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Role of local treatment in primary breast B-cell non-Hodgkin's lymphoma: a propensity score matching-based analysis from SEER database

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Abstract. – OBJECTIVE: Primary breast lymphoma (PBL) has been defined as disease localized to breast with or without ipsilateral axillary nodal involvement. Primary breast B-cell non-Hodgkin's lymphoma is rare to be diagnosed clinically. The role of surgery and radiotherapy (RT) as local treatment is unclear. The aim of this study was to evaluate the prognostic factors and investigate the effect of local treatment in patients with primary breast B-cell non-Hodgkin's lymphoma.

MATERIALS AND METHODS: We identified patients with primary breast B-cell non-Hodgkin's lymphoma diagnosed between 1998 and 2015 in the Surveillance, Epidemiology, and End Results (SEER) database. Propensity score matching (PSM) was performed to reduce possible bias between groups. The overall survival (OS) and disease-specific survival (DSS) were calculated using the Kaplan-Meier method. Multivariate Cox regression analysis was used to identify independent prognostic factors.

RESULTS: Altogether 956 patients with primary breast B-cell non-Hodgkin's lymphoma were included. Most patients were white women over the age of 60. The most common histological type was diffuse large B cell lymphoma (DLBCL), and most patients present with stage I disease. Furthermore, old age (>60 years), DLBCL histology and stage IIE disease were the statistically significant factors associated with worse OS and DSS. Surgery did not improve survival of patients, and surgery combined with RT did not achieve a better prognosis than RT alone. RT was associated with better survival in patients with stage IE DLBCL, but patients with stage IE MZL and FL and stage IIE primary breast B-cell non-Hodgkin's lymphoma could not benefit from RT.

CONCLUSIONS: In local treatment, surgery offered no survival benefit for patients with primary breast B-cell non-Hodgkin's lymphoma, while RT is an effective choice because it can improve both OS and DSS in the stage IE DLBCL subgroup.

Key Words:
Primary breast B-cell non-Hodgkin's lymphoma, Surgery, Radiotherapy, Prognosis, Survival.

Introduction

The breast lymphoma is classified as primary breast lymphoma (PBL) and secondary breast lymphoma (SBL). PBL represents 2.2% of extranodal lymphomas and constitutes 0.04% to 0.5% of malignant breast neoplasms[1-4]. This may be because the mammary gland has less lymphoid tissue than the intestine and lungs[5]. The diagnostic criteria for PBL were proposed by Weisman and Liao[6] in 1972 and is still the standard definition of the disease. This definition restricts the stage of PBL to be stage IE (without ipsilateral axillary lymphadenopathy) and stage IIE (lymphoma limited to the breast and axillary lymph nodes). The typical clinical manifestation of PBL is painless breast mass. The predominant histology is B-cell non-Hodgkin's lymphoma[7,8].

Unlike other non-Hodgkin's lymphoma, PBL has a higher local recurrence rate (23%-62%), which may reflect poor local disease control[7,9]. Patients with recurrence of PBL have bad prognosis. But local treatment selection for PBL varied in the literature. The importance of surgery and radiotherapy (RT) are both reported. Dao et al[10] suggested the primary treatment for PBL should be the RT plus local excision. Moreover, Sun et al[11] showed lumpectomy with or without axillary lymphnode (ALN) dissection was a favorable factor for overall survival (OS). However, the retrospective study[12] found that mastectomy provides no survival benefit for patients with PBL. In addition, several studies[9,12] revealed that when treatment involved mastectomy, all-cause mortality and disease-specific mortality rates

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were higher, cause-specific survival (CSS) was lower. The role of local treatment remains unknown. The survival rates of PBL vary widely in the literature. Studies with larger sample size for clinical information and survival data are required.

In this study, we extracted data from the Surveillance, Epidemiology, and End Results (SEER) database to break the limitation of sample size. The primary aims of this retrospective analysis were to evaluate the prognostic factors and investigate the effect of local treatment in patients with primary breast B-cell non-Hodgkin's lymphoma through conventional methods and propensity score matching (PSM) approach.

Materials and Methods

Patient Selection and Data Collection

SEER Program database (National Cancer Institute) using the SEER*Stat software program (version 8.3.2; http://seer.cancer.gov/seerstat) was used under a data user agreement. No ethics committee review approval was needed because the data from SEER database were de-identified and from a third party. Patients diagnosed with primary breast B-cell non-Hodgkin's lymphoma were identified in the SEER database. We included patients diagnosed between 1998 and 2015. Only patients with primary breast B-cell non-Hodgkin's lymphoma as their only cancer were included. We chose site record as breast (C50.0-50.9). The stage, extension disease and pathology should be clearly recorded in order to divide the patient into primary breast B-cell non-Hodgkin's lymphoma. Patients with no information on surgery and disease laterality, bilateral disease diagnosed as stages I and II, with unknown race and the cause of death were excluded. The flow diagram for concrete steps to patient selection is shown in Figure 1. The datasets analyzed during the current study are available in SEER database (https://seer.cancer.gov/).

Statistical Analysis

The overall survival (OS) was defined as the number of months from the date of diagnosis to the date of death from any cause. Disease-specific survival (DSS) was defined as the number of months from the date of diagnosis to the date of death from primary breast B-cell non-Hodgkin's lymphoma. Covariates balance between two groups was examined by Chi-square test. To reduce differences between groups, we used one-to-one PSM analysis. A logistic regression model was established to calculate the propensity score based on the following covariates: sex, race, age, histology, tumor laterality, stage, surgery, RT and chemotherapy. The score-matched cohorts were used in the subsequent analyses.

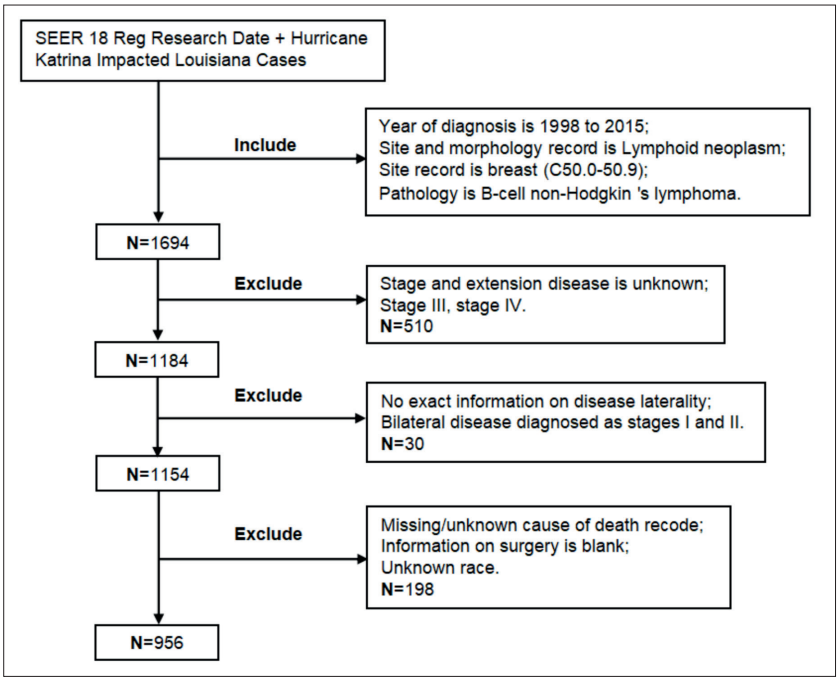

Figure 1. Patient enrollment and exclusion process of in the SEER database.

Survival curves for the study cohort were calculated using the Kaplan-Meier method. Multivariable Cox proportional hazards models were used to determine the influence of relative factors of known or potential prognostic value on survival. All data were analyzed using SPSS (version 25.0; SPSS, IBM, Armonk, NY, USA). All tests were two-tailed, and statistical significance was set at $p < 0.05$.

Results

Patient Characteristics

The study included 956 patients with primary breast B-cell non-Hodgkin's lymphoma. Table I summarized the clinical features of primary breast B-cell non-Hodgkin's lymphoma in detail. Sex, race and age were the basic information about the patient. The patients with primary breast B-cell non-Hodgkin lymphoma were predominantly white women older than 60 years old. DLBCL was the most observed histologic type in 956 (45.3%) patients. 76.9% of patients had stage I disease. Right- and left-sided primary breast B-cell non-Hodgkin's lymphomas were uniformly distributed.

Table I. Baseline characteristics of the included patients (n = 956).

Characteristic	NO.	%
Sex		
Female	926	96.9
Male	30	3.1
Race		
White	780	81.6
Black	89	9.3
Others	87	9.1
Age at diagnosis (years)		
Median	67	
< = 60	328	34.3
> 60	628	65.7
Histology		
DLBCL	433	45.3
MZL	237	24.8
FL	151	15.8
Others (B cell NHL)	135	14.1
Laterality		
Right	476	49.8
Left	480	50.2
Stage		
I	735	76.9
II	221	23.1

DLBCL, diffuse large B cell lymphoma; MZL, marginal zone lymphoma; FL, follicular lymphoma; NHL, none-Hodgkin lymphoma.

Multivariate Cox Regression Analysis

The median follow-up time was 55 months (range, 0-215 months). We evaluated all the patients without taking other factors into account. Sex, race, age, histology, tumor laterality and stage were evaluated for survival risk. Multivariate COX regression model was built to assess the clinicopathological factors related to survival. Age, histology, stage and sex were the independent prognostic factors in primary breast B-cell non-Hodgkin's lymphoma (Table II). The old age (>60 years) was the statistically significant factor associated with worse OS (HR = 4.48, $p < 0.001$) and DSS (HR = 4.29, $p < 0.001$). Other B cell NHL, including MZL, FL and others, were favorable factors for prognosis. Stage IIE disease was independent prognostic factors for worse OS (HR = 1.43, $p = 0.006$) and DSS (HR = 2.01, $p < 0.001$). Male sex was an independent unfavorable predictor for DSS (HR = 2.08, $p = 0.047$).

Effect of Surgery and RT on Prognosis

As shown in **Supplementary Figure 1**, before PSM, no survival difference could be observed between patients with and without surgery (OS: $p = 0.322$; DSS: $p = 0.302$). We conducted a PSM analysis to determine the effect of surgery on the prognosis. 336 pairs of patients were 1:1 matched in the two groups and no significant differences in clinical characteristics were found (**Supplementary Table I**). Our study revealed that surgery didn't improve both OS ($p = 0.380$) and DSS ($p = 0.724$) of patients with primary breast B-cell non-Hodgkin's lymphoma (Figure 2A, B).

In addition, we compared treatment results of surgery plus RT with RT alone. Before PSM, surgery combined with RT did not significantly prolong both OS ($p = 0.106$) and DSS ($p = 0.173$) of patients when compared with RT alone (**Supplementary Figure 2**). PSM was performed to balance baseline characteristics between these two groups. After PSM, a total of 140 patients who underwent surgery combined with RT were matched with 140 patients who only received RT (1:1) (**Supplementary Table II**). We found that addition of surgery did not achieve better prognosis (OS: $p = 0.868$; DSS: $p = 0.495$) (Figure 2C, D).

Before PSM, the RT group was superior to the no RT group in both OS ($p < 0.001$) and DSS ($p < 0.001$) (**Supplementary Figure 3**). PSM method was conducted to reduce the differences of variables between groups. After PSM, 394 pairs of patients were 1:1 matched in the two groups

Table II. Multivariate Cox regression analysis of prognostic factors for OS and DSS (n = 956).

Prognostic factors	OS			DSS		
	HR	*p*-value	95% CI	HR	*p*-value	95% CI
Sex						
Female	Reference			Reference		
Male		NS	0.59-2.09	2.08	0.047	1.01-4.28
Race						
White	Reference			Reference		
Black		NS	0.48-1.24		NS	0.44-1.62
Others		NS	0.64-1.36		NS	0.67-1.75
Age						
<=60	Reference			Reference		
>60	4.48	< 0.001	3.21-6.23	4.29	< 0.001	3.09-5.97
Histology						
DLBCL	Reference			Reference		
MZL	0.51	< 0.001	0.37-0.70	0.24	< 0.001	0.13-0.42
FL	0.45	< 0.001	0.31-0.65	0.24	< 0.001	0.13-0.45
Others (B cell NHL)	0.70	0.035	0.50-0.97	0.40	0.001	0.23-0.69
Laterality						
Right	Reference			Reference		
Left		NS	0.86-1.35		NS	0.76-1.45
Stage						
I	Reference			Reference		
II	1.43	0.006	1.11-1.85	2.01	< 0.001	1.43-2.82

The $p < 0.05$ was considered statistically significant. OS, overall survival; DSS, disease-specific survival; HR, hazard ratio; CI, confidence interval;NS, not significant; NHL, none-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma;MZL, marginal zone lymphoma; FL, follicular lymphoma.

and all baseline characteristics were well balanced (Table III). Kaplan-Meier survival curves suggested that RT benefited the survival of patients (OS: $p = 0.002$; DSS: $p = 0.001$) (Figure 3A, B). Subgroup analysis stratified by stage and histology were further performed in the matched population. The results showed RT could improve both OS ($p = 0.004$) and DSS ($p = 0.010$) in stage IE subgroup (**Supplementary Figure 4**). And OS in stage IE subgroup without RT was similar to that in stage IIE subgroup (Figure 3C, D). Furthermore, Kaplan-Meier curves indicated RT was related to better OS ($p = 0.015$) and DSS ($p = 0.015$) in patients with stage IE DLBCL (Figure 4A-B), but patients with stage IE MZL and FL and stage IIE primary breast B-cell non-Hodgkin's lymphoma could not benefit from RT (**Supplementary Figure 4**, 4C-F).

Discussion

The presentation of non-Hodgkin's lymphoma (NHL) in breast is rare (0.38% to 0.7% in NHL)[13]. The diagnostic criteria of PBL include: (1) adequate pathologic evaluation is obtained; (2) both mammary tissue and lymphomatous infiltrate in close association; 3. no evidence of concurrent widespread disease other than ipsilateral axillary lymphadenopathy; 4. no previous extramammary lymphoma[6]. The most common pathological type of PBL is B-cell non-Hodgkin's lymphoma.

This study used a large population-based database to identify the clinical features, prognostic factors and local treatment of primary breast B-cell non-Hodgkin's lymphoma. The effects of local treatments on prognosis were deeply analyzed. To our knowledge, this is the first population-based study using PSM analysis to evaluate the role of surgery and RT in treating primary breast B-cell non-Hodgkin's lymphoma. Our study indicated that surgery was found not to have a significant association with survival in primary breast B-cell non-Hodgkin's lymphoma, the main beneficiaries of RT were patients with stage IE DLBCL.

Although hematological tumors are not usually considered hormone-dependent cancers, most epidemiological studies have shown that lym-

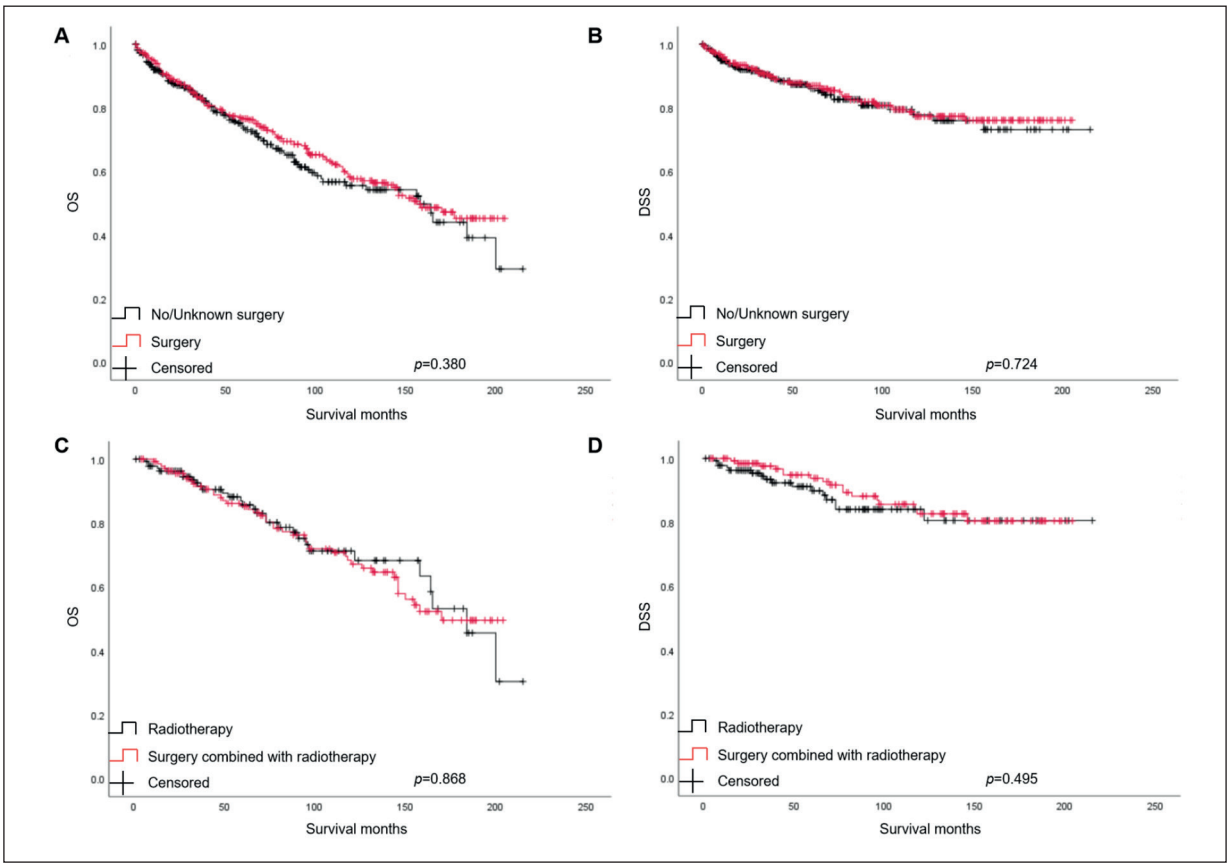

Figure 2. Kaplan-Meier curves for OS and DSS after PSM. Overall survival (**A**) and disease- specific survival (**B**) difference between surgery and no surgery groups, after 1:1 Propensity Score Matching analysis. Overall survival (**C**) and disease-specific survival (**D**) difference between surgery combined with radiotherapy and radiotherapy groups, after 1:1 Propensity Score Matching analysis. The $p < 0.05$ was considered statistically significant. OS, overall survival; DSS, disease-specific survival; PSM, propensity score matching.

phoma has gender differences in incidence and prognosis. Our analysis revealed that primary breast B-cell non-Hodgkin's lymphoma was predominantly female, white people and diagnosed around 67 years old. The pathogenesis of the sex hormones and the ERβ expression on B lymphocytes within breast cancer tissue could be the explanations of the sexual inclination[14]. A large prospective study[15] showed women who received estrogen hormone replacement therapy after menopause had a 29% higher risk of developing NHL than those who didn't. Additionally, our study also found DLBCL was the most common histological type, and most patients present with stage I disease, which was consistent with previous studies[8,12,16,17].

PBL is rare clinically, accounting for 0.04% to 0.5% of malignant breast neoplasms, which limits its investigation. Besides, most available studies are retrospective studies of small samples. Therefore, there is still no standard treatment. Systemic chemotherapy based on anthracycline is considered to be the mainstay for the treatment and can significantly improve the PFS and OS of PBL patients. PBL is characterized by extranodal recurrence, and mammary gland is the most common site of recurrence. More importantly, several studies[7,9] have shown the main reason for poor prognosis and treatment failure of PBL is recurrence. G. Ryan et al[9] found that median OS following progression after first-line therapy in PBL patients was only 1.0 year, and the overall 5-year and 10-year survival rate of patients with relapsed disease were 20% and 11%, respectively. However, treatment selection for PBL using surgery and/or RT varies in the literature. Currently, the choice of local treatment remains controversial.

Since the main symptom of PBL is a painless breast mass, and PBL lacks specific imag-

Table III. Characteristics among no radiotherapy (no RT) and radiotherapy (RT) in patients before and after propensity score matching.

Characteristics	Before PSM analysis			After PSM analysis		
	No RT (n = 515)	RT (n = 441)	*p*-value	No RT (n = 394)	RT (n = 394)	*p*-value
Sex						
Female	499	427		384	382	
Male	16	14	0.952	10	12	0.665
Race						
White	427	353		320	315	
Black	42	47		32	42	
Others	46	41	0.392	42	37	0.426
Age						
< = 60	164	164		143	147	
> 60	351	277	0.083	251	247	0.768
Histology						
DLBCL	215	218		191	176	
MZL	124	113		101	109	
FL	88	63		59	63	
Others (B cell NHL)	88	47	0.009	43	46	0.765
Laterality						
Right	257	219		193	192	
Left	258	222	0.940	201	202	0.943
Stage						
I	370	365		309	318	
II	145	76	< 0.001	85	76	0.427
Chemotherapy						
None/Unknown	286	204		193	203	
Yes	229	237	0.004	201	191	0.476
Surgery						
None/Unknown	321	294		256	262	
Yes	194	147	0.163	138	132	0.652

The $p < 0.05$ was considered statistically significant. PSM, propensity score matching; DLBCL, diffuse large B cell lymphoma; MZL, marginal zone lymphoma; FL, follicular lymphoma; NHL, none-Hodgkin lymphoma.

ing manifestations, it is indistinguishable from breast carcinoma, so most patients receive surgery. Several authors consider that breast tumor resection can improve the prognosis of PBL patients by reducing tumor load. Dao et al[10] found patients with lumpectomy with or without axillary lymph node (ALN) dissection had a better 5-year OS than those without lumpectomy with or without ALN dissection (5-year OS: 96.3% *vs*. 68.9%; $p = 0.003$). But most authors advocate that radical surgery is not recommended. Uesato et al[17] revealed for PBL patients only receiving surgical treatment, the overall 5-year survival rate was 40.5% in stage IE and 20.5% in stage IIE. Moreover, Jennings et al[12] indicated mastectomy offered no survival benefit or protection from recurrence, and all-cause mortality and disease-specific mortality rates were higher when treatment involved surgery. Additionally, Ryan et al[9] showed that patients who underwent radical mastectomy had significantly worse CSS (HR = 2.4; $p = 0.03$). The reason for poorer survival of radical mastectomy may be attributed to the delayed initiation of systemic chemotherapy.

Similarly, in our study, after PSM, Kaplan-Meier survival curves demonstrated that the surgery was not a favorable factor to prognosis, and surgery combined with RT did not achieve a better prognosis than RT alone. Meanwhile, we found that proportion of patients receiving surgery has been declining since 2005 (Figure 5). This may be due to the growing recognition that surgery offered no survival benefit for patients with primary breast B-cell non-Hodgkin's lymphoma. Therefore, surgery is limited to obtaining enough specimens for histopathological diagnosis.

Studies have shown that RT can improve the survival rate by consolidating the curative effect of systematic treatment and strengthening local control of the disease. Jeanneret-Sozzi et al[18]

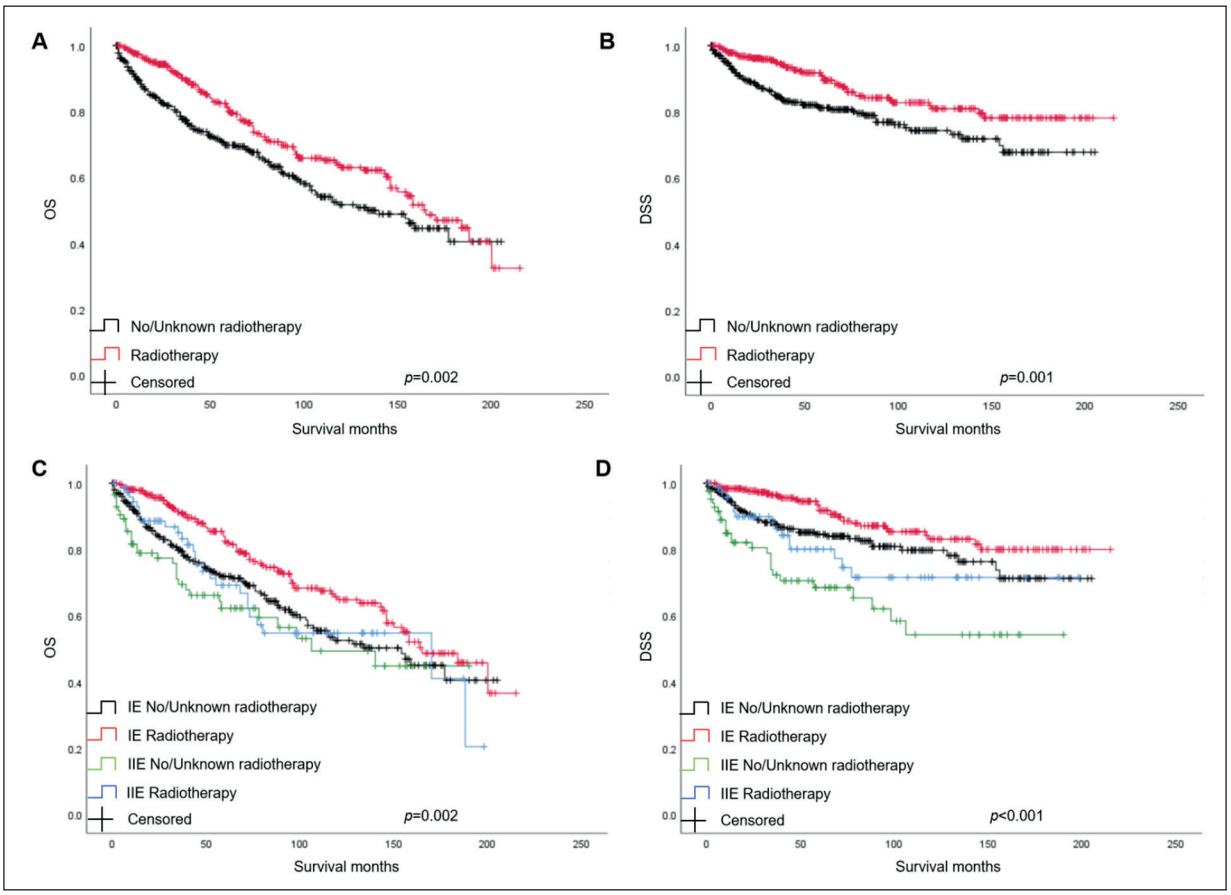

Figure 3. Kaplan-Meier curves for OS and DSS after PSM. Overall survival (**A**) and disease- specific survival (**B**) difference between radiotherapy and no radiotherapy groups, after 1:1 Propensity Score Matching analysis. Kaplan–Meier curves of overall (**C**) and disease-specific (**D**) survival of patients with primary breast B-cell non-Hodgkin's lymphoma by radiotherapy and stage, after 1:1 Propensity Score Matching analysis. The $p < 0.05$ was considered statistically significant. OS, overall survival; DSS, disease-specific survival; PSM, propensity score matching.

reported RT to the breast or to the thoracic wall improved local control of PBL patients, with 95% *vs*. 76% 5-year local control rate ($p = 0.02$). The IELSG study[9] also found that RT greatly reduced the risk of ipsilateral progression (HR RT: no RT = 0.4, $p = 0.29$) and improved OS (HR = 0.5; 95% CI = 0.3 - 1.0; $p = 0.03$). Additionally, Lin et al[19] revealed that the 5-year OS rate for RT and non-RT groups was 80.3% and 57.6%, respectively ($p = 0.038$); the 5-year relapse-free survival rate was 59.6% and 27.2% ($p = 0.004$) and the local-relapse-free survival rate was 100% and 63.5%, respectively ($p = 0.015$). However, the population of the above studies is small, and the baseline characteristics are unbalanced.

In our study, we used PSM to reduce possible bias between groups, and found RT was significantly associated with improved OS and DSS after PSM. This initiated us to think about the meaning of RT: Do all patients require RT? PBL patients under the definition of Wiseman–Liao are confined to 'early stage' and the 5-year survival rates differed significantly (78%-83% in stage IE, 20%-57% in stage IIE)[20]. And different histological types of PBL have different prognosis. Thus, we further investigated the role of RT in patients with different stages and histological types. In our analysis, RT was associated with better prognosis in stage IE patients. But it did not result in survival benefits for patients with stage IIE primary breast B-cell non-Hodgkin's lymphoma. This may be due to the relatively large range and dose of RT in stage IIE patients compared with stage IE patients, which increases the damage to normal tissues and the incidence of short-term and long-term complications associated with RT. Importantly, RT was significantly related to better OS and DSS in patients with stage IE DLBCL, but patients with

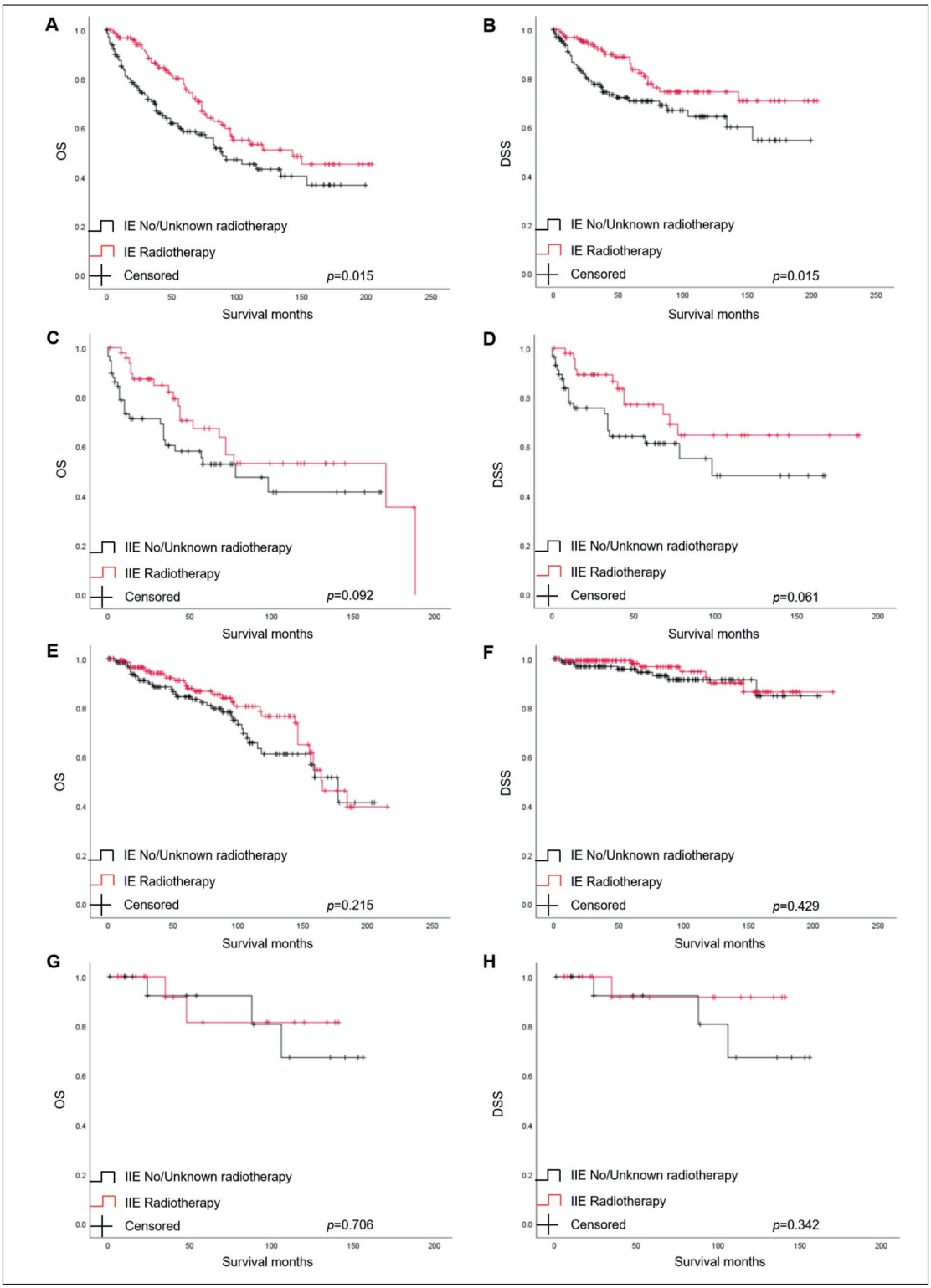

Figure 4. Kaplan-Meier curves for OS and DSS after PSM. Kaplan-Meier curves of overall (**A, C**) and disease-specific survival (**B, D**) of patients with primary breast B-cell non-Hodgkin's lymphoma of DLBCL type by radiotherapy and stage, after 1:1 Propensity Score Matching analysis. Kaplan-Meier curves of overall (**E, G**) and disease-specific survival (**F, H**) of patients with primary breast B-cell non-Hodgkin's lymphoma of MZL and FL types by radiotherapy and stage, after 1:1 Propensity Score Matching analysis. The $p < 0.05$ was considered statistically significant. OS, overall survival; DSS, disease-specific survival; PSM, propensity score matching.

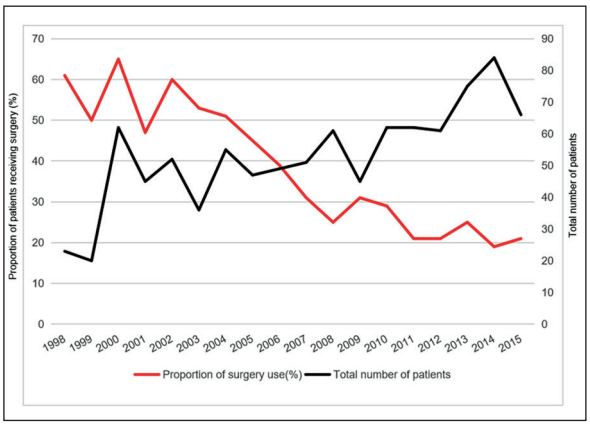

Figure 5. Proportion of patients receiving surgery and total number of patients.

stage IE MZL and FL could not benefit from RT. Hence, the MZL and FL may serve as factors predicting free of RT.

This study was based on a large population, and all baseline characteristics were well balanced by PSM, so it had some strength. But certain limitations also need to be addressed. Because of the nature of retrospective analyses, we could not exclude selection bias. Thus, prospective study is needed to make further validation. Besides, the detailed treatment is limited by the information available from the SEER database. Further analyses are planned in our own patients with complete clinical information.

Conclusions

Our study summarized the clinical features and prognostic factors of patients with primary breast B-cell non-Hodgkin's lymphoma from SEER database. Age, histology and stage were independent prognostic factors for both OS and DSS. More importantly, surgery offered no survival benefit for patients with primary breast B-cell non-Hodgkin's lymphoma, and only patients with stage IE DLBCL can obtain a longer survival time through RT.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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