–18] The largest study of PBL classified it as PBL IV_E, whereas others staged it as PBL I_E or II_E.[5,19,20] In our study, according to Ann Arbor staging, we found that PBL IV_E (only bilateral breast involvement) had a similar prognosis to SBL, and this was significantly worse than PBL I_E and II_E. There was no significant statistical difference between PBL I_E and II_E. As there is no direct connection between the two breasts, the bilateral involvement may indicate hematogenous dissemination. For this reason, we redefined breast lymphoma as local group (PBL I_E and II_E) and extended group (PBL IV_E and SBL). Although the three staging criteria all showed statistically significant difference in the univariate analysis, only the local/extended staging criterion was an independent prognostic factor for OS and CSS in the multivariate analysis. Both the former criteria (Ann Arbor stage and OED/MED stage) lost significance in the multivariate analysis. Therefore, we recommend local/extended staging criteria as a better reflection of the difference of treatment outcome and prognosis.

The main symptom of breast lymphoma is a painless breast mass, which is indistinguishable from breast carcinoma; so the initial treatment for most patients remains surgery. Jennings et al[13] found that 156 out of 465 patients underwent mastectomy, which decreased OS in a marginal trend (P=0.055). The IELSG study revealed that radical mastectomy was an adverse factor for CSS in multivariate analysis (HR =2.4; P=0.03).[5] Strikingly, our results reveal

Table 6 Univariate analysis of local group (log-rank test)

Variables	n	5y OS	*P*-value	5y PFS	*P*-value	5y LC	*P*-value	5y CSS	*P*-value
All patients	101	0.706		0.616		0.763		0.817	
Sex									
Male	5	0.400	0.353	0.267	0.176	0.533	0.295	0.400	0.236
Female	96	0.797		0.634		0.776		0.841	
LDH									
Normal	73	0.797	0.051	0.680	0.008	0.808	0.066	0.855	0.041
Elevated	28	0.706		0.408		0.628		0.706	
Age, years									
<60	49	0.834	0.563	0.638	0.389	0.768	0.441	0.865	0.815
≥60	52	0.701		0.598		0.766		0.760	
ECOG performance status									
0–1	96	0.786	0.016	0.637	0.164	0.763	0.889	0.829	0.006
2–4	5	0.600		0.375		0.750		0.600	
B symptoms									
Yes	4	0.750	0.212	0.500	0.032	0.500	0.054	0.750	0.148
No	97	0.776		0.622		0.755		0.819	
Primary site									
Left breast	55	0.732	0.095	0.606	0.988	0.810	0.435	0.818	0.141
Right breast	46	0.820		0.617		0.703		0.820	
Primary tumor size									
≤4 cm	54	0.785	0.086	0.727	0.004	0.866	0.010	0.866	0.048
>4 cm	47	0.748		0.475		0.643		0.748	
IPI									
Low	81	0.770	0.067	0.624	0.938	0.766	0.918	0.817	0.040
Low intermediate	17	0.863		0.478		0.695		0.863	
High intermediate	1								
High	2	0.500						0.500	
Lumpectomy ± ALN dissection									
Yes	34	0.963	0.003	0.728	0.062	0.841	0.112	0.917	0.011
No	67	0.689		0.564		0.723		0.729	
Rituximab use									
Yes	35	0.795	0.204	0.843	0.007	0.915	0.014	0.883	0.138
No	63	0.760		0.506		0.699		0.786	
Local radiotherapy									
Yes	34	0.821	0.668	0.708	0.275	0.773	0.551	0.867	0.658
No	67	0.793		0.569		0.761		0.793	
Cycles of chemotherapy									
<4 cycles	23	0.595	0.015	0.499	0.120	0.561	0.007	0.595	0.017
≥4 cycles	75	0.842		0.658		0.830		0.894	

Abbreviations: OS, overall survival; PFS, progression-free survival; LC, local control; CSS, cause-specific survival; LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; ALN, axillary lymph node.

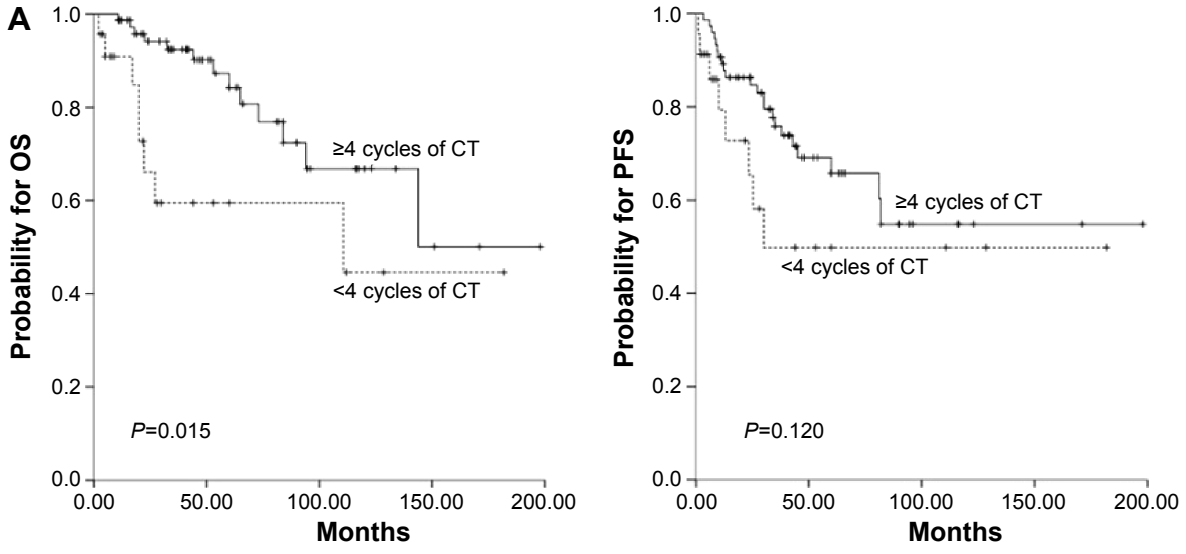

Figure 2 (*Continued*)

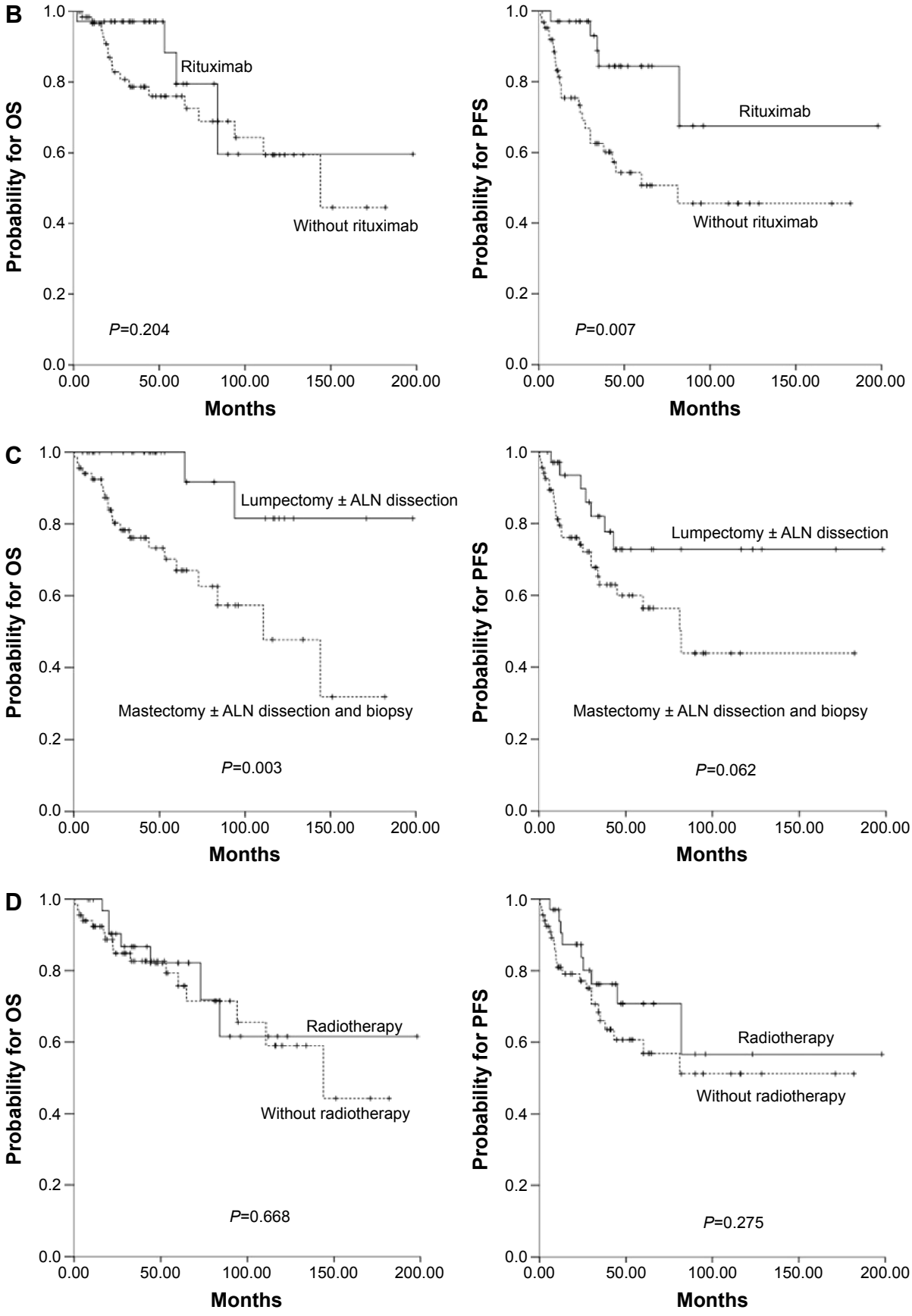

Figure 2 Survival curves for OS (left) and PFS (right) of each type of treatment in local group.
Notes: (**A**) Cycles of CT (≥4 or <4); (**B**) the use of rituximab; (**C**) different surgical interventions (lumpectomy ± ALN dissection or not); (**D**) the use of radiotherapy.
Abbreviations: OS, overall survival; PFS, progression-free survival; CT, chemotherapy; ALN, axillary lymph node.

Table 7 Multivariate analysis of local group

Variables	Hazard ratio	95% CI	*P*-value
OS			
Cycles of chemotherapy			
<4 cycles	1		
≥4 cycles	0.353	0.144–0.865	0.023
Lumpectomy ± ALN dissection			
No	1		
Yes	0.164	0.038–0.707	0.015
PFS			
Tumor size			
≤4 cm	1		
>4 cm	2.806	1.306–6.025	0.008
Rituximab use			
Yes	1		
No	3.311	1.264–8.673	0.015
LC			
Tumor size			
≤4 cm	1		
>4 cm	3.090	1.085–8.806	0.035
Rituximab use			
Yes	1		
No	4.477	1.024–19.570	0.046
CSS			
ECOG performance status			
0–1	1		
2–4	4.694	1.508–14.612	0.008
Cycles of chemotherapy			
<4 cycles	1		
≥4 cycles	0.333	0.127–0.875	0.026

Abbreviations: CI, confidence interval; OS, overall survival; ALN, axillary lymph node; PFS, progression-free survival; LC, local control; CSS, cause-specific survival; ECOG, Eastern Cooperative Oncology Group.

that lumpectomy with or without ALN dissection was associated with a better 5-year OS, PFS, and CSS in the univariate analysis compared with mastectomy with or without ALN dissection and biopsy. In multivariate analysis, lumpectomy with or without ALN dissection was a favorable factor for 5-year OS, both in the whole cohort and the local group. The reason for better prognosis of lumpectomy may be attributed to the decreasing of tumor load without the severe side effects of mastectomy. We recommend that surgical intervention should be limited to lumpectomy with or without ALN dissection, because this can also provide adequate specimens for pathological and immunohistological analysis.

The addition of rituximab to the CHOP regimen improved the survival of aggressive nodal DLBCL.[10,11] However, the role of rituximab in patients with breast lymphoma has never been investigated thoroughly. The three largest retrospective studies of PBL only included patients who had undergone older therapeutic regimens, during which rituximab was not in extensive clinical use. The results were disappointing.[5,12,13] In our study, 32.7% of the patients received rituximab and a standard chemotherapy regimen. In the univariate analysis, rituximab use was significantly associated with a superior 5-year PFS, LC, and CSS. It also remained significant for PFS and LC in multivariate analysis, for both the whole cohort and the local group. Another retrospective study including 31 patients also found that the patients with RCHOP use had a significantly better 5-year OS compared with patients undergoing the CHOP regimen alone (82.4% vs 67.5%; *P*=0.038).[19] Recently, a PBL and nodal DLBCL 1:3-matched retrospective study with RCHOP and involved field RT revealed that the OS was not significantly different between the two groups. The author suggested that the treatment outcomes of PBL were no longer inferior to those of nodal DLBCL in the rituximab era because it may change the poor prognosis of nongerminal center (GC) phenotype in PBL.[21] The only prospective study investigating the role of rituximab for PBL enrolled 32 patients. It was a single focus study on the R-CEOP-14 regimen. The 3-year EFS and OS were 75% and 63%, respectively, which was comparable to patients with CHOP regimen in the previous retrospective study.[22] However, the CNS relapse rate in this study was much lower than that in another prospective CHOP-21 regimen study by the same author (CNS relapse rate: 0% vs 11%).[4] The author attributed the difference to the intensive chemotherapy regimen CEOP-14. The CISL study also found no effect of rituximab on OS and PFS in patients with breast lymphoma. However, in this study, most patients with rituximab were at high risk, which may have masked its therapeutic effect.[6] Even though rituximab appears to have great success in aggressive nodal DLBCL, future prospective studies are needed to prove its role for patients with breast DLBCL.

There is no standard treatment regimen for breast DLBCL. Most studies recommend limited surgery, more than four cycles of systemic chemotherapy, and local RT as the standard therapy.[1,9] Our results revealed that more than four cycles of systemic chemotherapy were a favorable factor for survival. However, we have not found significant outcome improvements associated with local RT, which differs from some retrospective studies of PBL. Jennings et al[13] found that RT had a trend of improving OS, especially for stage I_E PBL (47.9% vs 37.1%; *P*=0.07). The IELSG study also found that RT improved OS significantly in multivariate analysis (HR =0.5; 95% CI =0.3–1.0; *P*=0.03).[5] The only controlled, randomized prospective study of PBL revealed that systemic chemotherapy plus local RT was associated with a significantly better 5-year OS and EFS compared with the

single-regimen group.[4] However, the previously mentioned studies all focused on different pathological subtypes and scarce use of rituximab. In our study, the most common local relapse site was the contralateral breast (42.9%). RT substantially decreased the risk of ipsilateral progression (HR RT: no RT =0.470; *P*=0.340). For this reason, further studies are needed to investigate the use of RT of the involved breast, or even the contralateral one, in the rituximab era.

The limitations of our study are as follows. First, it is a retrospective study with a relatively small number of patients, short follow-up time, heterogeneity of patients from our institution and literature, and the inability to control for all factors influencing clinical outcomes. IPI scores of most of our patients (92%) were ≤2, which may contribute to the good prognosis of our study subjects compared with subjects from other studies.[5,6] The fact that there are only a few cases of bilateral breast involvement in our study may bias the statistical analysis. Another important limitation is that molecular phenotypes were not available. It is widely accepted that DLBCL can be subdivided into germinal center B-cell (GCB) and nongerminal center B-cell (non-GCB) using gene expression profiling and immunohistochemistry. The non-GCB subtype has a much poorer prognosis than GCB.[23–25] The addition of rituximab to CHOP-like chemotherapy seemed to eliminate the prognostic difference between the non-GCB and GCB groups of nodal DLBCL.[26,27] Currently, only a few studies have investigated the subclassification of PB-DLBCL and have showed that the predominant subtype was nongerminal center phenotype.[28–30] Future studies are awaited on the prognosis of different molecular phenotypes, which may guide the treatment option.

Conclusion

This study reveals that the new local/extended staging criteria can reflect the difference of treatment outcomes and prognosis compared to traditional Ann Arbor staging. Extensive radical surgery may be harmful and may need to be avoided, hence our suggestion for limiting surgery to lumpectomy. The full course of anthracycline chemotherapy still appears to be an important treatment regimen for breast DLBCL. As there was improvement of PFS and LC in the rituximab group, both in the whole cohort and local group, this chemoimmunotherapy is recommended for breast DLBCL. Further prospective studies are warranted to investigate the role of RT in the rituximab era, using our new staging criteria.

Disclosure

The authors report no conflicts of interest in this work.

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