ORIGINAL ARTICLE

European Journal of BREAST HEALTH

DOI: 10.4274/ejbh.galenos.2026.2026-6-1
Eur J Breast Health 2026;22(4):466-475

A Rare Entity in Context: Breast Implant-Associated Anaplastic Large Cell Lymphoma Compared With Common Lymphoma Subtypes

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ABSTRACT

Objective: Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare CD30-positive, anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma now recognized as a distinct entity in the 5th edition World Health Organization Classification of haematolymphoid tumors. Its clinicopathologic profile, treatment patterns, and outcomes, relative to those of other primary breast lymphomas, have not been characterized in large population-based comparative studies.

Materials and Methods: Using the Surveillance, Epidemiology and End Results (SEER) database (2017–2022), we identified patients with primary breast lymphoma based on ICD-O-3 site (C50.0–C50.9) and morphology codes for BIA-ALCL (9715/3), diffuse large B-cell lymphoma (DLBCL, 9680/3), extranodal marginal zone [mucosa-associated lymphoid tissue (MALT)] lymphoma (9699/3), and Burkitt lymphoma (BL, 9687/3). Baseline characteristics, treatment, overall survival (OS), and cancer-specific survival (CSS) were compared between BIA-ALCL and other mammary lymphomas.

Results: Two hundred fifty-two patients with BIA-ALCL were identified and compared with 185,019 patients with other mammary lymphomas. Patients with BIA-ALCL were younger than those with DLBCL and MALT, but older than those with BL (mean age 62.8 years, $p<0.001$). BIA-ALCL demonstrated higher rates of surgical management and lower rates of radiotherapy compared with DLBCL and MALT. Chemotherapy utilization was intermediate among lymphoma subtypes. In unadjusted analyses, DLBCL was associated with worse OS [hazard ratio (HR) 1.46, 95% confidence interval (CI) 1.03–2.08] and CSS (HR 1.84, 95% CI 1.21–2.79) relative to BIA-ALCL; BL was associated with worse CSS (HR 2.08, 95% CI 1.37–3.16); MALT lymphoma showed better CSS (HR 0.54, 95% CI 0.35–0.81). Multivariable analysis yielded HRs that were not statistically distinguishable from those for BIA-ALCL, but estimates were imprecise (adjusted OS for DLBCL: HR 1.53, 95% CI 0.21–10.90; for BL: HR 2.66, 95% CI 0.37–19.20); these wide CIs reflect sparse events within the BIA-ALCL cohort and preclude conclusions about survival equivalence.

Conclusion: In this SEER-based analysis, breast-localized ALK-negative ALCL showed a distinct demographic and treatment profile characterized by surgical management, with favorable crude survival compared with that of DLBCL and BL. Early recognition and complete surgical excision remain central to the management of localized BIA-ALCL.

Keywords: Breast; lymphomas; breast implant-associated anaplastic large cell lymphoma; treatment; outcome

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Received: 11.06.2026 **Accepted:** 02.08.2026 **Available Online Date:** 23.09.2026
Cite this article as: Tluli D, Tluli O, Abujbara MM, Boudaka R, Ahmed SA, Babu GR, et al. A rare entity in context: breast implant-associated anaplastic large cell lymphoma compared with common lymphoma subtypes. Eur J Breast Health. 2026;22(4):466-475

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KEY POINTS

- Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is a rare CD30-positive, anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma now recognized as a distinct entity in the 5th edition World Health Organization Classification of haematolymphoid tumors.
- Its clinicopathologic profile, treatment patterns, and outcomes relative to other primary breast lymphomas have not been characterized in large population-based comparative studies.
- In this Surveillance, Epidemiology and End Results-based analysis, breast-localized ALK-negative ALCL showed a distinct demographic and treatment profile characterized by surgical management, with a favorable crude survival compared with diffuse large B-cell lymphoma and Burkitt lymphoma.

Introduction

Primary breast lymphomas (PBLs) are rare extranodal malignancies, accounting for less than 1% of all non-Hodgkin lymphomas and a similarly small proportion of all breast cancers. Despite their rarity, they represent a clinically important entity due to their distinct biology, diagnostic challenges, and management strategies, which differ fundamentally from those of primary breast carcinomas (1, 2). Histologically, PBLs comprise a heterogeneous group of lymphoid neoplasms, most commonly diffuse large B-cell lymphoma (DLBCL), followed by extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT), with more aggressive subtypes such as Burkitt lymphoma (BL) occurring less frequently (3, 4). These subtypes exhibit substantial variability in clinical behavior, ranging from indolent, localized disease to rapidly progressive systemic malignancies, underscoring the need for subtype-specific diagnostic and therapeutic approaches.

Breast implant-associated anaplastic large cell lymphoma (BIA-ALCL) is now recognized as a distinct clinicopathologic entity in the 5th edition of the World Health Organization (WHO) Classification of haematolymphoid tumors (2022) and the International Consensus Classification, having been introduced as a provisional entity in the 2016 WHO revision. It is a mature CD30-positive, anaplastic lymphoma kinase (ALK)-negative peripheral T-cell lymphoma arising in association with breast implants (4, 5). Unlike conventional PBLs, which originate within breast parenchyma, BIA-ALCL typically develops in the peri-implant fluid or fibrous capsule and most commonly presents as a delayed seroma or capsular mass years after implantation (6). Immunophenotypically, it is characterized by uniform CD30 expression and absence of ALK rearrangement, distinguishing it from systemic forms of anaplastic large cell lymphoma (7).

The epidemiology of BIA-ALCL has evolved rapidly over the past decade, driven by increased awareness, improved diagnostic recognition, and the establishment of international registries. Accumulating evidence has identified a strong association between BIA-ALCL and textured-surface breast implants, with risk estimates varying widely but consistently demonstrating a markedly higher incidence compared with smooth implants (8, 9). Proposed pathogenic mechanisms emphasize the role of chronic inflammation that is induced by bacterial biofilm formation on implant surfaces, leading to sustained immune activation and eventual malignant transformation of T-cell populations within the peri-implant microenvironment (10). Although the absolute risk remains low, the widespread use of breast implants globally has made BIA-ALCL an issue of growing clinical and public health significance.

BIA-ALCL tends to exhibit a more favorable clinical course than other mammary lymphomas when diagnosed at an early stage. Disease confined to the capsule or seroma is often effectively treated with complete surgical excision, including implant removal and total capsulectomy, which is associated with high rates of durable remission (11). In contrast, advanced disease with regional or systemic involvement may require multimodal therapy, including systemic chemotherapy and targeted agents such as brentuximab vedotin (12). These management strategies differ substantially from those employed in B-cell PBLs, where systemic chemoimmunotherapy and radiotherapy play a central role, reflecting fundamental differences in tumor biology.

Despite the expanding body of literature describing BIA-ALCL, most studies have focused on single-disease cohorts, case series, or registry-based incidence analyses. Direct comparative evaluations of BIA-ALCL and other primary mammary lymphomas remain limited. Such comparisons are critical for contextualizing its clinical behavior, clarifying whether its apparent survival advantage persists after accounting for confounding factors, and better defining its position within the broader spectrum of breast-associated lymphoid malignancies. Moreover, understanding similarities and differences in demographics, treatment patterns, and outcomes across lymphoma subtypes may inform risk stratification, optimize management strategies, and support evidence-based clinical decision-making.

Using the Surveillance, Epidemiology and End Results (SEER) database, we aimed to: (i) describe the demographic and clinicopathologic profile of breast-localized BIA-ALCL relative to primary breast DLBCL, MALT lymphoma, and BL; (ii) characterize first-course treatment patterns; and (iii) compare overall and cancer-specific survival (CSS) between subtypes, both before and after adjustment for measurable confounders. We did not seek to establish equivalence or non-inferiority in survival, and

we treated the BIA-ALCL cohort as code-based (ICD-O-3 9715/3, breast-localized) rather than implant-confirmed, since SEER does not capture implant exposure.

Materials and Methods

Study Design and Data Source

This retrospective population-based cohort study was conducted using data from the SEER database, a program of the National Cancer Institute that collects detailed information on cancer incidence, patient demographics, tumor characteristics, treatment, and survival outcomes across multiple U.S. registries.

Patient Selection and Cohort Definition

Patients with PBLs diagnosed between 1 January 2017 and 31 December 2022 were identified from SEER using SEER*Stat. Cases were restricted to those with the breast as the primary site (ICD-O-3 topography codes C50.0–C50.9) and to female patients. Histologic subtypes were defined by ICD-O-3 morphology codes: 9715/3 (used here as a proxy for BIA-ALCL), 9680/3 (DLBCL), 9699/3 (MALT lymphoma), and 9687/3 (BL). We acknowledge that ICD-O-3 code 9715/3 corresponds to anaplastic large cell lymphoma, ALK-negative, and is not specific to the implant-associated variant; SEER does not record implant exposure, surface texture, or capsule confinement. The 9715/3 cohort comprises breast-localized, ALK-negative ALCL cases, of which BIA-ALCL is the principal, but not the sole, contributor. Only microscopically confirmed cases were included. Patients identified solely through a death certificate or autopsy, as well as those with missing key demographic or survival data, were excluded.

Demographic variables extracted included age at diagnosis, sex, race, marital status, and median household income. Age was categorized into three groups: 18–49 years, 50–69 years, and ≥70 years. Clinical variables included laterality and sequence number, the latter categorized as single versus multiple primary malignancies. Treatment variables were defined according to SEER first-course therapy classifications and included surgery, radiotherapy, and chemotherapy, each recorded as received or not received. The SEER database does not provide details regarding the specific surgical procedure, the extent of axillary lymph node surgery, or the completeness of resection. Therefore, analyses were limited to surgery as a binary variable (performed *vs.* not performed).

Outcomes

The primary outcomes of interest were overall survival (OS) and CSS. OS was defined as the time from diagnosis to death from any cause or to the last follow-up. CSS was defined as the time from diagnosis to death attributable to lymphoma based on the SEER cause-specific death classification. Survival time was measured in months.

Statistical Analysis

All statistical analyses were performed using Stata/SE version 18.5 (StataCorp, College Station, TX, USA). Descriptive statistics were used to summarize baseline characteristics. Categorical variables were reported as frequencies and percentages, while continuous variables were summarized as means with standard deviations.

Comparisons across lymphoma subtypes were conducted using Pearson's chi-squared test for categorical variables and one-way analysis of variance for continuous variables. A two-sided p-value <0.05 was considered statistically significant.

Survival outcomes were estimated using the Kaplan-Meier method, with differences between groups assessed using the log-rank test. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and corresponding 95% confidence intervals (CIs).

Within the BIA-ALCL cohort, univariate Cox regression was used to evaluate associations of demographic, clinical, and treatment variables with OS or CSS. To compare lymphoma subtypes, we fitted Cox proportional hazards models, both unadjusted and multivariable, with BIA-ALCL as the reference, and a priori adjusted for age category, race, marital status, income category, and receipt of surgery, radiotherapy, and chemotherapy. The proportional hazards assumption was assessed using scaled Schoenfeld residuals, and when it was violated, time-stratified models were fitted as sensitivity analyses. For CSS, we additionally performed competing-risks regression using the Fine-Gray subdistribution hazard model, treating death from non-lymphoma causes as the competing event. Given the small BIA-ALCL cohort relative to the comparator groups, model stability was examined by inspecting standard errors and CI widths; categorical levels with zero events were merged or excluded to avoid quasi-separation, and Firth's penalized likelihood was applied to univariable models with sparse cells. We did not perform formal equivalence or non-inferiority testing; non-significant HRs are therefore not interpreted as evidence of equivalent survival.

Results

Baseline Characteristics of the Cohort

A total of 185,271 patients were identified across the four diagnostic subgroups, including 252 with BIA-ALCL, 102,662 with DLBCL, 70,838 with MALT lymphoma, and 11,519 with BL. Baseline demographic and clinicopathologic characteristics are summarized in Table 1.

The mean age at diagnosis differed significantly across groups (p<0.001). Patients with BIA-ALCL had a mean age of 62.8±14.5 years, comparable to DLBCL (65.3±15.4 years) and MALT lymphoma (65.9±13.9 years), and older than BL (50.8±18.5 years). Within the BIA-ALCL cohort, most patients were aged 50–69 years (48.8%), followed by those ≥70 years (35.3%) and those aged 18–49 years (15.9%). In contrast, BL had the highest proportion of younger patients (49.7% aged 18–49 years).

Racial distribution differed significantly across subgroups (p<0.001). The majority of BIA-ALCL patients were categorized as "Other" race (71.4%), followed by White (23.4%) and Black (5.2%). A similar pattern was observed in the DLBCL, MALT lymphoma, and BL cohorts, with "Other" comprising approximately 55% of each group.

Marital status distributions were comparable among patients with BIA-ALCL (56.8% married), DLBCL (55.8% married), and MALT lymphoma (55.4% married); by contrast, patients with BL had a higher proportion of unmarried patients (52.0%). Median household income was similar across all groups, with most patients falling within the $40,000–120,000 range (BIA-ALCL: 88.5%; DLBCL: 87.8%; MALT lymphoma: 92.5%; BL: 90.5%). A greater proportion of BIA-ALCL patients was in the >$120,000 income category (11.1%) than in other subgroups (range: 4.7–6.7%).

Laterality was unknown in the majority of cases across all groups (74.2% in BIA-ALCL). Among patients with known laterality, left-sided involvement was slightly more frequent than right-sided involvement in BIA-ALCL (13.1% *vs.* 12.3%). Most BIA-ALCL cases were a single primary malignancy (67.1%), while 32.9% had two or more primaries; this proportion was higher than that observed in BL (18.2%) and comparable to that observed in MALT lymphoma (35.8%).

Table 1. Demographic and clinicopathologic characteristics of BIA-ALCL v/s DLBCL v/s MALT v/s BL

Parameter		BIA-ALCL (252)	DLBCL (102,662)	MALT (70,838)	BL (11,519)	*p*-value
Age	Mean ± SD	62.8±14.5	65.3±15.4	65.9±13.9	50.8±18.5	<0.001
	18–49	40 (15.9)	16,626 (16.2)	8,964 (12.7)	5,720 (49.7)	<0.001
	50–69	123 (48.8)	38,517 (37.5)	30,319 (42.8)	3,511 (30.5)	
	≥70	89 (35.3)	47,519 (46.3)	31,555 (44.6)	2,288 (19.9)	
Race	Black	13 (5.2)	3,248 (3.2)	2,668 (3.8)	522 (4.5)	<0.001
	White	59 (23.4)	42,462 (41.4)	28,360 (40.0)	4,611 (40.0)	
	Other	180 (71.4)	56,784 (55.3)	39,370 (55.6)	6,373 (55.3)	
	Unknown	0 (0.0)	168 (0.2)	440 (0.6)	13 (0.1)	
Marital status	Married	143 (56.8)	57,286 (55.8)	39,251 (55.4)	5,118 (44.4)	<0.001
	Other	94 (37.3)	40,521 (39.5)	25,161 (35.5)	5,993 (52.0)	
	Unknown	15 (6.0)	4,855 (4.7)	6,426 (9.1)	408 (3.5)	
Median household income	<$40,000	1 (0.4)	906 (0.9)	496 (0.7)	73 (0.6)	<0.001
	$40,000–120,000	223 (88.5)	90,090 (87.8)	65,543 (92.5)	10,422 (90.5)	
	>$120,000	28 (11.1)	5,599 (5.5)	4,773 (6.7)	544 (4.7)	
	Unknown	0 (0.0)	6,067 (5.9)	26 (0.0)	480 (4.2)	
Laterality	Left	33 (13.1)	6,703 (6.5)	8,951 (12.6)	370 (3.2)	<0.001
	Right	31 (12.3)	7,072 (6.9)	9,681 (13.7)	364 (3.2)	
	Bilateral	0 (0.0)	846 (0.8)	1,584 (2.2)	81 (0.7)	
	Paired side	1 (0.4)	609 (0.6)	613 (0.9)	51 (0.4)	
	Only one side, side unspecified	0 (0.0)	51 (0.1)	67 (0.1)	4 (0.0)	
	Unknown	187 (74.2)	87,381 (85.1)	49,942 (70.5)	10,649 (92.5)	
Sequence number	Only one primary	169 (67.1)	73,966 (72.1)	45,484 (64.2)	9,418 (81.8)	<0.001
	Two or more primaries	83 (32.9)	28,696 (28.0)	25,350 (35.8)	2,101 (18.2)	
	Unknown	0 (0.0)	0 (0.0)	4 (0.0)	0 (0.0)	

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MALT: Mucosa-associated lymphoid tissue; BL: Burkitt lymphoma; SD: Standard deviation

Treatment Modalities

Treatment patterns are detailed in Table 2. Surgical intervention was performed in 31.4% of patients with BIA-ALCL, a higher rate than in patients with DLBCL (24.5%), MALT lymphoma (26.7%), and BL (24.3%) ($p<0.001$). Radiotherapy was utilized in 12.7% of BIA-ALCL cases, compared with 20.7% in DLBCL, 23.6% in MALT lymphoma, and 10.4% in BL ($p<0.001$). Among BIA-ALCL patients, radiotherapy was most commonly administered postoperatively (4.0%). Chemotherapy was administered to 65.9% of BIA-ALCL patients, representing an intermediate rate compared with those in DLBCL (74.6%), BL (84.2%), and MALT lymphoma (25.1%) ($p<0.001$). Postoperative chemotherapy was more frequently observed in BIA-ALCL (16.7%) than in DLBCL (9.9%), MALT lymphoma (4.3%), and BL (10.7%).

Survival Outcomes

At the last follow-up, 80.2% of BIA-ALCL patients were alive, compared with 37.3% of DLBCL patients, 59.4% of MALT lymphoma patients, and 41.5% of BL patients ($p<0.001$). Cancer-specific mortality occurred in 13.1% of BIA-ALCL patients, compared with 40.9% of DLBCL patients, 13.7% of MALT lymphoma patients, and 47.1% of BL patients. Mean survival time for BIA-ALCL was 71.8±6.5 months. Corresponding mean survival times were 63.6±78.4 months for DLBCL, 86.4±70.4 months for MALT lymphoma, and 63.2±82.9 months for BL ($p<0.001$).

Univariate Analysis in BIA-ALCL

Univariate analyses of prognostic factors within the BIA-ALCL cohort are presented in Tables 3 and 4. Age ≥70 years was significantly associated with worse OS compared with the 18–49 year reference group (HR 8.55, 95% CI 1.13–64.77; $p = 0.038$). A similar trend was observed for CSS (HR 5.60, 95% CI 0.72–43.73; $p = 0.101$), although this did not reach statistical significance. Age 50–69 years was not significantly associated with OS or CSS. Race, marital status, laterality, and sequence number (single *vs.* multiple primaries) were not significantly associated with either of the survival outcomes. Among treatment variables, absence of chemotherapy was associated with worse CSS (HR 2.42, 95% CI 1.05–5.60; $p = 0.038$). Surgical treatment was not significantly associated with OS (HR 1.33; $p = 0.467$) or CSS (HR 1.47; $p = 0.419$).

Comparative Survival Analysis

Comparative survival analyses relative to BIA-ALCL are summarized in Table 4 and Figure 1. In unadjusted analyses, DLBCL was associated with worse OS compared with BIA-ALCL (HR 1.46, 95% CI 1.03–2.08; $p = 0.035$), while MALT lymphoma and BL did not show statistically significant differences in OS.

In unadjusted CSS analyses, DLBCL (HR 1.84, 95% CI 1.21–2.79; $p = 0.004$) and BL (HR 2.08, 95% CI 1.37–3.16; $p = 0.001$) were associated with worse outcomes compared with BIA-ALCL,

Table 2. Treatment modalities (surgery, chemotherapy, radiotherapy) and survival outcomes of BIA-ALCL v/s DLBCL v/s MALT v/s BL

Parameter		BIA-ALCL (252)	DLBCL (102,662)	MALT (70,838)	BL (11,519)	*p*-value
Surgery	Performed	79 (31.4)	25,172 (24.5)	18,926 (26.7)	2,794 (24.3)	<0.001
	Not performed	171 (67.9)	76,149 (74.2)	51,356 (72.5)	8,611 (74.8)	
	Unknown	2 (0.8)	1,341 (1.3)	556 (0.8)	114 (1.0)	
Radiotherapy	Yes	32 (12.7)	21,241 (20.7)	16,706 (23.6)	1,199 (10.4)	<0.001
	No	0 (0.0)	515 (0.5)	378 (0.5)	18 (0.2)	
	Unknown	220 (87.3)	80,906 (78.8)	53,754 (75.9)	10,302 (89.4)	
Chemotherapy	Yes	166 (65.9)	76,545 (74.6)	17,755 (25.1)	9,702 (84.2)	<0.001
	No	86 (34.1)	26,117 (25.4)	53,083 (74.9)	1,817 (15.8)	
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Cause of death	Alive	202 (80.2)	38,297 (37.3)	42,079 (59.4)	4,784 (41.5)	<0.001
	Breast cancer	33 (13.1)	41,957 (40.9)	9,700 (13.7)	5,428 (47.1)	
	Other	17 (6.7)	22,408 (21.8)	19,059 (26.9)	1,307 (11.4)	
	Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Survival months	Mean ± SD	71.8±6.5	63.6±78.4	86.4±70.4	63.2±82.9	<0.001
	Unknown	0 (0.0)	333 (0.3)	38 (0.1)	42 (0.4)	

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; MALT: Mucosa-associated lymphoid tissue; BL: Burkitt lymphoma; SD: Standard deviation

Table 3. Univariate analysis of demographic risk factors affecting overall survival and cancer-specific survival of BIA-ALCL

Parameter		Overall survival		Cancer-specific survival	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age	18–49	Reference		Reference	
	50–69	5.12 (0.68–38.75)	0.114	3.75 (0.48–29.02)	0.206
	≥70	8.55 (1.13–64.77)	0.038	5.60 (0.72–43.73)	0.101
Race	Black	Reference		Reference	
	White	1.99 (0.25–16.24)	0.519	1.70 (0.20–14.14)	0.625
	Other	1.41 (0.19–10.49)	0.739	0.99 (0.13–7.51)	0.990
Marital status	Married	Reference		Reference	
	Other	0.74 (0.35–1.54)	0.415	0.76 (0.32–1.82)	0.545
Median household income	<$40,000	Reference		Reference	
	$40,000–120,000	2.46e+07 (.–.)	.	2.47e+07 (.–.)	.
	>$120,000	2.16e+07 (.–.)	.	2.08e+07 (.–.)	.

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; HR: Hazard ratio; CI: Confidence interval

Table 4. Univariate analysis of clinicopathologic risk factors and treatment modalities affecting overall survival and cancer-specific survival of BIA-ALCL

Parameter		Overall survival		Cancer-specific survival	
		HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Laterality	Left	Reference		Reference	
	Right	5.20 (0.61–44.57)	0.132	4.19 (0.47–37.57)	0.200
	Bilateral	. (.–.)	.	. (.–.)	.
	Paired side	5.59e-16 (.–.)	.	3.59e-15 (.–.)	.
	Only one side, side unspecified	. (.-.)	.	. (.–.)	.
Sequence number	Only one primary	Reference		Reference	
	Two or more primaries	1.65 (0.81–3.36)	0.172	0.84 (0.33–2.16)	0.725
Surgery	Performed	Reference		Reference	
	Not performed	1.33 (0.61–2.90)	0.467	1.47 (0.58–3.77)	0.419
Radiotherapy	Yes	Reference		Reference	
	No	. (.–.)	.	. (.–.)	.
Chemotherapy	Yes	Reference		Reference	
	No	1.58 (0.76–3.26)	0.217	2.42 (1.05–5.60)	0.038

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; HR: Hazard ratio; CI: Confidence interval

whereas MALT lymphoma was associated with improved CSS (HR 0.54, 95% CI 0.35–0.81; $p = 0.003$).

In multivariable models adjusted for age category, race, marital status, income, and treatment, the point estimates for OS were attenuated for DLBCL (adjusted HR 1.53, 95% CI 0.21–10.90; $p = 0.671$), MALT lymphoma (adjusted HR 0.56, 95% CI 0.08–4.00; $p = 0.564$), and BL (adjusted HR 2.66, 95% CI 0.37–19.20; $p = 0.331$). The corresponding adjusted HRs for CSS were 0.85 (95% CI 0.12–6.05; $p = 0.868$) for DLBCL, 0.15 (95% CI 0.02–1.05; $p = 0.056$) for MALT lymphoma, and 1.60 (95% CI 0.22–11.68; $p = 0.641$) for BL. CIs spanning 50- to 100-fold reflect the small number of events within the BIA-ALCL reference cohort relative to the number of estimated parameters, and the presence of substantial sparse-data bias; these estimates are statistically unstable and should not be interpreted as evidence of equivalent survival across subtypes.

Discussion and Conclusion

In this SEER-based comparative analysis, breast-localised ALK-negative ALCL—used here as a registry proxy for BIA-ALCL—differed from primary breast DLBCL, MALT lymphoma, and BL in demographic profile, treatment composition, and crude survival. Surgery was the dominant first-course modality;

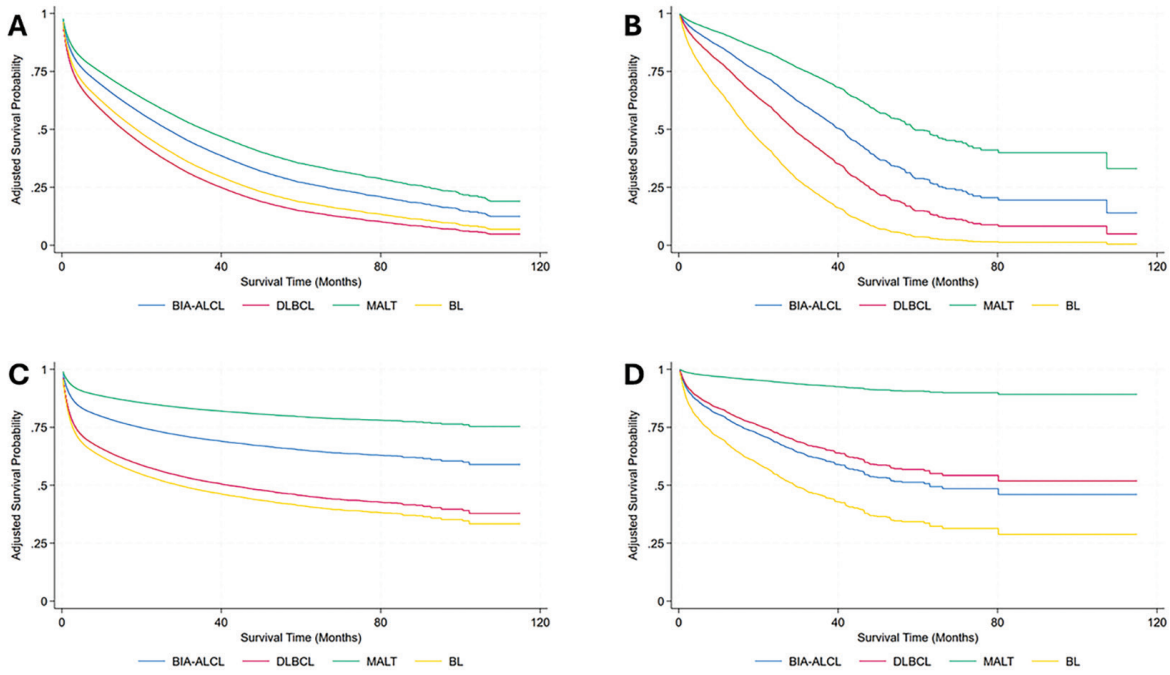

Figure 1. Comparative survival analysis of primary mammary lymphoma subtypes relative to BIA-ALCL. (A) Unadjusted Cox proportional hazards analysis comparing overall survival across lymphoma subtypes, with BIA-ALCL as the reference group. DLBCL: HR 1.46 (95% CI 1.03–2.08), $p = 0.035$; MALT lymphoma: HR 0.80 (95% CI 0.56–1.13), $p = 0.209$; BL: HR 1.29 (95% CI 0.90–1.83), $p = 0.164$. (B) Multivariable-adjusted Cox proportional hazards analysis of overall survival, with BIA-ALCL as the reference group. DLBCL: HR 1.53 (95% CI 0.21–10.90), $p = 0.671$; MALT lymphoma: HR 0.56 (95% CI 0.08–4.00), $p = 0.564$; BL: HR 2.66 (95% CI 0.37–19.20), $p = 0.331$. (C) Unadjusted Cox proportional hazards analysis of cancer-specific survival, with BIA-ALCL as the reference group. DLBCL: HR 1.84 (95% CI 1.21–2.79), $p = 0.004$; MALT lymphoma: HR 0.54 (95% CI 0.35–0.81), $p = 0.003$; BL: HR 2.08 (95% CI 1.37–3.16), $p = 0.001$. (D) Multivariable-adjusted Cox proportional hazards analysis of cancer-specific survival, with BIA-ALCL as the reference group. DLBCL: HR 0.85 (95% CI 0.12–6.05), $p = 0.868$; MALT lymphoma: HR 0.15 (95% CI 0.02–1.05), $p = 0.056$; BL: HR 1.60 (95% CI 0.22–11.68), $p = 0.641$

BIA-ALCL: Breast implant-associated anaplastic large cell lymphoma; DLBCL: Diffuse large B-cell lymphoma; HR: Hazard ratio; CI: Confidence interval; MALT: Mucosa-associated lymphoid tissue; BL: Burkitt lymphoma

radiotherapy was used sparingly, and chemotherapy was used at an intermediate level. Crude OS and CSS estimates appeared superior in the BIA-ALCL cohort, but these differences were attenuated and were no longer statistically significant after multivariable adjustment. We caution against interpreting non-significance as biological or clinical equivalence: CIs for adjusted HRs span more than a 50-fold range in several cases, reflecting sparse events and an unstable variance structure rather than true similarity in prognosis. The four entities differ fundamentally in cell of origin, mutational landscape, treatment paradigm, and natural history; a registry that does not capture stage, implant exposure, or treatment intensity cannot adjudicate their relative prognoses.

Several population-based studies have utilized the SEER database to investigate PBLs, consistently demonstrating the rarity of this disease. Peng et al. identified 1,427 patients with PBL diagnosed between 1975 and 2011, while other SEER-based analyses focusing on specific histological subtypes, such as primary breast DLBCL, have reported cohorts ranging from approximately 800 to 1,000 patients (13, 14). Our study builds upon these prior investigations by evaluating BIA-ALCL, DLBCL, MALT lymphoma, and BL comparatively within a contemporary SEER cohort.

The age distribution observed in this study is consistent with existing literature describing BIA-ALCL as a disease primarily affecting middle-aged and older women, typically presenting several years after breast implants. Large cohort studies and systematic reviews have reported a median age at diagnosis ranging from the fifth to sixth decades of life, with a latency period often exceeding 8-10 years following the implantation (7, 8). In contrast, BL demonstrated a younger age profile in our cohort, which aligns with its known epidemiology as an aggressive, high-grade lymphoma that more commonly affects

younger individuals and immunocompromised populations (15). DLBCL and MALT lymphomas showed older age distributions, consistent with the increasing incidence of B-cell lymphomas with advanced age (4).

The observed socioeconomic distribution, with a greater proportion of BIA-ALCL patients in higher-income brackets, likely reflects the sociodemographic composition of the population undergoing cosmetic or reconstructive breast implantation rather than indicating a direct biological association. Prior epidemiological studies have highlighted that BIA-ALCL is more frequently reported in regions with higher rates of breast implant utilization, particularly in developed countries with established cosmetic surgery practices (9). While socioeconomic status was not independently associated with survival in this study, disparities in access to specialized surgical care and early diagnosis may still influence outcomes and warrant further investigation.

Management patterns in this study reinforce the central role of surgery in BIA-ALCL. The higher rate of surgical treatment, compared with other lymphoma subtypes, is consistent with current consensus guidelines, which recommend complete surgical excision, including total capsulectomy and implant removal, as the cornerstone of therapy for localized disease. Multiple studies have demonstrated that complete surgical resection is associated with excellent long-term outcomes and may be curative in early-stage disease (11). In contrast, systemic therapy is reserved for patients with advanced disease, nodal involvement, or incomplete resection. The intermediate rate of chemotherapy use observed in this cohort likely reflects this risk-adapted approach. Notably, targeted therapies such as brentuximab vedotin have shown efficacy in relapsed or advanced CD30-positive T-cell lymphomas, including ALCL (12).

Radiotherapy utilization was lower in BIA-ALCL than in B-cell lymphomas, consistent with differences in disease biology and treatment paradigms. MALT lymphoma, in particular, is highly radiosensitive and often treated with involved-site radiotherapy in early-stage disease, achieving excellent local control rates (16, 17). In contrast, radiotherapy plays a limited role in BIA-ALCL and is generally reserved for residual or unresectable disease. These differences further underscore that BIA-ALCL requires a distinct therapeutic approach compared with other PBLs.

The higher proportion of patients alive at follow-up in the BIA-ALCL cohort likely reflects a combination of earlier clinical presentation, effective surgical management, and favorable tumor biology. BIA-ALCL most commonly presents as a delayed peri-implant seroma, prompting early clinical evaluation and facilitating diagnosis at a localized stage (7). This contrasts with other lymphoma subtypes, which may present with systemic disease or more aggressive clinical features. However, the attenuation of survival differences after adjustment highlights the importance of confounding variables, particularly age, treatment modality, and disease extent. These findings suggest that when appropriately treated, patients with different primary mammary lymphoma subtypes may have comparable outcomes.

Within the BIA-ALCL subgroup, advanced age was associated with worse OS, consistent with broader oncologic data demonstrating poorer outcomes in older adults due to comorbidities, reduced treatment tolerance, and competing mortality risks. The association between lack of chemotherapy and worse CSS should be interpreted with caution. While it may suggest a benefit of systemic therapy in higher-risk patients, this finding is likely influenced by selection bias inherent in retrospective analyses, as patients who do not receive chemotherapy may differ significantly in disease severity or fitness for treatment.

This study has several limitations. The most consequential issue is case ascertainment: the ICD-O-3 morphology code 9715/3 captures all anaplastic large cell lymphomas of ALK-negative type, of which BIA-ALCL is the principal but not exclusive subset. SEER does not record implant exposure, implant surface (textured *vs.* smooth), implant manufacturer, latency from implantation, or whether the disease was confined to the peri-implant capsule. The 252-case cohort almost certainly admixes implant-associated and sporadic ALK-negative ALCL of the breast, and we cannot separate them. Independent registries such as the PROFILE registry (US) and the Australian BIA-ALCL registry, which collect implant-specific data, provide more accurate incidence and outcome estimates, and should be considered the gold-standard data sources for definitive comparisons. A second, consequential limitation is that the study window (2017–2022) straddles the July 2019 food and drug administration (FDA)-requested global recall of Allergan Biocell textured implants and the associated increase in patient and clinician awareness; both the ascertainment of incidence and treatment patterns may differ between pre- and post-recall periods. Third, SEER is subject to inherent biases, including missing data, misclassification, and limited availability of clinical variables. Several important parameters, such as implant characteristics (e.g., textured versus smooth surfaces), duration of implantation, and detailed staging information were not available for BIA-ALCL patients. This is particularly relevant given the well-established association between textured implants and increased risk of BIA-ALCL (9, 10). Additionally, information on specific treatment regimens, completeness of surgical excision, and disease recurrence was not captured, which limited the ability to perform more detailed analyses of outcomes. Despite these limitations, the population-based design provides valuable comparative insights across rare lymphoma subtypes.

Several research priorities follow from these findings. First, linkage between SEER and prospective implant-exposure registries (PROFILE, national breast implant registry, Australian BIA-ALCL registry) would allow distinguishing implant-associated from sporadic ALK-negative ALCL of the breast and enable accurate estimation of incidence stratified by latency, manufacturer, and texture. Second, the TNM-based BIA-ALCL staging system proposed by Clemens and colleagues should be uniformly applied to enable stage-adjusted survival comparisons. Third, characterization of recurrent driver mutations (JAK1, STAT3, DNMT3A, TP53) and their relationship to bacterial biofilm composition would clarify the mechanism of T-cell lymphomagenesis in the peri-implant microenvironment and identify candidates for targeted therapy beyond brentuximab vedotin. Finally, era-stratified analyses comparing periods before and after 2019 (when the FDA-requested global recall of Allergan Biocell textured implants altered both exposure and ascertainment) are essential for interpreting incidence trends and treatment patterns.

BIA-ALCL is a biologically distinct, CD30-positive, ALK-negative peripheral T-cell lymphoma, now formally recognized in the WHO-HAEM5 classification. In this population-based analysis, the breast-localized ALK-negative ALCL cohort (used as a SEER proxy for BIA-ALCL) showed a demographic and treatment profile dominated by surgical management, with an apparently favorable crude survival relative to primary breast DLBCL and BL. Adjusted comparisons were inconclusive: CIs were too wide to support claims of superiority or equivalence, and lack of statistical significance should not be interpreted as evidence that survival outcomes are similar across these biologically distinct entities. Complete surgical excision with total capsulectomy remains the cornerstone of management for capsule-confined disease, and brentuximab vedotin-based regimens have an established role in advanced disease. The most pressing methodological gap is the absence of implant-specific variables in SEER; definitive comparative outcome studies will require linkage between cancer registries and prospective implant-exposure registries such as PROFILE and the national breast implant registry.

Ethics

Ethics Committee Approval: The study used the anonymized data from the Surveillance, Epidemiology, and End Results (SEER) Program. Since no identifiable patient information is accessed, ethics committee approval are not required. The corresponding author signed a data-use agreement with the SEER (no: SEER-ID: 17257-Nov2018, date: October 24, 2019).

Informed Consent: Not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: D.T., O.T., M.M.A., R.B., S.A.A., G.R.B., S.V.; Concept: O.T., G.R.B., S.V.; Design: D.T., O.T., G.R.B., S.V.; Data Collection or Processing: D.T., O.T., G.R.B., S.V.; Analysis or Interpretation: D.T., O.T., M.M.A., R.B., S.A.A., G.R.B., S.V.; Literature Search: D.T., O.T., G.R.B., S.V.; Writing: D.T., O.T., G.R.B., S.V.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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