Invasive Lobular Carcinoma Has Worse Outcome Compared with Invasive Ductal Carcinoma in Stage IV Breast Cancer with Bone-Only Metastasis

Yunbo Luo a Aimin Ma b Shengkai Huang c Yinghua Yu c

aDepartment of Thyroid and Breast Surgery, Affiliated Hospital of North Sichuan Medical College, Nanchong, China; bDepartment of Breast Surgery, Wuming Hospital of Guangxi Medical University, Nanning, China; cDepartment of Breast Surgery, the Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China

Abstract

Background: Invasive lobular carcinoma (ILC) is more likely to have bone metastasis than invasive ductal carcinoma (IDC). However, the prognosis for bone metastasis in ILC and IDC is barely known. So, the aim of this study was to investigate the difference of prognosis between ILC and IDC accompanied by bone metastasis. Methods: We evaluated the women with bone-only metastasis of defined IDC or ILC reported to the Surveillance, Epidemiology and End Results program from 2010 to 2016. Pearson’s χ² test was used to compare the differences of clinicopathologic factors between ILC and IDC. Univariate and multivariate analyses were performed to verify the effects of histological types (IDC and ILC) and other clinicopathologic factors on the overall survival (OS) and cancer-specific survival (CSS). Results: Overall, 3,647 patients with IDC and 945 patients with ILC met the inclusion criteria and were analyzed in our study. The patients with ILC were more likely to be older and to have lower histological grade and a higher proportion of the HR+/HER2– subtype. However, less treatment was administered to ILC than IDC, such as surgery of the breast, radiation, and chemotherapy. Compared to patients with IDC, patients with ILC showed worse OS (median OS, 36 and 42 months, respectively, p < 0.001) and CSS (median CSS, 39 and 45 months, respectively, p < 0.001), especially in subgroups with HR+/HER2– subtype (OS, hazard ratio: 1.501, 95% CI 1.270–1.773, p < 0.001; CSS, hazard ratio: 1.529, 95% CI 1.281–1.825, p < 0.001), lower histological grade (I–II) (OS, hazard ratio: 1.411, 95% CI 1.184–1.683, p < 0.001; CSS, hazard ratio: 1.488, 95% CI 1.235–1.791, p < 0.001), or tumor burden, such as T0–2 (OS, hazard ratio: 1.693, 95% CI 1.368–2.096, p < 0.001; CSS, hazard ratio: 1.76, 95% CI 1.405–2.205, p < 0.001) and N1–2 (OS, hazard ratio: 1.451, 95% CI 1.171–1.799, p = 0.001; CSS, hazard ratio: 1.488, 95% CI 1.187–1.865, p = 0.001). Furthermore, older age, black race, unmarried status, higher tumor burden (T3–4 and N3), triple-negative subtype, and higher histological grade were independent risk factors for both OS and CSS. Surgery of the breast and chemotherapy could significantly improve the prognosis for patients. Conclusion: Patients with ILC have worse outcomes compared to those with IDC when associated with bone-only metastasis, especially in subgroups with lower histological grade or tumor burden. More effective treatment measures may be needed for ILC, such as cyclin-dependent kinase 4/6 inhibitors, new targeted drugs, etc.

Introduction

Breast cancer is the most common malignancy among women and is also the second cause of cancer death in women [1]. Although breast cancer screening has been widespread and people’s awareness of cancer prevention has improved significantly, 5–10% of patients might have...
distant metastasis at the diagnosis of breast cancer [2, 3]. Also, approximately 20–30% of early breast cancer patients may develop distant metastasis [4]. Therefore, metastatic breast cancer is still the main problem for the treatment of breast cancer, especially bone metastasis (BM), which is the most common form of metastasis in breast cancer. BM can trigger a series of skeletal-related events, such as pathological fractures, spinal cord compression, and the need for surgery or radiotherapy to bone, which increases patients’ suffering and consumes a lot of medical resources. Bone-only metastasis (BOM) accounts for 17–37% of metastatic breast cancer among females [5–7]. Some studies have shown that breast cancer with BOM has better prognosis than multiple metastases [8, 9]. So, it is important to understand the risk factors for BM and find the patients with BM as early as possible. Previous studies have shown that older age, larger tumor size, and more lymph nodes involvement were risk factors for BM [10–12]. In addition, hormone receptor-positive status and lower tumor grade can also significantly increase the risk of BM [10, 13].

Invasive lobular carcinoma (ILC) is the second most common histological type of breast cancer and accounts for 5–15% of breast cancers [14–16]. ILC is more likely to be hormone receptor positive and is associated with larger tumor size and older age than invasive ductal carcinoma (IDC) [14, 17]. Therefore, theoretically, ILC has a higher risk of BM than IDC, which was demonstrated by previous research [8, 17, 18]. However, the prognosis of IDC and ILC with BM has rarely been studied. A previous study [18] including 196 patients whose first metastatic site was bone showed that ILC had better outcomes than IDC. However, recent studies [8, 19] drew the opposite conclusion, demonstrating worse outcomes for ILC than IDC. So, the purpose of this study was to investigate the difference in prognosis between IDC and ILC with BOM by analyzing the Surveillance, Epidemiology and End Results (SEER) database.

Materials and Methods

Data Source and Patient Selection

We conducted a retrospective study using data from the SEER database which collects patients’ demographics, tumor characteristics, first course of treatment, and important follow-up data from 18 population-based cancer registries, representing approximately 28% of the US population. Because the records of the SEER database have contained information about distant metastasis since 2010, we used the SEER*Stat version 8.3.6 to identify potentially eligible patients based on the following inclusion criteria: female, years of diagnosis from 2010 to 2016, more than 1 month of follow-up, breast cancer with BOM as the first and only malignant cancer diagnosis, and defined histological type of IDC or ILC (Fig. 1; flowchart). Finally, 4,592 patients met the inclusion criteria, and their clinicopathologic data, including age, race, marital and insurance status, laterality, tumor and lymph node stage, histological grade, tumor subtype, treatment methods, and survival months, were collected and analyzed. Because personally identifiable information of this study cannot be reached from the SEER database, this study was deemed exempt from review by the ethics committee of our institution.

Statistical Analysis

Pearson’s χ² test was used to compare the differences of clinicopathologic factors between IDC and ILC. The endpoints of this study were overall survival (OS) and cancer-specific survival (CSS). OS was defined as the interval from the diagnosis of breast cancer to mortality from all causes or the final follow-up in censored cases. CSS was defined as the interval from the diagnosis to mortality caused by breast cancer or the final follow-up in censored cases. Kaplan-Meier analysis was performed to estimate the differences of prognosis between IDC and ILC, and also the log-rank test was applied to determine the effect of each variable on OS and CSS. A Cox proportional hazards model was used for the univariate and multivariate analyses and to estimate hazard ratios with 95% confidence intervals (CIs). SPSS Statistical software (version 25.0; IBM Corporation) was applied for all statistical analyses. The forest plot was made by Microsoft Excel (Microsoft Office Professional Plus 2010). All tests were two sided and p values <0.05 were considered statistically significant.

Results

Clinicopathologic Features

In total, 4,592 patients with BOM met the criteria and were analyzed in this study. Among them, 945 patients had ILC (20.6%) and 3,647 patients had IDC (79.4%). The age of patients ranged from 20 to 97 years, and patients with ILC were significantly older than those with IDC (median age, 65 and 59 years, respectively), while patients with IDC presented higher T stage than those with ILC (T4, 26.7% and 15.4%, respectively) and were also more often treated with surgery of the breast, chemotherapy, and radiotherapy than patients with ILC (<0.001). Patients with IDC were more often treated with surgery of the breast, chemotherapy, and radiotherapy than patients with ILC (<0.001) as shown in Table 1.

Univariate Survival Analysis for Patients with BOM

The follow-up time of this cohort ranged from 1 to 82 months, with a median of 22 months. Finally, 2,046 patients, including 1,577 (77.1%) with IDC and 469 (22.9%) with ILC, had died. Patients with ILC had a shorter OS than patients with IDC, with a median OS of 36 and 42 months, respectively (<0.001, shown in Fig. 2a). Also, the CSS of ILC patients was shorter than that of IDC patients, with a median CSS of 39 and 45 months, respectively (<0.001, shown in Fig. 2b). In addition to histo-
logical types (ILC and IDC), other clinicopathologic factors can also affect the outcomes of patients with BOM. As shown in Table 2, decreased OS and CSS were seen in those patients who were older, were of black race, had unmarried status, higher histological grade (II–IV), higher tumor burden (T 3–4 , N 3), and triple-negative subtype. However, surgery of the breast, chemotherapy, and radiation therapy could significantly improve patients’ survival.

Multivariate Survival Analysis of Patients with BOM

When multivariate survival analysis was performed by the Cox proportional hazards model (Table 3), the OS and CCS of ILC were still significantly worse than for IDC (OS, hazard ratio: 1.39, 95% CI 1.192–1.620, p < 0.001; CSS, hazard ratio: 1.428, 95% CI 1.215–1.679, p < 0.001). Then, older age (50–65 and >65 years), unmarried status, black race, later tumor stage (T 3–4 ), higher lymph node stage (N 3), higher histological grade (II–IV), and triple-negative subtype were independent risk factors for OS and CSS in these two groups (ILC and IDC). Surgery of the breast and chemotherapy significantly improved patients’ survival, but radiotherapy had no effect on survival.

Subgroup Survival Comparation for IDC and ILC

Furthermore, when subgroup analysis was performed (Fig. 3), the patients with ILC also showed worse outcomes than those with IDC in most subgroups. Especially in groups with lower histological grade (I–II) (OS, hazard ratio: 1.411, 95% CI 1.184–1.683, p < 0.001; CSS, hazard ratio: 1.428, 95% CI 1.215–1.679, p < 0.001). Then, older age (50–65 and >65 years), unmarried status, black race, later tumor stage (T 3–4 ), higher lymph node stage (N 3), higher histological grade (II–IV), and triple-negative subtype were independent risk factors for OS and CSS in these two groups (ILC and IDC). Surgery of the breast and chemotherapy significantly improved patients’ survival, but radiotherapy had no effect on survival.

Discussion

ILC is the second most common histological type of breast cancer and accounts for 5–15% of breast cancers [14–16]. Numerous previous studies [14, 17, 20, 21] have shown that ILC and IDC differ greatly in clinicopathologic features and prognosis, but most of these studies have been limited to early-stage breast cancer instead of metastatic breast cancer. Actually, the metastatic sites of ILC and IDC are very different. IDC is more prone to brain and visceral metastasis than ILC [14, 17], such as liver and lung. However, the risks of gastrointestinal tract and ovary metastasis for ILC are higher than in IDC [22]. In addition, recent studies [8, 17] have also shown that ILC is particularly prone to BM, and BM accounts for approximately 70% of metastatic breast cancers and increases the patients’ suffering by a series of skeletal-related events [23]. A retrospective study [8] analyzing the SEER database illustrated that the risk of BM for ILC is almost twice as high as for IDC (hazard ratio: 1.996, p < 0.001). However, the difference in prognosis between ILC and IDC with BM is barely known. Therefore, we used the SEER database to investigate the influence of histological
Table 1. Clinicopathologic features of patients according to histology subtypes (ILC and IDC)

| Variables                      | Total number | IDC        | ILC       | p value |
|--------------------------------|--------------|------------|-----------|---------|
|                                | n            | %          | n         | %       |
| All patients                   | 4,592        | 3,647      | 945       | 20.6    |
| Age                            |              |            |           |         |
| <50 years                      | 1,043        | 938        | 105       | 11.1    | <0.001  |
| 50-65 years                    | 1,948        | 1,558      | 390       | 41.3    |
| >65 years                      | 1,601        | 1,151      | 450       | 47.6    |
| Race                           |              |            |           |         |
| White                          | 3,557        | 2,779      | 778       | 82.3    | <0.001  |
| Black                          | 683          | 568        | 115       | 12.2    |
| Others                         | 329          | 283        | 46        | 4.9     |
| Unknowna                       | 23           | 17         | 6         | 0.6     |
| Marital status                 |              |            |           |         |
| Married                        | 2,098        | 1,638      | 460       | 48.7    | 0.043   |
| Unmarried                      | 2,273        | 1,831      | 442       | 46.8    |
| Unknowna                       | 221          | 178        | 43        | 4.5     |
| Insurance status               |              |            |           |         |
| Insured                        | 4,366        | 3,450      | 916       | 96.9    | 0.08    |
| Uninsured                      | 141          | 120        | 21        | 2.2     |
| Unknowna                       | 85           | 77         | 8         | 0.9     |
| Laterality                     |              |            |           | 0.793   |
| Left                           | 2,329        | 1,875      | 454       | 48.0    |
| Right                          | 2,169        | 1,729      | 440       | 46.6    |
| Bilateral                      | 14           | 11         | 3         | 0.3     |
| Unknowna                       | 80           | 32         | 48        | 5.1     |
| T stage                        |              |            |           |         |
| T0/T1                          | 616          | 454        | 162       | 17.1    | <0.001  |
| T2                             | 1,587        | 1,329      | 258       | 27.3    |
| T3                             | 785          | 571        | 214       | 22.6    |
| T4                             | 1,118        | 973        | 145       | 15.4    |
| T4a                            | 486          | 320        | 166       | 17.6    |
| Nodal stage                    |              |            |           |         |
| N0                             | 1,106        | 849        | 257       | 27.2    | 0.003   |
| N1                             | 2,008        | 1,650      | 358       | 37.9    |
| N2                             | 550          | 449        | 101       | 10.7    |
| N3                             | 603          | 479        | 124       | 13.1    |
| Unknowna                       | 325          | 220        | 105       | 11.1    |
| Grade                          |              |            |           |         |
| I                              | 407          | 242        | 165       | 17.5    | <0.001  |
| II                             | 1,950        | 1,551      | 399       | 42.2    |
| III–IV                         | 1,533        | 1,429      | 104       | 11.0    |
| Unknowna                       | 702          | 425        | 277       | 29.3    |
| Tumor subtype                  |              |            |           |         |
| HR+/HER2–                      | 3,083        | 2,320      | 763       | 80.7    | <0.001  |
| HR+/HER2+                      | 645          | 596        | 49        | 5.2     |
| HR–/HER2+                      | 197          | 182        | 15        | 1.6     |
| Triple-negative                | 319          | 288        | 31        | 3.3     |
| Unknowna                       | 348          | 261        | 87        | 9.2     |
| Surgery                        |              |            |           |         |
| Yes                            | 1,571        | 1,315      | 256       | 27.1    | <0.001  |
| No                             | 2,989        | 2,308      | 681       | 72.1    |
| Unknowna                       | 32           | 24         | 8         | 0.8     |
| Radiation                      |              |            |           | <0.001  |
| Yes                            | 1,792        | 1,522      | 270       | 28.6    |
| No                             | 2,800        | 2,125      | 675       | 71.4    |
| Chemotherapy                   |              |            |           | <0.001  |
| Yes                            | 2,385        | 2,013      | 372       | 39.4    |
| No                             | 2,207        | 1,634      | 573       | 60.6    |

IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor 2. a Patients with unknown information and T4 stage were excluded from the comparative analysis.
types (ILC and IDC) and other clinicopathologic factors on the prognosis of patients with BOM.

A retrospective research [18] including 196 patients whose first metastatic site was bone showed that ILC had a better outcome compared to that of IDC (hazard ratio: 0.5, 95% CI 0.30–0.84), but merely 35 patients with ILC presented BM in that study. On the contrary, recent studies [8, 19] have shown that ILC had worse prognosis than IDC when developing BM. The reason for the opposite outcomes may be differences in the inclusion population. Firstly, the recent studies included patients with BM at the initial diagnosis of breast cancer, but the 196 patients of the previous research developed BM after receiving systematic therapy during the treatment of primary breast cancer, such as chemotherapy, endocrinotherapy, and Her2-targeted therapy. Moreover, these treatments might differ between IDC and ILC, which might have further affected the following treatment of BM in the previous research. Additionally, the first metastatic site of the 196 patients was only bone in the previous research, while the patients of the recent studies were affected not only by BM but also by brain and visceral metastasis. As previous research [8, 14, 17, 22] has illustrated, the metastatic sites of ILC and IDC are very different, which might have resulted in the differences in prognosis between ILC and IDC in recent studies. So, we excluded patients with visceral or brain metastasis and validated the differences in prognosis between IDC and ILC with BOM by analyzing the SEER database. Consistent with recent studies, the patients with ILC showed worse outcomes than those with IDC, no matter whether for OS or CSS, in our research. Especially in the lower histological grade (I–II) or tumor burden (T0–2, N1–2) groups, patients with ILC showed significantly worse outcomes than those with IDC. Part of the reason may be less treatment for ILC than for IDC in those groups, such as surgery or chemotherapy, which could improve the survival for patients with BM [5, 19, 24, 25]. Furthermore, patients with ILC had a larger proportion of the HR+/HER2– subtype than patients with IDC (80.7% and 63.6%, respectively), but had significantly worse survival than the IDC group in this subtype. In metastatic breast cancer with HR+/HER2– subtype, the 2016 American Society of Clinical Oncology recommends cyclin-dependent kinase 4/6 inhibitors (CDKs)-based treatment in the first-line or second-line protocols [26]. Also, recent research [27–29] revealed that patients with BOM or lobular histology benefited from CDK4/6 inhibitors combined with endocrine therapy. Thus, we speculate that ILC patients with BOM may be more likely to benefit from CDKs-based regimens than simple endocrine therapy, which might be proven by further studies. While ILC and IDC had the same prognosis in triple-negative subtype, the reason may be similar treatment for ILC and IDC in this group, such as the only effective systemic treatment of chemotherapy for the triple-negative subtype.

Apart from the histology types (IDC and ILC), other clinicopathologic factors can also affect the prognosis of patients with BOM. Notably, we found that patients showed worse prognosis with increasing age, which was also demonstrated by a previous study [8]. This is partly because older patients have more comorbid conditions and frailty, which makes aggressive systemic therapy inexecutable in older patients. Besides, unmarried or uninsured status increased the risk of mortality slightly, which is consistent with a previous study [8]. Higher tumor bur-
| Variables                  | N (%)  | OS median, months | p value | CSS median, months | p value |
|----------------------------|--------|-------------------|---------|-------------------|---------|
| Age                        |        |                   |         |                   |         |
| <50 years                  | 1,043  | 56                | <0.001  | 59                | <0.001  |
| 50–65 years                | 1,948  | 42                | 44      |                   |         |
| >65 years                  | 1,601  | 30                | 35      |                   |         |
| Race                       |        |                   |         |                   |         |
| White                      | 3,557  | 42                | <0.001  | 45                | <0.001  |
| Black                      | 683    | 31                | 35      |                   |         |
| Others                     | 329    | 43                | 47      |                   |         |
| Marital status             |        |                   |         |                   |         |
| Married                    | 2,098  | 46                | <0.001  | 49                | <0.001  |
| Unmarried                  | 2,273  | 35                | 38      |                   |         |
| Insurance status           |        |                   |         |                   |         |
| Insured                    | 4,366  | 41                | 0.096   | 44                | 0.041   |
| Uninsured                  | 141    | 36                | 38      |                   |         |
| Laterality                 |        |                   |         |                   |         |
| Left                       | 2,329  | 41                | 0.057   | 44                | 0.079   |
| Right                      | 2,169  | 42                | 45      |                   |         |
| Bilateral                  | 14     | 13                | 30      |                   |         |
| T stage                    |        |                   |         |                   |         |
| T0/T1                      | 616    | 47                | <0.001  | 52                | <0.001  |
| T2                         | 1,587  | 46                | 50      |                   |         |
| T3                         | 785    | 41                | 44      |                   |         |
| T4                         | 1,118  | 34                | 35      |                   |         |
| Nodal stage                |        |                   |         |                   |         |
| N0                         | 1,106  | 41                | 0.343   | 44                | 0.454   |
| N1                         | 2,008  | 43                | 45      |                   |         |
| N2                         | 550    | 41                | 43      |                   |         |
| N3                         | 603    | 42                | 44      |                   |         |
| Histology type             |        |                   |         |                   |         |
| IDC                        | 3,647  | 42                | <0.001  | 45                | <0.001  |
| ILC                        | 945    | 36                | 39      |                   |         |
| Grade                      |        |                   |         |                   |         |
| I                          | 407    | 49                | <0.001  | 56                | <0.001  |
| II                         | 1,950  | 45                | 49      |                   |         |
| III–IV                     | 1,533  | 42                | 36      |                   |         |
| Subtype                    |        |                   |         |                   |         |
| HR+/HER2–                  | 3,083  | 42                | <0.001  | 44                | <0.001  |
| HR+/HER2+                  | 545    | 56                | 58      |                   |         |
| HR–/HER2+                  | 197    | 73                | NA      |                   |         |
| Triple-negative            | 319    | 14                | 14      |                   |         |
| Surgery                    |        |                   |         |                   |         |
| Yes                        | 1,571  | 54                | <0.001  | 59                | <0.001  |
| No                         | 2,989  | 34                | 37      |                   |         |
| Radiation                  |        |                   |         |                   |         |
| Yes                        | 1,792  | 45                | <0.001  | 47                | <0.001  |
| No                         | 2,800  | 38                | 42      |                   |         |
| Chemotherapy               |        |                   |         |                   |         |
| Yes                        | 2,385  | 46                | <0.001  | 50                | <0.001  |
| No                         | 2,207  | 35                | 39      |                   |         |

OS, overall survival; CSS, cancer-specific survival; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; NA, not available.
| Variables                      | OS hazard ratio | 95% CI       | p value | CSS hazard ratio | 95% CI       | p value |
|-------------------------------|----------------|--------------|---------|----------------|--------------|---------|
| Age                          |                |              |         |                |              |         |
| <50 years Ref                 | 1.277          | 1.052–1.430  | 0.009   | 1.187          | 1.012–1.392  | 0.035   |
| 50–65 years                   | 1.705          | 1.445–2.011  | <0.001  | 1.601          | 1.347–1.902  | <0.001  |
| >65 years Ref                 |                |              |         |                |              |         |
| Race                          |                |              |         |                |              |         |
| White Ref                     |                |              |         |                |              |         |
| Black                         | 1.248          | 1.076–1.448  | 0.003   | 1.210          | 1.034–1.416  | 0.018   |
| Others                        | 0.999          | 0.793–1.258  | 0.99    | 1.022          | 0.805–1.298  | 0.86    |
| Marital status                |                |              |         |                |              |         |
| Married Ref                   | 1.251          | 1.113–1.405  | <0.001  | 1.234          | 1.092–1.395  | 0.001   |
| Unmarried                     |                |              |         |                |              |         |
| Insurance status              |                |              |         |                |              |         |
| Insured Ref                   |                |              |         |                |              |         |
| Uninsured                     | 1.276          | 0.951–1.696  | 0.092   | 1.356          | 1.014–1.813  | 0.04    |
| Laterality                    |                |              |         |                |              |         |
| Left Ref                      |                |              |         |                |              |         |
| Right                         | 0.989          | 0.885–1.105  | 0.843   | 0.981          | 0.873–1.103  | 0.751   |
| Bilateral                     | 2.378          | 0.876–6.457  | 0.089   | 2.584          | 0.949–7.036  | 0.063   |
| T stage                       |                |              |         |                |              |         |
| T0/T1 Ref                     |                |              |         |                |              |         |
| T2                            | 1.184          | 0.981–1.429  | 0.078   | 1.119          | 0.920–1.361  | 0.261   |
| T3                            | 1.355          | 1.100–1.670  | 0.004   | 1.282          | 1.031–1.594  | 0.025   |
| T4                            | 1.478          | 1.216–1.796  | <0.001  | 1.419          | 1.158–1.738  | 0.001   |
| Nodal stage                   |                |              |         |                |              |         |
| N0 Ref                        |                |              |         |                |              |         |
| N1                             | 0.919          | 0.789–1.059  | 0.242   | 0.985          | 0.825–1.114  | 0.581   |
| N2                             | 1.086          | 0.896–1.316  | 0.399   | 1.131          | 0.923–1.386  | 0.235   |
| N3                             | 1.226          | 1.026–1.465  | 0.025   | 1.292          | 1.070–1.559  | 0.008   |
| Histology type                |                |              |         |                |              |         |
| IDC Ref                       |                |              |         |                |              |         |
| ILC                           | 1.390          | 1.192–1.620  | <0.001  | 1.428          | 1.215–1.679  | <0.001  |
| Grade                         |                |              |         |                |              |         |
| I Ref                         |                |              |         |                |              |         |
| II                             | 1.315          | 1.062–1.629  | 0.012   | 1.392          | 1.104–1.755  | 0.005   |
| III–IV                        | 1.809          | 1.443–2.267  | <0.001  | 1.953          | 1.531–2.492  | <0.001  |
| Tumor subtype                 |                |              |         |                |              |         |
| HR+/HER2− Ref                 |                |              |         |                |              |         |
| HR+/HER2+                     | 0.834          | 0.696–1.000  | 0.05    | 0.859          | 0.711–1.038  | 0.166   |
| HR−/HER2+                     | 0.637          | 0.447–0.908  | 0.013   | 0.684          | 0.477–0.982  | 0.039   |
| Triple-negative               | 3.188          | 2.642–3.848  | <0.001  | 3.360          | 2.762–4.087  | <0.001  |
| Surgery                       |                |              |         |                |              |         |
| Yes Ref                       |                |              |         |                |              |         |
| No                            | 2.078          | 1.826–2.364  | <0.001  | 2.057          | 1.796–2.356  | <0.001  |
| Radiation                     |                |              |         |                |              |         |
| Yes Ref                       |                |              |         |                |              |         |
| No                            | 0.968          | 0.861–1.088  | 0.58    | 0.963          | 0.851–1.089  | 0.548   |
| Chemotherapy                  |                |              |         |                |              |         |
| Yes Ref                       |                |              |         |                |              |         |
| No                            | 1.343          | 1.182–1.525  | <0.001  | 1.361          | 1.189–1.556  | <0.001  |

OS, overall survival; CSS, cancer-specific survival; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; CI, confidence interval; Ref, reference.
den was also significantly related to poorer survival in previous studies, such as larger tumor size and more positive lymph nodes [18, 30]. Our study revealed that later tumor stage or higher lymph node stage will significantly increase the risk of death for patients with BOM, as well. The fact that histological grade has a great impact on the prognosis of patients with breast cancer is widely recognized. Many studies [8, 31] illustrated that higher histological grade will increase the mortality of breast cancer with BM, which was also confirmed in our study.

Previous retrospective studies [32, 33] have shown that surgery of the breast can improve survival for stage IV breast cancer, especially for patients with BOM [24, 25]. This was also demonstrated in our study: the risk of death for patients without surgery was twice as high as for patients receiving surgery. Chemotherapy is the main treatment to delay the progression of advanced breast cancer and is widely applied to patients with visceral metastasis. Palliative chemotherapy has been shown to significantly improve the survival of patients with BM [5, 19]. This was also confirmed in our study, especially for patients with IDC, whose median OS increased from 36 months to 48 months, while chemotherapy extended the median OS for ILC only by 5 months, which may be due to less sensitivity to chemotherapy for ILC than IDC [20]. ILC has a higher proportion of hormone receptor-positive status and may receive more endocrine therapy in the era of standardized therapy, although no information can be acquired from the SEER database whether and which endocrine treatment was given. Therefore, ILC received less chemotherapy than IDC although both developed BM in our study. Since patients with ILC also benefited from chemotherapy in our study, chemotherapy can be used for the treatment of ILC with BM. Generally speaking, radiotherapy has the benefits to release pain and obtain satisfactory local control. Some previous studies have demonstrated that breast radiotherapy can improve survival significantly for patients with metastatic breast cancer [34]. However, radiotherapy had no impact on patients with BM in our study, which was consistent with another study [19].

Several limitations of this study must be clarified. Firstly, baseline conditions of ILC and IDC were not completely balanced due to the retrospective nature of the study, and propensity score matching failed to balance the difference. So, we applied subgroup analysis to show the difference in prognosis between IDC and ILC explicitly, and we also performed a multivariable Cox propor-
Patients with ILC have worse outcomes compared to those with IDC when associated with BOM, especially in subgroups with lower histological grade or tumor burden. Surgery of the breast and chemotherapy could improve the prognosis for both ILC and IDC. Thus, more effective treatment measures may be needed for ILC with BOM, such as more aggressive chemotherapy regimes, CDK4/6 inhibitors, new targeted drugs, etc.

Conclusion

Patients with ILC have worse outcomes compared to those with IDC when associated with BOM, especially in subgroups with lower histological grade or tumor burden. Surgery of the breast and chemotherapy could improve the prognosis for both ILC and IDC. Thus, more effective treatment measures may be needed for ILC with BOM, such as more aggressive chemotherapy regimes, CDK4/6 inhibitors, new targeted drugs, etc.

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Statement of Ethics

This study used previously collected data without personally identifiable information; the need for informed consent had been waived due to the retrospective nature of the study, and the study was deemed exempt from review by the Ethics Committee of the Guangxi Medical University Cancer Hospital.

Conflict of Interest Statement

The authors declare that they have no competing interests.

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Author Contributions

Y.L. and Y.Y. conceived and designed this study. Y.L., S.H., and A.M. collected and analyzed the data. Y.L. and A.M. organized the manuscript. Y.L. and Y.Y. reviewed the paper and revised the manuscript. All authors have read and approved the final manuscript.

Data Availability Statement

The data were abstracted from an open database, the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov).

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Author Contributions

Y.L. and Y.Y. conceived and designed this study. Y.L., S.H., and A.M. collected and analyzed the data. Y.L. and A.M. organized the manuscript. Y.L. and Y.Y. reviewed the paper and revised the manuscript. All authors have read and approved the final manuscript.

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