Primary Breast Double-hit Lymphoma Management and Outcomes: A Real-world Multicentre Experience

Tingting Zhang
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital https://orcid.org/0000-0001-8598-6769
Yuanfeng Zhang
Qindao University Medical College Affiliated Yantai Yuhuangding Hospital
Hairong Fei
The Affiliated Hospital of Qingdao University
Xue Shi
The Affiliated Hospital of Qingdao University
Liang Wang
Shengli Oilfield Central Hospital
Peijun Wang
Qingdao Center Hospital: Qingdao Center Medical Group
Jie Yu
Weihai Municipal Hospital
Sizhou Feng (doctor_szhfeng@sina.com)
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital https://orcid.org/0000-0001-5304-3301
Yuyan Shen
Chinese Academy of Medical Sciences Institute of Hematology and Blood Diseases Hospital

Primary research

Keywords: Primary breast lymphoma, Double-hit lymphoma, High-grade B-cell lymphomas, Therapy, Relapse, Prognosis

Posted Date: June 16th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-614958/v1

Abstract

Background: Primary breast double-hit lymphoma (PB-DHL) is a rare, highly aggressive malignancy that poses challenges regarding accurate diagnoses and selecting optimal treatment regimens.

Methods: We retrospectively reviewed cases of patients diagnosed with PB-DHL in six academic centres between June 2014 and June 2020 in China. Study-specific data were recorded, including treatment options, therapeutic evaluation, prognostic factors and relapse patterns, and the overall survival (OS) and progression-free survival (PFS) were evaluated.

Results: In total, 48 patients were enrolled, and the overall five-year OS and PFS rates were 41.7% (95% confidence interval [CI], 22.4–64.7%) and 37.5% (95% CI, 23.7–58.6%), respectively. Of the three treatment regimens, the five-year OS was higher in the dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R)/alternating with high-dose methotrexate and cytarabine (MA) group than in the DA-EPOCH-R or rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone alternating with cytarabine plus methotrexate (R-HyperCVAD) subgroups (57.1% vs. 38.9% vs. 31.3%; P = 0.016), as was the five-year PFS (50.0% vs. 38.9% vs. 25.0%; P = 0.038). Autologous stem cell transplantation (ASCT) prolonged the OS and PFS compared with non-ASCT patients (five-year OS: 72.2% vs. 23.3%; P < 0.001; five-year PFS: 72.2% vs. 16.7%, P < 0.001). Multivariate analysis identified tumour size, risk stratification, treatment with DA-EPOCH-R/MA, breast irradiation, and ASCT as significant prognostic factors.

Conclusions: DA-EPOCH-R/MA is a promising regimen for PB-DHL, and breast irradiation yields complementary benefits for relapse reduction. ASCT significantly decreased disease relapse, providing a potential curative PB-DHL intervention and justifying ASCT as first-line therapy for young patients. More effective treatment strategies for PB-DHL patients remain encouraging.

Introduction

Primary breast lymphoma (PBL) is a rare subtype of breast malignancy, accounting for 1% of non-Hodgkin lymphomas and less than 3% of extra-nodal lymphomas [1–3]. The definition of PBL was proposed by Wiseman and Liao [4] in 1972, in which breast tissue was infiltrated by lymphoma cells with or without regional lymph node involvement. More than 95% of all diagnosed breast lymphoid malignancies are expected to be B-cell non-Hodgkin lymphomas, such as follicular lymphoma and diffuse large B-cell lymphoma (DLBCL) [5, 6]. The typical presentation is a unilateral painless breast mass in middle-aged women [2, 7]. However, accumulating evidence indicates that the disease continues to increase for younger women with increasing incidence over the last four decades. Consequently, more attention is required [8]. Double-hit lymphoma is high-grade B-cell lymphoma (HGBL) with MYC and B-Cell Leukaemia/Lymphoma (BCL)2 or BCL6 gene translocations detected by fluorescence in situ hybridisation or standard cytogenetics according to the National Comprehensive Cancer Network guidelines [9], representing a rare subtype with typical resistance to conventional therapy [10].

There are no accepted guidelines for standardised primary breast double-hit lymphoma (PB-DHL) treatment strategies, although combined chemotherapy and radiotherapy are presently the first-line therapeutics [3, 11, 12]. Nonetheless, most studies still recommend the routine use of prophylactic central nervous system (CNS) therapy. However, the optimal approach for CNS prophylaxis remains unclear, and the CNS recurrence rate varies widely among studies [12, 13]. In light of the scarcity of data on Chinese patients, the disease is poorly understood, and no large studies have reported on PB-DHL treatment, making an accurate diagnosis and disease management a challenge [12]. The multicentre North-China collaboration was initiated to analyse the clinicopathologic features, explore effective curative options, and facilitate the development of effective prophylactic CNS strategies.

Patients And Methods

The clinical data of consecutive patients between June 2014 and June 2020 were derived from six hospital databases in China. All diagnostic materials were recategorised and met the 2016 World Health Organization's (WHO) classification of lymphoid neoplasms [14]. The patients' pathological sections were rechecked by two senior pathologists. The inclusion criteria were: breast was the definite primary site, patients with HGBL with MYC and BCL2 or BCL6 gene translocations, and patients diagnosed at 60 years old or younger. Patients were excluded if they had a primary site that was difficult to confirm, had breast involvement secondary to systemic disease, had a prior diagnosis of haematologic malignancy, were histologically confirmed as non-HGBL, or had incomplete or missing outcome data. Based on the PBL definition, patients with bilateral breast involvement at the first diagnosis were classified as stage IV in this study. The collected data included clinicopathological results, the Ann Arbor staging classification, treatment strategies, adverse effects, and survival. After PB-DHL was diagnosed, computed tomography or positron emission tomography scans were performed for staging purposes. The response was evaluated by the time of completion or the initial treatment interim based on the revised version of the International Working Group in 2007 [15]. Toxic effects and haematological and non-haematological toxicity profiles were evaluated and graded based on the WHO's Common Toxicity Criteria (http://ctep.cancer.gov, version 3.0). All patients were followed up until 1 July 2020. Informed consent was obtained from the patients or guardians of the study participants. All procedures followed the ethical standards of the Institutional Research Committee, and this study was approved by an appropriate ethics committee. The process of screening and identifying eligible patients is presented in Fig. 1.

Statistical analyses

The primary endpoints were overall survival (OS) and progression-free survival (PFS). The secondary endpoints were toxic effects and overall response rate (ORR), including complete remission (CR) and partial remission (PR). The baseline characteristics across the disease subgroups were compared using the Fisher's exact test. Survival was evaluated by Kaplan-Meier survival analysis, and any differences in survival were estimated using the log-rank test. Prognostic factors ($P < 0.1$) in univariate analysis were subjected to the Cox proportional-hazards model for multivariate survival analysis to determine the simultaneous impact of prognostic factors on survival. Interactions between prognostic factors were also assessed using the Cox proportional-hazards model. OS was determined from the on-study date until the death date. PFS was calculated from the on-study date to the date of the first progression, relapse, or death of any cause. All statistical analyses were performed using GraphPad Prism software version 8.0 (GraphPad Software Inc., San Diego, CA, USA) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set as a two-tailed P-value < 0.05.

Results

Baseline characteristics

The baseline characteristics of the 48 enrolled patients are presented in Table 1. Sixteen patients were treated with rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with cytarabine plus methotrexate (R-HyperCVAD); 18 were treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab (DA-EPOCH-R); and 14 were treated with dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab, alternating with high-dose of cytarabine plus methotrexate (DA-EPOCH-R/MA). The median age was 48.5 years (range, 24–60 years). A painless unilateral breast mass was present in 38 patients (79.2%), and the left breast was involved more often than the right (45.8% vs. 33.3%). The median tumour size was 2.6 cm (range, 0.9–11.5 cm); 17 patients had a tumour > 5 cm, and one had a tumour > 10 cm. There were 15 patients classified as Ann Arbor stage IE, 21 classified as IIE, and 12 classified as IV. Risk stratification was investigated based on age-adjusted International Prognostic Index scores; 27 patients fell into the low- and low-intermediate risk categories and 21 patients into the high-intermediate and high-risk categories. Based on the cell of origin, 29 patients (60.4 %) were of the non-germinal centre B-cell type. Chromosomal abnormalities were observed in 12 of 48 patients. Nineteen patients underwent autologous stem cell transplantation (ASCT) after the initial therapy. After a median follow-up of 27 months (range, 6.5–39 months), 28 patients died until the last follow-up day (1 January 2020). The causes of death were infection-related (n = 7), disease progression (n = 16), second malignancy (n = 2), and non-treatment-related (n = 2), and transplant-related (n = 1).

Table 1
Clinical characteristics of PB-DHL patients (n = 48)

Variable	DA-EPOCH-R/MA (n = 18)	DA-EPOCH-R (n = 14)	R-HyperCVAD (n = 16)	P value
Age				
≤ 50 years	10	11	6	0.160
50–60 years	4	7	10	
Laterality				
Right	3	5	4	0.810
Left	7	8	7	
Bilateral	3	5	6	
Tumour size				
< 5cm	8	11	11	0.930
≥ 5cm	6	7	5	
Cell of origin				
Non-GCB	10	8	11	0.214
GCB	4	10	5	
Chromosomal abnormality				
Absent	11	12	13	0.700
Present	3	6	3	
Ann Arbor Staging				
IE	4	6	3	0.832
IIE	7	7	7	
IV	3	5	6	
B symptoms				
Absent	4	8	6	0.652
Present	10	10	10	
LDH level				
Normal	9	11	7	0.544
Elevated	5	7	9	
Risk stratification				
L and L-I	9	9	9	0.665
H and H-I	5	9	7	
ASCT				
Yes	6	7	5	0.798
No	8	11	11	

PB-DHL, primary breast double-hit lymphoma; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with cytarabine plus methotrexate; DA-EPOCH-R, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. DA-EPOCH-R/MA, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, alternating with high-dose methotrexate and cytarabine; LDH, lactate dehydrogenase; GCB, germinal centre B-cell; L, low risk; L-I, low-intermediate risk; H-I, high-intermediate risk; H, high risk; ASCT, autologous stem cell transplantation.

Treatment and efficacy

The treatment options are summarised in Table 2, and the regimen doses are outlined in Table 3. Rituximab-containing chemical regimens were scheduled to be administered to all patients. R-HyperCVAD was used in 16 cases, DA-EPOCH-R in 18 cases, and DA-EPOCH-R/MA in 14 cases. In the R-HyperCVAD subgroup, 12 of 16 patients alternated A and B cycles, and four of 16 patients discontinued alternating A and B cycles in the last few courses owing to poor tolerance and severe bone marrow suppression. There were nine CR cases and two PR cases, and the ORR was 68.8%. In the DA-

EPOCH-R subgroup, five of 18 patients underwent the DA-EPOCH-R regimen for 4–6 treatment cycles, and the rest underwent 6–8 cycles. There were eight CR cases and three PR cases, and the ORR was 61.1%. In the DA-EPOCH-R/MA subgroup, 10 of 14 patients received 6–8 treatment cycles, and four received 4–6 cycles. There were seven CR cases and two PR cases, and the ORR was 64.3%.

Table 2
Summary of treatment

Treatment strategy	PB-DHL, N (%)
Breast irradiation	19 (39.6)
Sequence of breast irradiation	
Breast irradiation with concurrent chemotherapy	11 (22.9)
Breast irradiation following chemotherapy	20 (41.7)
Chemotherapy protocol	
R-HyperCVAD	16 (47.1)
DA-EPOCH-R/MA	18 (52.9)
DA-EPOCH-R	14 (29.2)
ASCT	19 (39.6)

PB-DHL, primary breast double-hit lymphoma; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with cytarabine plus methotrexate; DA-EPOCH-R, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. DA-EPOCH-R/MA, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, alternating with high-dose methotrexate and cytarabine; ASCT, autologous stem cell transplantation.

Table 3
Treatment dosage and days of administration

Drug	Dose	Days of administration
R-HyperCVAD regimen		
Cycle A		
Rituximab	375 mg/m^2	1
Cyclophosphamide	300 mg/m^2 every 12 h	2–4
Vincristine	1.4 mg/m^2	4, 11
Doxorubicin	50 mg/m^2	4
Dexamethasone	40 mg per day	1–4, 11–14
Cycle B		
Rituximab	375 mg/m^2	1
Methotrexate	1 g/m^2 continuous intravenous infusion for 24 h	2
Cytarabine	3 g/m^2 every 12 h	3, 4
DA-EPOCH-R regimen [a]		
Rituximab	375 mg/m^2	1
Etoposide	50 mg/m^2 continuous intravenous infusion for 24 h	2–5
Doxorubicin	10 mg/m^2 continuous intravenous infusion for 24 h	2–5
Vincristine	0.4 mg/m^2 continuous intravenous infusion for 24 h	2–5
Cyclophosphamide	750mg/m^2	6
Prednisone	60 mg/m^2	2–6
DA-EPOCH-R/MA regimen		
DA-EPOCH-R		
Rituximab	375 mg/m^2	1
Etoposide	50 mg/m^2 continuous intravenous infusion for 24 h	2–5
Doxorubicin	10 mg/m^2 continuous intravenous infusion for 24 h	2–5
Vincristine	0.4 mg/m^2 continuous intravenous infusion for 24 h	2–5
Cyclophosphamide	750 mg/m^2	6
Prednisone	60 mg/m^2	2–6
Alternating with MA		
Methotrexate	3 g/m^2	1
Cytarabine	2 g/m^2 every 12 h	2–3
Intrathecal prophylaxis		
Methotrexate	10 mg	
Dexamethasone	10 mg	

[a] The doses of etoposide, doxorubicin, and cyclophosphamide were adjusted 20% in the next cycle, depending on the nadir value of the absolute neutrophil count. G-CSF was administered on the 6th day of each cycle until the absolute neutrophil count achieved 0.5 x 10^9/L[23,35].

PB-DHL, primary breast double-hit lymphoma; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with cytarabine plus methotrexate; DA-EPOCH-R, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. DA-EPOCH-R/MA, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, alternating with high-dose methotrexate and cytarabine; MA, high-dose methotrexate and cytarabine.

Drug	Dose	Days of administration
Cytarabine	50 mg	

[a] The doses of etoposide, doxorubicin, and cyclophosphamide were adjusted 20% in the next cycle, depending on the nadir value of the absolute neutrophil count. G-CSF was administered on the 6th day of each cycle until the absolute neutrophil count achieved 0.5 x 10^9/L[23,35].

PB-DHL, primary breast double-hit lymphoma; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with cytarabine plus methotrexate; DA-EPOCH-R, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. DA-EPOCH-R/MA, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, alternating with high-dose methotrexate and cytarabine; MA, high-dose methotrexate and cytarabine.

Breast irradiation was performed in 31 of 48 patients (66.7%) with a median dose of 30 Gy. Twenty patients received breast irradiation following chemotherapy and 11 received breast irradiation with concurrent chemotherapy. The breast radiotherapy sequence did not affect ORR ($P > 0.05$). None of the patients underwent contralateral breast or cranial radiotherapy. Breast irradiation achieved good tumour control with better remission compared with non-irradiated patients (48.4% vs. 17.6%; $P = 0.035$).

ASCT was performed in 19 patients; there were 13 CR cases and six PR cases in the pre-transplantation setting. Among the 13 CR patients, nine achieved first complete remission (CR1) status, and four achieved second complete remission (CR2) before ASCT. Based on the efficacy data, patients receiving ASCT had more durable remission than patients not receiving ASCT (68.4% vs. 17.2%; $P < 0.001$). However, remission did not differ between CR1 and CR2 patients ($P > 0.05$). Notably, those receiving ASCT had a decreased relapse rate compared to those not receiving ASCT (10.5% vs. 48.3%; $P = 0.007$).

Toxic effects

Information on toxic effects was recorded and assessed based on the WHO's Common Toxicity Criteria; haematologic toxicity was the most common adverse effect. Grade 3/4 myelosuppression in the R-HyperCVAD subgroup was more severe than that in the DA-EPOCH-R and DA-EPOCH-R/MA subgroups (Fisher's exact test; 75% vs. 16.7% vs. 28.6%, respectively; $P = 0.001$). Other toxic effects, such as liver and kidney function damage, gastrointestinal reactions, haemorrhage, and cardiotoxicity, were mild and manageable, and the differences were insignificant. These side effects returned to normal after a short period of symptomatic and supportive treatment.

Survival analysis

The univariate and multivariate analyses of prognostic factors are outlined in Table 4. The median OS was 29.0 ± 7.2 months (95% confidence interval [CI], 14.9–43.1 months) and the median PFS was 25.0 ± 8.5 months (95% CI, 8.3–41.7 months). As shown in Fig. 2, the overall five-year OS and PFS were 41.7% (95% CI, 29.4–64.7%) and 37.5% (95% CI, 23.7–58.6%), respectively. The potentially significant factors from the univariate analysis ($P < 0.1$) included laterality, tumour size, the Ann Arbor staging classification, risk stratification, chemical regimens, breast radiotherapy, and ASCT and were included in the multivariate analysis. Multivariate analysis with the Cox proportional-hazards model identified tumour size (Fig. 3A, B), risk stratification (Fig. 3C, D), treatment with DA-EPOCH-R/MA (Fig. 4), breast radiotherapy (Fig. 5A, B), and ASCT (Fig. 5C, D) as independent prognostic factors.

Table 4
Univariate and multivariate analysis for OS and PFS in the study cohort.

Factors		Univariate Analysis						Multivariate Analysis					
		OS			PFS			OS			PFS		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Age	≤ 50 years	0.605	0.285–1.286	0.192	0.531	0.257–1.098	0.088						
	50–60 years												
Laterality	Left	0.277	0.113–0.680	0.005	0.270	0.113–0.645	0.003	2.366	0. 350-16.009	0.377	0.318	0.082–1.234	0.098
	Right	0.216	0.077-0.600	0.003	0.239	0.091–0.626	0.004	0.471	0.115–1.920	0.294	0.616	0.094–4.034	0.616
	Bilateral												
Tumor size	≥ 5cm	2.302	1.086–4.880	0.030	2.342	1.133–4.842	0.022	4.192	1.440-12.205	0.009	4.105	1.538–10.959	0.005
	< 5cm												
Cell of origin	GCB	1.343	0.618–2.919	0.456	1.463	0.683–3.132	0.328						
	Non-GCB												
Ann Arbor staging	IE	0.108	0.030–0.393	0.001	0.146	0.047–0.455	0.001	0. 634	0. 137-2.942	0.561	0.416	0. 097-1.795	0.240
	IIE	0.347	0.154–0.780	0.010	0.353	0.161–0.773	0.009	0.508	0.035–7.292	0.618	0.219	0.016–3.032	0.257
	IV												
B symptom	Absent	0.436	0.185–1.027	0.057	0.463	0.206–1.041	0.062						
	Present												
LDH level	Normal	0.729	0.346–1.535	0.405	0.864	0.419–1.784	0.693						
	Elevated												
Chromosomal abnormality	Present	1.075	0.453–2.549	0.869	1.109	0.473–2.601	0.811						
	Absent												
Risk stratification	L and L-I	0.413	0.194–0.880	0.022	0.423	0.204–0.874	0.020	0.180	0.040–0.810	0.026	0.175	0.042–0.730	0.017
	H and H-I												
Breast irradiation	Yes	0.344	0.156–0.757	0.008	0.365	0.173–0.770	0.008	0.261	0.088–0.770	0.015	0.288	0.108–0.768	0.013
	No												
Chemical regimen	R-DAEPOCH	0.392	0.163–0.939	0.036	0.423	0.181–0.989	0.047	0.105	0.031–0.350	< 0.001	0.134	0.044–0.402	< 0.001
	R-DAEPOCH/MA	0.268	0.095–0.755	0.013	0.341	0.130–0.896	0.029	0.180	0.055–0.595	0.005	0.251	0.083–0.674	0.015
	R-HyperCVAD												
ASCT	Yes	0.184	0.069–0.487	0.001	0.208	0.084–0.513	0.001	0.103	0.025–0.424	0.002	0.082	0.020–0.336	0.001
	No												

OS, overall survival; PFS, progression-free survival; HR, hazard ratio; 95% CI, 95% confidence interval; GCB, germinal centre B-cell; LDH, lactate dehydrogenase; L, low-risk; L-I, low-intermediate risk; H, high-risk; H-I, high-intermediate risk; DA-EPOCH-R, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. DA-EPOCH-R/MA, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, alternating with high-dose methotrexate and cytarabine; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with cytarabine plus methotrexate; ASCT, autologous stem cell transplantation.

Disease relapse

Disease relapse occurred in 16 patients; three patients without breast irradiation had contralateral breast relapse, six had CNS relapse, and seven had lymph node relapse. Among ASCT patients, one PR and one CR2 patient developed breast relapse before ASCT and lymph node relapse in the post-ASCT setting, respectively. All patients received the prophylactic CNS strategy; 26 received intrathecal chemoprophylaxis 6–8 times, and 22 received intrathecal chemoprophylaxis 4–6 times. Kaplan-Meier survival analysis showed that the intrathecal chemoprophylaxis time did not affect long-term survival.

The CNS recurrence rate was 11.1% in patients who received the MA-containing regimen and 20% in patients who did not ($P > 0.05$). In contrast, CNS did not progress in any patient following ASCT, but 20.7% of patients who did not receive ASCT had progression. Therefore, ASCT was associated with a significantly decreased risk of early CNS progression ($P = 0.039$).

Contralateral breast tissue was the second most involved extranodal site. In this cohort, three patients without breast irradiation experienced contralateral breast relapse, including one with contralateral breast relapse occurring during salvage therapy. Tumour size and axillary lymph nodes were not related to the recurrence of the contralateral breast in this cohort.

Discussion

PB-DHL is rare but deserves discussion because its biological characteristics are quite different from those of the more typical B-cell lymphoma [4]. PB-DHL typically presents in the 50s or 60s as a painless, solitary, palpable breast lump, indistinguishable from breast cancer [5]. Previous studies identified that PB-DHL predominantly occurs in women, commonly perimenopausal women. However, some reports have included male patients [16, 17]. In this study, all cases were women, consistent with other reports.

Immunochemotherapy combined with breast radiotherapy is the currently recognised first-line therapy for PBL [2], and surgical treatment offers little benefit to long-term prognosis [6, 13]. Therefore, in this study, surgery was only employed for excisional biopsies rather than for treatment. The role of radiotherapy was clarified in clinical trials during the pre-rituximab era [18], but the benefits of radiotherapy for PB-DHL patients receiving rituximab-containing regimens remains controversial. The research indicates that immunochemotherapy alone was insufficient to achieve excellent control of local tumours, and the combination of radiotherapy and chemotherapy had the strongest benefit before ASCT. Breast irradiation also contributed to durable remission with improved OS and PFS, justifying its consideration for high-risk young patients. Relevant observations have also highlighted the beneficial effects of radiotherapy in PBL patients treated with rituximab-based regimens, which compensated for the deficiency of immunochemotherapy in the local control of residual disease or recurrence [19]. A median breast irradiation dose of 30 Gy is widely recommended [2, 3, 6].

Because there are no standard guidelines for PB-DHL [20], making an accurate diagnosis and choosing optimal regimens is challenging [21, 22]. This research showed that the efficacy benefits of the three treatment schemes were not significant, but the DA-EPOCH-R/MA group had the best survival outcomes, followed by the DA-EPOCH-R group. Although the R-HyperCVAD remission rate was slightly higher than that of the other two groups, severe bone marrow suppression might lead to treatment interruption, hampering its application. Kieron et al. [23] conducted a prospective Phase II study of DA-EPOCH-R in aggressive B-cell lymphoma with MYC rearrangement and emphasised that the DA-EPOCH-R regimen produced durable remission and could be applied for treating aggressive B-cell lymphoma. The Spanish PETHEMA group [24] conducted a Phase II study of DA-EPOCH-R in untreated patients with poor prognosis for large B-cell lymphoma and stressed that DA-EPOCH-R showed an excellent outcome with a tolerable toxicity profile in high-risk large B-cell lymphoma patients. We also found that the DA-EPOCH-R group had a lower myelosuppression risk than the R-HyperCVAD, suggesting that DA-EPOCH-R was relatively safe and well-tolerated. The DA-EPOCH-R/MA regimen, based on DA-EPOCH-R, initially exhibited satisfactory five-year OS and PFS outcomes, indicating that high-dose methotrexate and cytarabine can consolidate the efficacy of DA-EPOCH-R to some extent.

CNS relapse is a common and devastating complication of PB-DHL, and the CNS relapse rate is much higher than that of PBL-DLBCL [25]. To date, the underlying CNS progression mechanism is unknown, and prophylactic strategies have become an integral part of current treatment protocols [26]. CNS relapse mainly involves the brain parenchyma, and leptomeningeal involvement is rare. Thus, intrathecal chemoprophylaxis, which does not adequately penetrate the brain parenchyma, insufficiently prevents parenchymal CNS recurrence [27, 28]. Holte et al. [29] conducted a study of 156 eligible patients with aggressive B-cell lymphomas and implemented a high-dose of cytarabine plus methotrexate regimen (MA regimen) to reduce the incidence of CNS-related events. The results showed a satisfactory CNS relapse rate of 4.5%, which is much lower than that in other published reports. Considering that high-dose methotrexate and cytarabine can penetrate the blood-brain barrier, the risk of CNS progression could be further reduced [30] [31]. The MA regimen was expected to reduce the risk of CNS progression, but, in this series, the MA regimen was not superior for CNS prophylaxis in PB-DHL. As a result, the prevention of CNS progression depending on chemotherapy alone was insufficient. In contrast, CNS progression was not detected after ASCT, and more durable remission was achieved in patients who received ASCT than in those who did not ($P < 0.001$). Considering the fatal outcome of CNS relapse and the limited efficacy of high-dose chemotherapy, ASCT is strongly recommended to reduce the CNS relapse rate and prolong survival.

The contralateral breast tissue is the second most common recurrence site, except in the CNS [17]. This study's results indicated that breast radiotherapy was better for local control. The survival and relapse rates of patients who received concurrent chemotherapy or post-chemotherapy breast irradiation did not differ. Thus, the breast irradiation sequence of breast irradiation and chemotherapy remains ambiguous in this study. Breast

irradiation produced durable remission, justifying its consideration in treating young patients with PB-DHL. If contralateral breast relapse occurred, the clinical outcomes were dismal with unsatisfactory salvage therapies [12]. Therefore, for high-risk young patients, the first-line treatment of PB-DHL patients could be to apply ASCT, despite ASCT not being the first-line treatment for lymphoma.

Since high-intensive chemotherapy alone is insufficient to induce long-term disease control, ASCT could be the most appropriate treatment method if CR or PR is attained, especially for high-risk young patients. ASCT may overcome the poor prognostic implications of this kind of aggressive disease subtype, and there is no doubt that young patients with excellent performance statuses and few comorbidities are the best candidates for ASCT. In this multicentre study, patients who received ASCT had significantly superior outcomes compared to those who did not, suggesting that ASCT greatly reduced the disease progression risk. Similarly, Kim et al. [32] explored a high dose of chemotherapy combined with ASCT for high-risk DLBCL patients and found that ASCT yielded superior OS and PFS. The three-year OS in the ASCT group was 85.0% and was 75.8% in the non-ASCT group (P = 0.038). Further, the three-year PFS was also better in the ASCT group (76.6% vs. 63.3%; P = 0.007). To date, the ASCT status has not been challenged by high-intensity chemotherapy or novel targeted agents, and it remains an appropriate choice to abrogate the negative prognostic impact of PB-DHL [33]. High-dose chemotherapy followed by ASCT in an upfront setting currently remains the second-line treatment for DLBCL [34], and ASCT is the only feasible therapy offering a cure. Due to the limited efficacy of conventional chemotherapy, dynamic dose-adjusted chemotherapy supported by ASCT should be administered to young PB-DBL patients [35] [36]. The ASCT results showed excellent efficacy and durable remission among patients with CR in a pre-transplantation setting, which is an important initial step for developing ASCT as a first-line treatment strategy for highly aggressive PB-DHL. To further assess the long-term prognosis, a larger-scale investigation that includes more patients receiving ASCT is should be conducted in the future.

Limitations

Major limitations of this study include the relatively small sample size and retrospective nature. The sample size may have limited our ability to detect significant differences. Additionally, follow-up for the evaluation of other complications, including secondary malignancies, was short. Nevertheless, considering the rarity of PB-DHL and the lack of a previously published cohort study, the results of this study still have great guiding significance.

Conclusion

This multicentre North-China collaboration provides insights into effective therapeutic management and failure patterns of PB-DHL. DA-EPOCH-R/MA was a promising regimen for PB-DHL, and breast irradiation yielded complementary benefits for relapse reduction. Notably, ASCT significantly decreased disease relapse and provided a potential curative PB-DHL intervention, justifying ASCT as a first-line therapy for young patients. The exploration of more effective treatment strategies for patients with PB-DHL remains promising.

Declarations

Acknowledgements

We acknowledge the Affiliated Hospital of Qingdao University, Qingdao Central Hospital, Yuhuangding Hospital of Yantai, Linyi Central Hospital, Weihai Municipal Hospital. This work was supported by the Youth Program of National Natural Science Foundation of China (No. 81900182).

Author contributions

Sizhou Feng and Yuyan Shen conceived and designed the research study. Yuanfeng Zhang and Hairong Fei performed the research. Tingting Zhang wrote the first draft of the manuscript and analysed the data. Liang Wang and Xue Shi provided input on data analysis and critically revised the manuscript. Peijun Wang and Jie Yu supervised the research. The final version of this manuscript was approved by all authors.

Funding

This work was supported by the Youth Program of National Natural Science Foundation of China (No. 81900182).

Availability of data and materials

All relevant data generated or analyzed was included in this article and its additional files.

Ethics approval and consent to participate

Data collection was approved by the Ethics Committee of Chinese Academy of Hematology and Blood Diseases Hospital.

Consent for publication

Not applicable.

Conflicts of interest

All authors declared no competing interests.

References

1. Cheah CY, Campbell BA, Seymour JF. Primary breast lymphoma. Cancer treatment reviews. 2014;40(8):900–8.
2. Jia Y, Sun C, Liu Z, Wang W, Zhou X. Primary breast diffuse large B-cell lymphoma: a population-based study from 1975 to 2014. Oncotarget. 2018;9(3):3956–67.
3. Shao YB, Sun XF, He YN, Liu CJ, Liu H. Clinicopathological features of thirty patients with primary breast lymphoma and review of the literature. Medical oncology (Northwood, London, England). 2015;32(2):448.
4. Wiseman C, Liao KT. Primary lymphoma of the breast. Cancer. 1972;29(6):1705–12.
5. Avilés A, Castañeda C, Neri N, Cleto S, Nambo MJ. Rituximab and dose dense chemotherapy in primary breast lymphoma. Haematologica. 2007;92(8):1147–8.
6. Zhao S, Zhang QY, Ma WJ, Zhang MH, Sun WZ, Li HB, et al. Analysis of 31 cases of primary breast lymphoma: the effect of nodal involvement and microvascular density. Clinical lymphoma myeloma leukemia. 2011;11(1):33–7.
7. Wadhwa A, Senebouttarath K. Primary lymphoma of the breast: A case series. Radiology case reports. 2018;13(4):815–21.
8. Thomas A, Link BK, Altekruse S, Romitti PA, Schroeder MC. Primary Breast Lymphoma in the United States: 1975–2013. Journal of the National Cancer Institute. 2017;109(6).
9. Sesques P, Johnson NA. Approach to the diagnosis and treatment of high-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements. Blood. 2017;129(3):280–8.
10. Davies A. Double-hit lymphoma: So what? Hematol Oncol. 2019;37(Suppl 1):19–23.
11. Eyre TA. Another disappointment in treating relapsed, refractory high-risk aggressive B-cell lymphomas. Br J Haematol. 2020;188(2):202–4.
12. Franco Pérez F, Lavernia J, Aguiar-Bujanda D, Miramón J, Gumá J, Álvarez R, et al. Primary Breast Lymphoma: Analysis of 55 Cases of the Spanish Lymphoma Oncology Group. Clinical lymphoma, myeloma & leukemia. 2017;17(3):186 – 91.
13. Zhang N, Cao C, Zhu Y, Liu P, Liu L, Lu K, et al. Primary breast diffuse large B-cell lymphoma in the era of rituximab. OncoTargets therapy. 2016;9:6093–7.
14. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127(20):2375–90.
15. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2007;25(5):579–86.
16. Wei ZL, Huang DP. [Advances in Diagnosis and Treatment of Primary Breast Lymphoma -Review]. Zhongguo shi yan xue ye xue za zhi. 2017;25(2):604–7.
17. Ludmir EB, Milgrom SA, Pinnix CC, Gunther JR, Westin J, Oki Y, et al. Primary breast diffuse large B-cell lymphoma: treatment strategies and patterns of failure < sup/>. Leukemia & lymphoma. 2018;59(12):2896–903.
18. Vitolo U, Seymour JF, Martelli M, Illerhaus G, Illidge T, Zucca E, et al. Extranodal diffuse large B-cell lymphoma (DLBCL) and primary mediastinal B-cell lymphoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of oncology: official journal of the European Society for Medical Oncology. 2016;27(suppl 5):v91–102.
19. Yahalom J, Illidge T, Specht L, Hoppe RT, Li YX, Tsang R, et al. Modern radiation therapy for extranodal lymphomas: field and dose guidelines from the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys. 2015;92(1):11–31.
20. Rosenthal A, Younes A. High grade B-cell lymphoma with rearrangements of MYC and BCL2 and/or BCL6: Double hit and triple hit lymphomas and double expressing lymphoma. Blood reviews. 2017;31(2):37–42.
21. Ma Q, Chang Y, Li L, Li X, Wang X, Wu J, et al. Efficacy of dose-adjusted EPOCH plus rituximab/R-CHOP regimens and the prognosis analysis in patients with MYC, BCL2/BCL6 gene copy number gain lymphoma and double-hit lymphoma: results from a single institution retrospective clinical study. Cancer management research. 2019;11:1363–72.
22. Pejša V, Prka Ž, Lucijanić M, Mitrović Z, Piršić M, Jakšić O, et al. Rituximab with dose-adjusted EPOCH as first-line treatment in patients with highly aggressive diffuse large B-cell lymphoma and autologous stem cell transplantation in selected patients. Croatian Med J. 2017;58(1):40–8.
23. Dunleavy K, Fanale MA, Abramson JS, Noy A, Caimi PF, Pittaluga S, et al. Dose-adjusted EPOCH-R (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, and rituximab) in untreated aggressive diffuse large B-cell lymphoma with MYC rearrangement: a prospective, multicentre, single-arm phase 2 study. The Lancet Haematology. 2018;5(12):e609-e17.
24. Purroy N, Bergua J, Gallur L, Prieto J, Lopez LA, Sancho JM, et al. Long-term follow-up of dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) in untreated patients with poor prognosis large B-cell lymphoma. A phase II study conducted by the Spanish PETHEMA Group. Br J Haematol. 2015;169(2):188–98.
25. Savage KJ, Slack GW, Mottok A, Sehn LH, Villa D, Kansara R, et al. Impact of dual expression of MYC and BCL2 by immunohistochemistry on the risk of CNS relapse in DLBCL. Blood. 2016;127(18):2182–8.
26. Savage KJ. Secondary CNS relapse in diffuse large B-cell lymphoma: defining high-risk patients and optimization of prophylaxis strategies. Hematology American Society of Hematology Education Program. 2017;2017(1):578–86.

27. Gleeson M, Counsell N, Cunningham D, Chadwick N, Lawrie A, Hawkes EA, et al. Central nervous system relapse of diffuse large B-cell lymphoma in the rituximab era: results of the UK NCRI R-CHOP-14 versus 21 trial. Annals of oncology: official journal of the European Society for Medical Oncology. 2017;28(10):2511–6.
28. Kansara R. Central Nervous System Prophylaxis Strategies in Diffuse Large B Cell Lymphoma. Curr Treat Options Oncol. 2018;19(11):52.
29. Holte H, Leppä S, Björkholm M, Fluge O, Jyrkkiö S, Delabie J, et al. Dose-densified chemoimmunotherapy followed by systemic central nervous system prophylaxis for younger high-risk diffuse large B-cell/follicular grade 3 lymphoma patients: results of a phase II Nordic Lymphoma Group study. Annals of oncology: official journal of the European Society for Medical Oncology. 2013;24(5):1385–92.
30. Hosein PJ, Maragulia JC, Salzberg MP, Press OW, Habermann TM, Vose JM, et al. A multicentre study of primary breast diffuse large B-cell lymphoma in the rituximab era. Br J Haematol. 2014;165(3):358–63.
31. Siegal T, Goldschmidt N. CNS prophylaxis in diffuse large B-cell lymphoma: if, when, how and for whom? Blood reviews. 2012;26(3):97–106.
32. Kim YR, Kim SJ, Cheong JW, Yang DH, Lee H, Eom HS, et al. The different roles of molecular classification according to upfront autologous stem cell transplantation in advanced-stage diffuse large B cell lymphoma patients with elevated serum lactate dehydrogenase. Annals of hematology. 2016;95(9):1491–501.
33. Herrera AF, Rodig SJ, Song JY, Kim Y, Griffin GK, Yang D, et al. Outcomes after Allogeneic Stem Cell Transplantation in Patients with Double-Hit and Double-Expressor Lymphoma. Biology of blood and marrow transplantation: journal of the American Society for Blood and Marrow Transplantation. 2018;24(3):514–20.
34. Xiao Z, Li J, Miao K. Allogeneic Hematopoietic Stem Cell Transplantation in Relapsed/ Refractory Diffuse Large B Cell Lymphoma. Curr Stem Cell Res Therapy. 2017;12(1):14–8.
35. Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. Blood. 2002;99(8):2685–93.
36. Hu K, Gao JJ, Li QH, Tian L, Wan W, Zhao W, et al. Autologous hematopoietic stem cell transplantation as first-line consolidation therapy can improve the prognosis of diffuse large B-cell lymphoma with high expression of MYC protein. Kaohsiung J Med Sci. 2019;35(7):425–31.

Figures

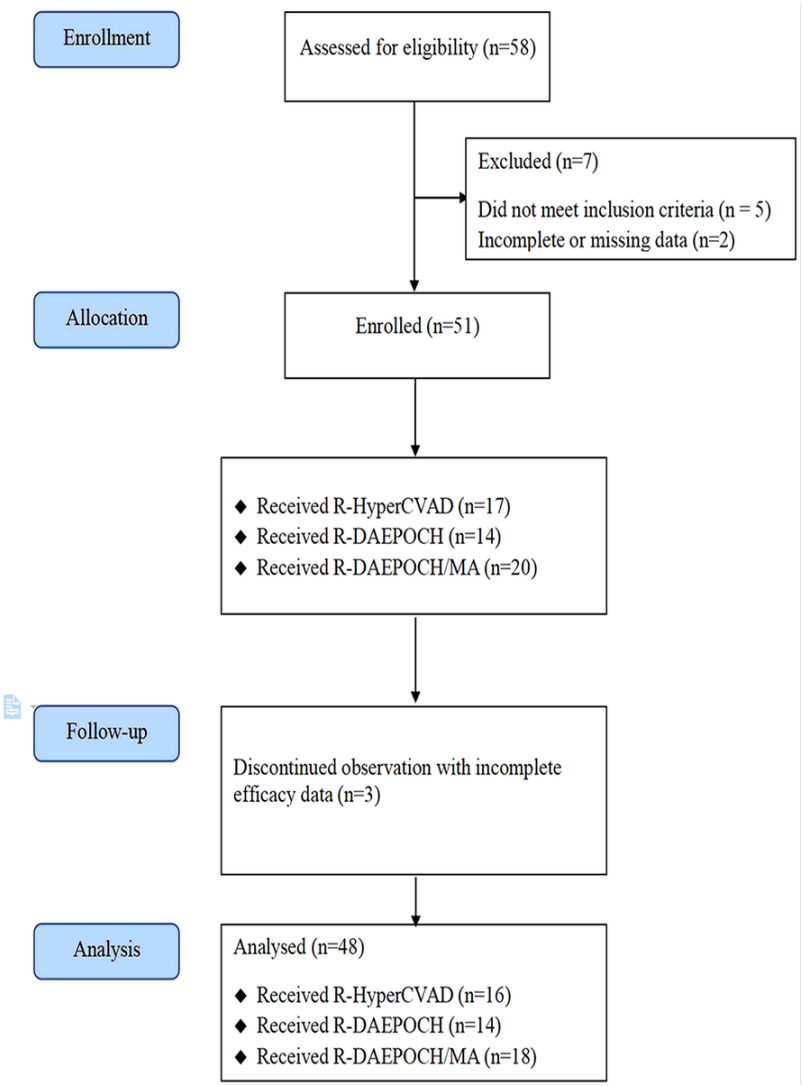

Figure 1

Flow diagram to identify patients with PB-DHL. PB-DHL, primary breast double-hit lymphoma; R-HyperCVAD, rituximab, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with cytarabine plus methotrexate. DA-EPOCH-R, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin. DA-EPOCH-R/MA, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, alternating with high-dose methotrexate and cytarabine.

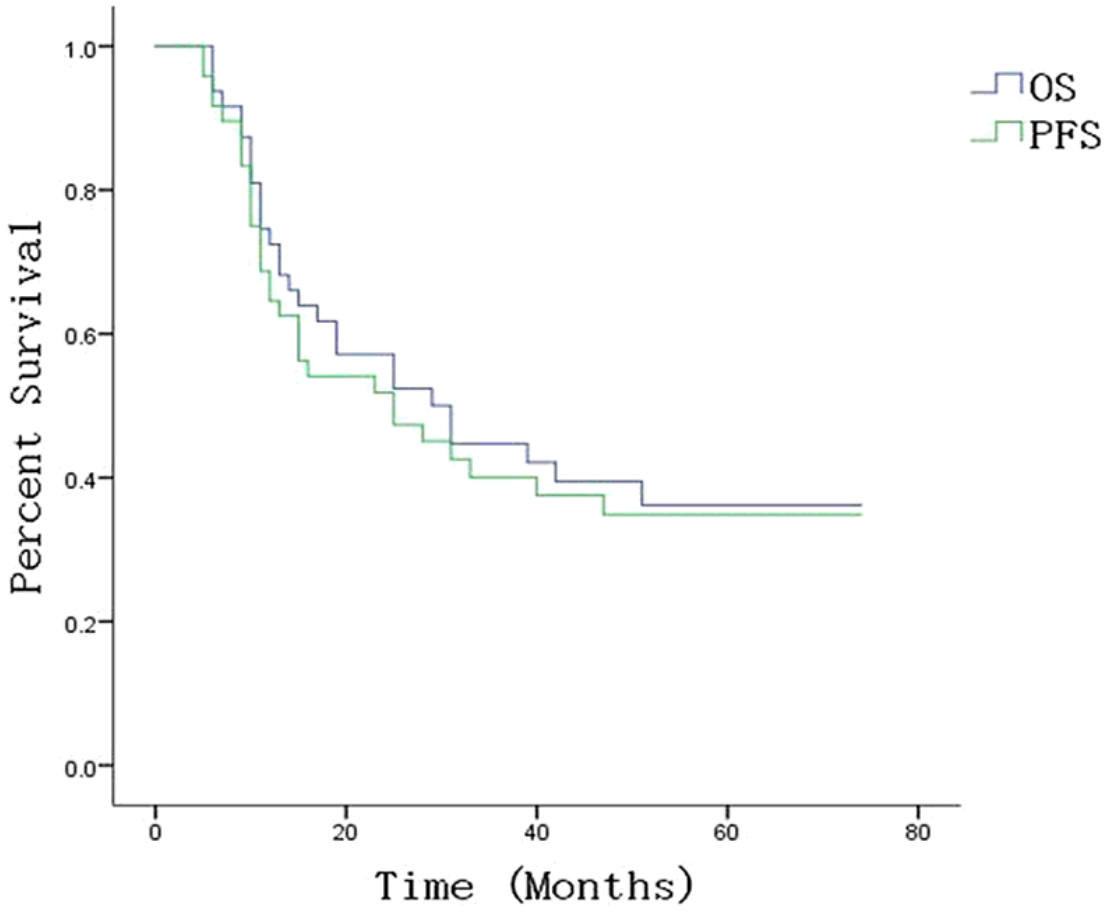

Figure 2

The Kaplan-Meier overall (A) and progression-free (B) survival curves.

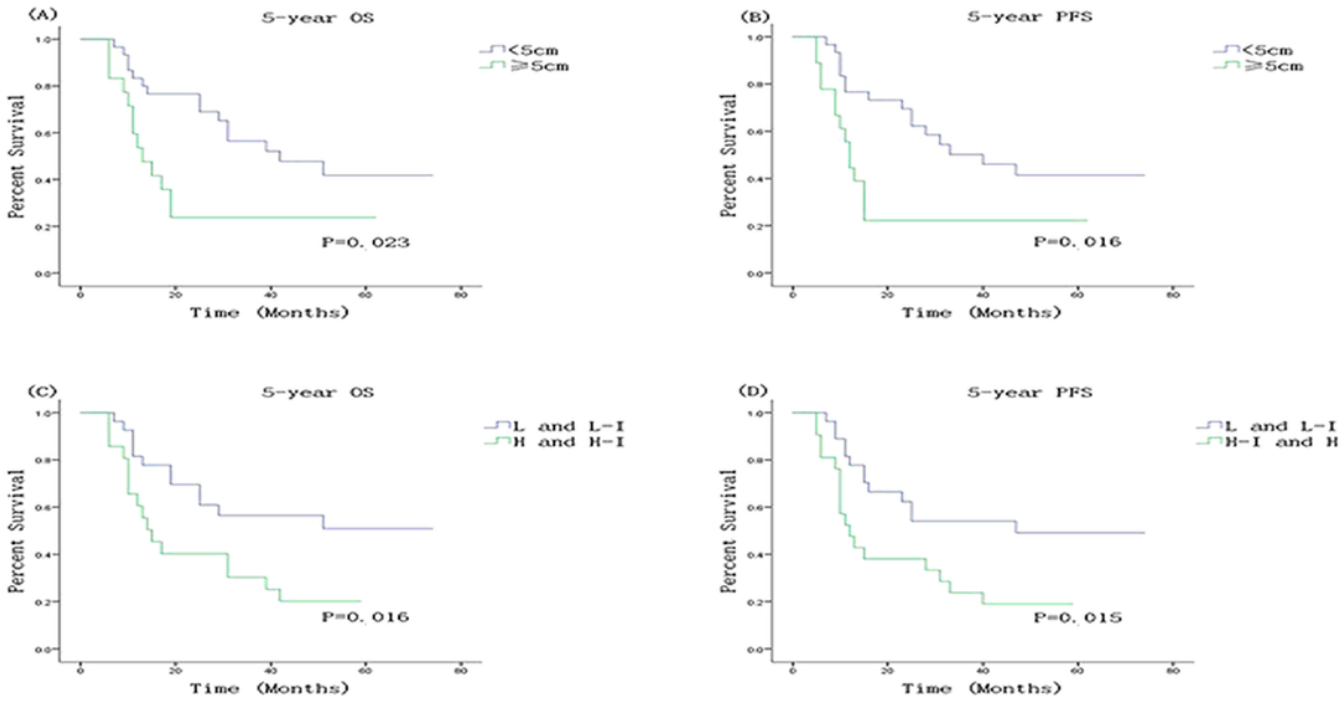

Figure 3

Overall and progression-free survival comparisons for patients with different tumour sizes (A, B) and risk stratifications (C, D).

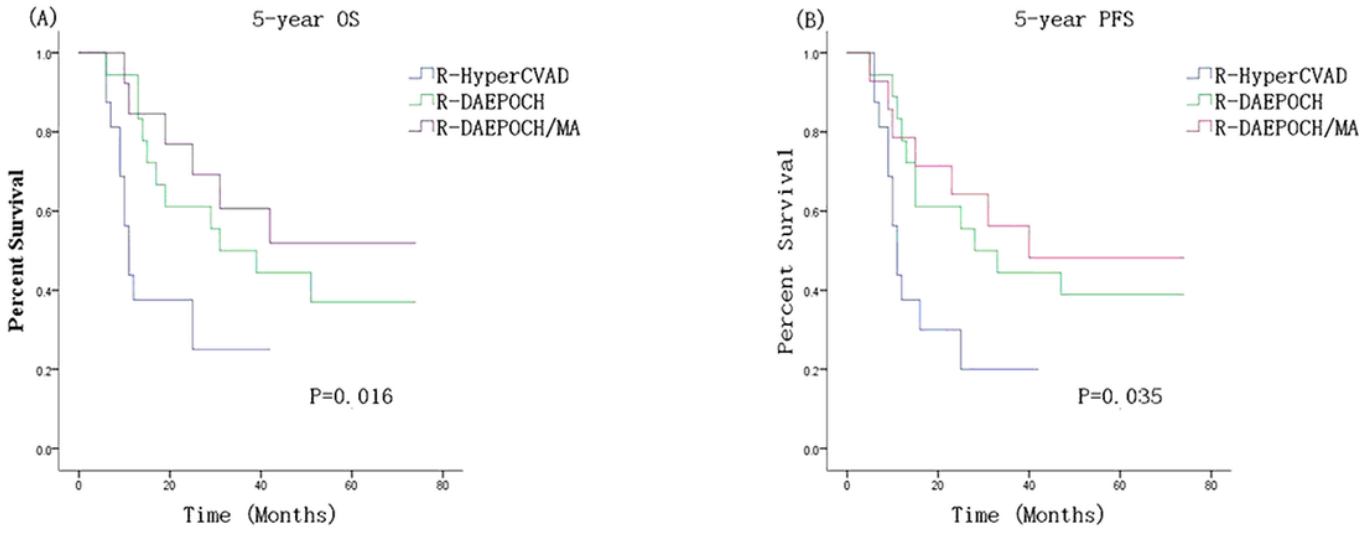

Figure 4

Overall (A) and progression-free (B) survival comparisons among the three treatment regimens.

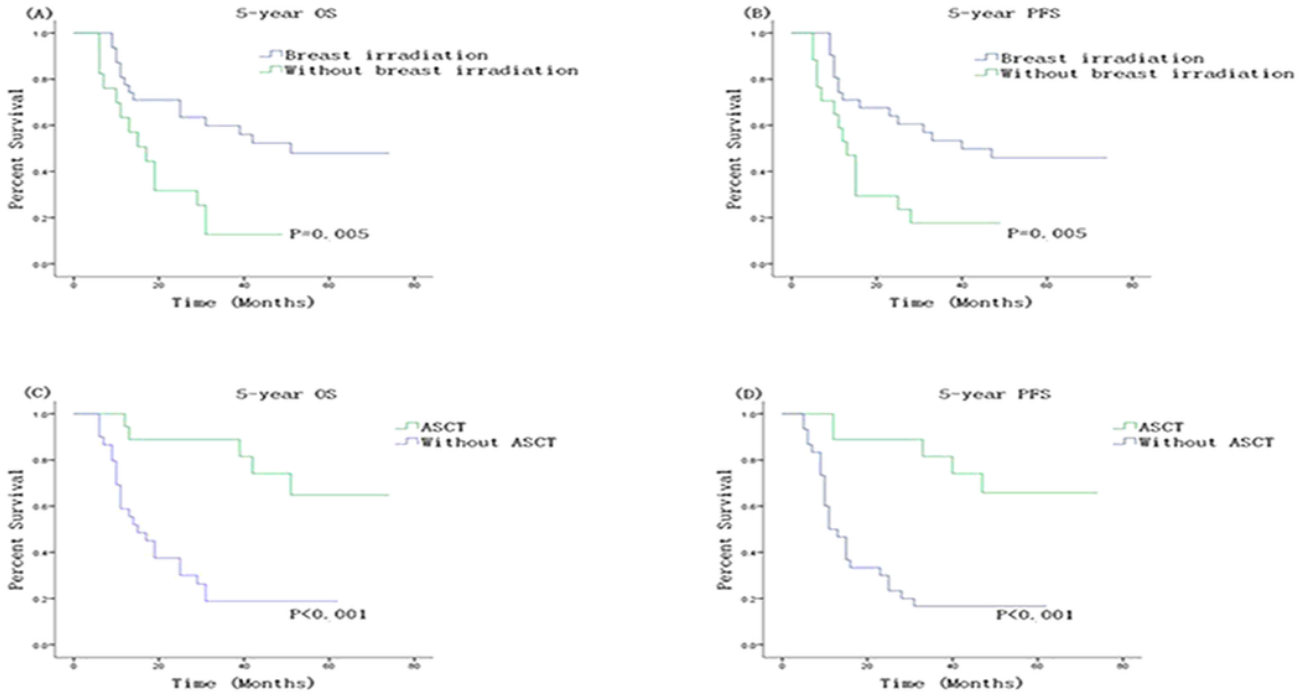

Figure 5

Overall and progression-free survival comparisons for breast radiotherapy (A, B) and autologous stem cell transplantation (C, D).