Different Clinicopathological Characteristics and Prognostic Factors for Occult and Non-occult Breast Cancer: Analysis of the SEER Database

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Purpose: The aim of our study was to evaluate the different clinicopathological characteristics and prognostic factors for occult and non-occult breast cancer.

Methods: 572 OBC cases and 117,217 non-OBC patients between 2004 and 2015 was selected from Surveillance, Epidemiology, and End Results (SEER) database. We analyzed the clinicopathological characteristics and survival outcomes between OBC and non-OBC patients. Furthermore, the propensity score matching method was utilized to reduce the influences of baseline differences in demographic and clinical characteristics on outcome differences. Univariable and multivariable analyses were used to evaluate the prognostic factors of OBC patients.

Results: Compared with non-OBC patients, OBC patients in this study presented a higher proportion of older age, American Joint Committee on Cancer (AJCC) N3 stage, estrogen receptor (ER)-negative status, progesterone receptor (PR)-negative status, and human epidermal growth factor receptor-2 (HER-2)-positive status, and underwent more chemotherapy. Multivariate analysis revealed a better survival in overall patients with OBC patients according to breast cancer-specific survival (BCSS) and overall survival (OS). Propensity score analysis also achieved a similar result for OBC patients. Stratified analyses by nodal status and molecular subtypes indicated that these survival advantage were mainly presented in patients with AJCC N2/N3 stage or hormone receptor (HR)-positive tumors. In addition, nodal status, HER-2 status, and radiation status were demonstrated to be three independent prognostic factors for OBC patients.

Conclusion: Patients with OBC retained exclusive clinical characteristics and were shown to have a better outcome compared with non-OBC patients, especially for those with N2/N3 stage or HR-positive tumors.

Keywords: occult breast cancer, breast cancer-specific survival, overall survival, SEER database, prognostic factor
INTRODUCTION

Occult breast cancer (OBC) is a rare type of breast cancer which generally presents as axillary lymph node metastases without identified primary breast lesion. It is reported to be only account for 0.3–1.0% of all breast cancers, with a peak incidence at about 55 years old (1–5). Although it is generally believed that OBC has a similar biological behavior compared with node-positive non-OBC, the clinicopathological characteristics of this disease are still unclear (6–8). Some previous studies have indicated that the estrogen receptor (ER) status, triple negative subtype, and at least four positive lymph nodes were individual prognostic factors for occult breast cancer (6, 9–11). The survival outcomes of patients with OBC are also controversial. Compared with non-OBC cases, OBC patients were shown to have a similar or less unfavorable outcome (12, 13), while the others have drawn contrary conclusions (14, 15).

Up to now, the majority of the studies on OBC only consisted of a small, single-institution sample size. Prospective randomized trials have also not been performed due to the rarity of these patients. Ge et al. (13) conducted a study based on large population database (the Surveillance, Epidemiology, and End Results, SEER) to evaluate the survival difference between occult and non-occult breast cancer patients. The other SEER-based study by Johnson et al. (16) assessed the effect of local therapy and other clinical variables on risk of breast cancer-specific mortality in OBC patients. However, these two studies mainly focused on the importance of local regional treatment (type of surgery or radiation) in OBC. The clinicopathological characteristics and prognostic factors between OBC and non-OBC patients in different tumor stages and molecular subtypes have not been fully elucidated. Therefore, we conducted this study based on SEER database with newest data from 2004 to 2015 and utilize with propensity matching score method, aiming to better demonstrate the different clinicopathological characteristics and prognostic factors (especially the nodal status and molecular subtypes) between OBC and non-OBC patients.

MATERIALS AND METHODS

Compliance With Ethical Standards

In the United States, cancer is a reportable disease. So we did not need to get patient consent. The SEER database is available to public. We signed a Data-Use Agreement for the SEER 1973–2015 Research Data File to get access conditions.

Data Source and Study Population

We used SEER*Stat version 8.3.5 to generate a case list. We enrolled 117,789 patients according to the following inclusion criteria: female; year of diagnosis from 2004 to 2015; age of diagnosis between 20 and 79 years; breast cancer as the only primary malignant cancer diagnosis; unilateral cancer; American Joint Committee on Cancer (AJCC) sixth edition stage T0–T3; AJCC N1–N3; one or more positive LNs. Patients who present with distant metastasis, in situ disease, or had not undergone surgery were expelled from the study. Patients with stage T0N1–3M0 were defined as OBC and stage T1–3N1–3M0 were defined as non-OBC. We calculated follow-up durations from January 1, 2004 to December 31, 2015. Of 117,789 patients enrolled, 572 patients were diagnosed as OBC and 117,217 patients as non-OBC. Patient characteristics and treatment courses in our study were identified, including age, race, year of diagnosis, marital status, mastectomy or breast conserving surgery (BCS), radiotherapy and chemotherapy status. Tumor characteristics included laterality, tumor grade, AJCC stage, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER-2) status, and tumor subtype. The HER-2 status was not recorded in the SEER database until 2010, the variable was not available or could not be used by some patients. The definition of breast subtype was as follows: Her2+/HR- (ER and/or PR positive, HER2 positive), Her2+/HR- (ER and PR negative, HER2 positive), Her2-/HR+ (ER and/or PR positive, HER2 negative), Triple negative (ER, PR, and HER2 negative).

Outcome Measurement

In our study, breast cancer-specific survival (BCSS) was used as a primary study outcome. It was calculated from the date of diagnosis to the date of death that due to breast cancer. Overall survival (OS), served as secondary outcome, was defined as from the date of diagnosis to the date of death, whether the patient died of breast cancer or not. Patients who were alive on the date of last contact were censored.

Statistical Analysis

The chi-square test were conducted to describe the demographic and clinical characteristics of the OBC and non-OBC cases, in both the whole groups and 1:1 propensity score matched groups. The Kaplan–Meier method was utilized to generate the survival curves while the log-rank test was conducted to identify whether the differences in BCSS or OS rates between OBC patients and non-OBC patients was statistically significant. Hazard ratio (HR) with 95% confidence intervals (CI) was calculated by using a Cox proportional hazard regression model to determine the outcome-related factors. Factors with a P-value of 0.05 or less in univariate analysis were included as candidate variables in the multivariate analysis. These statistical analyses were conducted by using SPSS version 24.0 and R software version 3.6.1. In order to reduce the influences of baseline differences in demographic and clinical characteristics on outcome differences, the psmatch2 module were used to perform propensity score matching (17) in Stata version 13.0. The command matched OBC patients to non-OBC patients were with the following factors: age, year of diagnosis, race, marital status, grade, laterality, AJCC N status, ER status, PR status, HER-2 status, mastectomy or not, chemotherapy status, radiation status. All statistical analyses were two-sided, and a P-value of <0.05 was considered as a significance level.

RESULTS

Demographics and Clinical Characteristics of the Study Population

Overall, 117,789 eligible patients were enrolled in our study, including 572 cases of OBC and 117,217 cases of non-OBC.
The median follow-up time was 63 months. The baseline characteristics of the OBC and non-OBC are summarized in Table 1. There were significant differences in characteristics between OBC and non-OBC cases, including age, grade, nodal status, ER status, PR status, HER-2 status, breast subtype, type of surgery, and chemotherapy status. The OBC patients presented a higher proportion of older age (50–79 years old, 76.2 vs. 65.2%, \( p < 0.001 \)), unknown grade (71.9 vs. 3.3%, \( p < 0.001 \)), N3 stage

| Characteristics               | OBC \((n = 572)\) | Non-OBC \((n = 117,217)\) | Total \((n = 117,789)\) | \( P^{c} \) |
|-------------------------------|------------------|---------------------------|------------------------|-------|
| Median follow-up (months) (IQR) | 61.5 (30–100.75) | 63 (33–102) | 63 (33–102) | 0.128 |
| Year of diagnosis             |                  |              |            |       |
| 2004–2009                     | 254 44.4         | 55,784 47.6   | 56,038 47.6 | 0.128 |
| 2010–2015                     | 318 55.6         | 76,419 65.2   | 76,755 65.2 | 0.536 |
| Age (years)                   |                  |              |            |       |
| 20–49                         | 136 23.8         | 40,798 34.8   | 40,934 34.8 | <0.001 |
| <0.001                        | 50–79            | 76,419 65.2   | 76,755 65.2 |       |
| Race                          |                  |              |            |       |
| White                         | 450 78.7         | 91,273 77.9   | 91,723 77.9 | 0.536 |
| Black                         | 76 13.3          | 14,957 12.8   | 15,033 12.8 |       |
| Othera                        | 46 8.0           | 10,987 9.4    | 11,033 9.4  |       |
| Marital status                |                  |              |            |       |
| Married                       | 340 59.4         | 72,521 61.9   | 72,861 61.9 | 0.233 |
| Not marriedb                  | 232 40.6         | 44,696 38.1   | 44,928 38.1 |       |
| Laterality                    |                  |              |            |       |
| Left                          | 306 53.5         | 59,336 50.6   | 59,642 50.6 | 0.170 |
| Right                         | 266 46.5         | 57,881 49.4   | 58,147 49.4 |       |
| Grade                         |                  |              |            |       |
| I and II                      | 29 5.1           | 62,969 53.7   | 62,925 53.4 | <0.001 |
| III and IV                    | 132 23.1         | 50,422 43.0   | 50,554 42.9 |       |
| Unknown                       | 411 71.9         | 3,899 3.3     | 4,310 3.7  |       |
| AJCC stage                    |                  |              |            |       |
| II                            | 368 64.3         | 78,516 67.0   | 78,884 67.0 | 0.179 |
| III                           | 204 35.7         | 38,781 33.0   | 38,905 33.0 |       |
| Nodal status                  |                  |              |            |       |
| 1 to 3                        | 368 64.3         | 86,604 73.9   | 86,972 73.8 | <0.001 |
| 4 to 9                        | 105 18.4         | 20,636 17.6   | 20,741 17.6 |       |
| >9                            | 99 17.3          | 9,977 8.5     | 10,076 8.6 |       |
| ER status                     |                  |              |            |       |
| Positive                      | 302 52.8         | 90,613 77.3   | 90,915 77.2 | <0.001 |
| Negative                      | 221 38.6         | 23,750 20.3   | 23,971 20.4 |       |
| Others                        | 49 8.6           | 2,854 2.4     | 2,903 2.5  |       |
| PR status                     |                  |              |            |       |
| Positive                      | 202 35.3         | 77,786 66.4   | 77,988 66.2 | <0.001 |
| Negative                      | 310 54.2         | 35,779 30.5   | 36,089 30.6 |       |
| Others                        | 60 10.5          | 3,652 3.1     | 3,712 3.2  |       |
| HER-2 status                  |                  |              |            |       |
| Positive                      | 88 15.4          | 11,478 9.8    | 11,566 9.8  | <0.001 |
| Negative                      | 185 32.3         | 47,530 40.5   | 47,715 40.5 |       |
| Others                        | 299 52.3         | 58,209 49.7   | 58,508 49.7 |       |
| Breast subtype                |                  |              |            |       |
| Her2+/HR+                     | 54 9.4           | 7,981 6.8     | 8,035 6.8  | <0.001 |
| Her2+/HR-                     | 32 5.6           | 3,477 3.0     | 3,509 3.0  |       |
| Her2-/HR+                     | 114 19.9         | 40,574 34.6   | 40,688 34.5 |       |
| Triple negative               | 71 12.4          | 6,904 5.9     | 6,975 5.9  |       |
| Unknown                       | 301 52.6         | 58,281 49.7   | 58,582 49.7 |       |
| Mastectomy                    |                  |              |            |       |
| Yes                           | 202 35.3         | 66,315 56.6   | 66,517 56.5 | <0.001 |
| No                            | 370 64.7         | 50,902 43.4   | 51,272 43.5 |       |
| Chemotherapy                  |                  |              |            |       |
| Yes                           | 480 83.9         | 88,848 75.8   | 89,328 75.8 | <0.001 |
| No/Unknown                    | 92 16.1          | 28,369 24.2   | 28,461 24.2 |       |
| Radiation                     |                  |              |            |       |
| Yes                           | 320 55.9         | 65,740 56.1   | 66,060 56.1 | 0.769 |
| No                            | 252 44.1         | 51,477 43.9   | 51,729 43.9 |       |

OBC, occult breast cancer; non-OBC, non-occult breast cancer; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; IQR, interquartile range.

\(^{a}\)Other includes American Indian/Alaskan native and Asian/Pacific Islander and Unknown.

\(^{b}\)Not married includes divorced, separated, single (never married), unmarried or domestic partner, and widowed.

\(^{c}\)The \(P\)-value of the Chi-square test was calculated between the OBC and non-OBC groups, and bold type indicates significance.
Comparison of Survival Between OBC and Non-OBC Patients

As shown in Table 2, compared to overall patients with non-OBC, multivariate analysis revealed a better survival in overall patients with OBC according to BCSS and OS (HR = 0.646, 95% CI = 0.504–0.828, p = 0.001; HR = 0.709, 95% CI = 0.575–0.874, p = 0.001, respectively). We also stratified the different nodal stages to validate the different survival outcomes between OBC and non-OBC cases. In patients with N1 stage, the OBC patients demonstrated a better prognosis than non-OBC patients in terms of both BCSS and OS (HR = 0.661, 95% CI = 0.456–0.959, p = 0.029; HR = 0.767, 95% CI = 0.572–1.029, p = 0.077, respectively). For N2 stage, no statistical survival difference were identified between OBC cases and non-OBC cases. Compared to overall patients with non-OBC, multivariate analysis revealed a better survival in overall patients with OBC according to BCSS and OS (HR = 0.542, 95% CI = 0.312–0.943, p = 0.030; HR = 0.607, 95% CI = 0.378–0.974, p = 0.039, respectively). While for patients with N3 stage, no statistical survival differences were identified between OBC and non-OBC patients. In addition, stratified analyses by nodal status and molecular subtype was also conducted to validate the different outcomes between OBC cases and non-OBC cases. Compared to overall patients with non-OBC, multivariate analysis revealed a better prognosis than non-OBC patients in terms of both BCSS and OS (HR = 0.646, 95% CI = 0.504–0.828, p = 0.001; HR = 0.709, 95% CI = 0.575–0.874, p = 0.001, respectively). For patients with N1 stage, no statistical survival differences were identified between OBC and non-OBC patients. While for patients with N2/N3 stage (shown in Table 4), the OBC patients demonstrated a better prognosis than non-OBC patients in terms of both BCSS and OS (HR = 0.651, 95% CI = 0.466–0.907, p = 0.011; HR = 0.673, 95% CI = 0.499–0.908, p = 0.009).

Analyses on the Outcome-Related Factors of OBC Using Cox Proportional Hazard Regression Models

We investigated the prognostic factors that related with BCSS and OS in the cohort of OBC patients. The univariate Cox regression analysis for each variable of OBC was shown in Supplementary Table S1. AJCC stage, nodal status, ER, PR, or HER-2 status and radiation status significantly correlated with BCSS and OS, thereby were selected into multivariate Cox regression analysis.

As shown in Table 6, nodal status, HER-2 status, and radiation status were three independent prognostic factors for OBC patients in the multivariate Cox regression analysis. Compared of N2/N3 patients, OBC had better survival compared with non-OBC (BCSS, HR = 0.651, 95% CI = 0.466–0.907, p = 0.011; OS, HR = 0.673, 95% CI = 0.499–0.908, p = 0.009).
TABLE 3 | Baseline characteristics of patients with OBC and non-OBC in the propensity score matched group.

| Characteristics          | OBC (n = 572) | Non-OBC (n = 572) | Total (n = 1,144) | P<sup>c</sup> |
|--------------------------|---------------|-------------------|-------------------|--------------|
| Median follow-up (months) (IQR) | 60.5 (30–100.75) | 61.5 (32–101.75) | 61 (31–101) |              |
| Year of diagnosis        |               |                   |                   | 0.721        |
| 2004–2009                | 254           | 260               | 514               |              |
| 2010–2015                | 318           | 312               | 630               |              |
| Age (years)              |               |                   |                   |              |
| 20–49                    | 136           | 142               | 278               | 0.679        |
| 50–79                    | 436           | 430               | 866               |              |
| Race                     |               |                   |                   |              |
| White                    | 450           | 458               | 908               | 0.444        |
| Black                    | 76            | 79                | 155               |              |
| Other<sup>a</sup>        | 46            | 35                | 81                |              |
| Marital status           |               |                   |                   |              |
| Married                  | 340           | 346               | 686               | 0.717        |
| Not married<sup>b</sup>  | 232           | 226               | 458               |              |
| Laterality               |               |                   |                   |              |
| Left                     | 306           | 309               | 615               | 0.859        |
| Right                    | 266           | 263               | 529               |              |
| Grade                    |               |                   |                   |              |
| I and II                 | 29            | 29                | 58                | 1.000        |
| III and IV               | 132           | 132               | 264               |              |
| unknown                  | 411           | 411               | 822               |              |
| Nodal status             |               |                   |                   |              |
| 1 to 3                   | 368           | 367               | 735               | 0.642        |
| 4 to 9                   | 105           | 96                | 201               |              |
| >9                       | 99            | 109               | 208               |              |
| ER status                |               |                   |                   |              |
| Positive                 | 302           | 304               | 606               | 0.666        |
| Negative                 | 221           | 211               | 432               |              |
| Others                   | 49            | 57                | 106               |              |
| PR status                |               |                   |                   |              |
| Positive                 | 202           | 201               | 403               | 0.982        |
| Negative                 | 310           | 309               | 619               |              |
| Others                   | 60            | 62                | 122               |              |
| HER-2 status             |               |                   |                   |              |
| Positive                 | 88            | 73                | 161               | 0.371        |
| Negative                 | 185           | 200               | 385               |              |
| Others                   | 299           | 299               | 598               |              |
| Breast subtype           |               |                   |                   |              |
| Her2+/HR+                | 54            | 43                | 97                | 0.729        |
| Her2+/HR–                | 32            | 29                | 61                |              |
| Her2–/HR+                | 114           | 119               | 233               |              |
| Triple negative          | 71            | 80                | 151               |              |
| Unknown                  | 301           | 301               | 602               |              |
| Mastectomy               |               |                   |                   |              |
| Yes                      | 202           | 210               | 412               | 0.622        |
| No                       | 370           | 362               | 732               |              |
| Chemotherapy             |               |                   |                   |              |
| Yes                      | 480           | 490               | 970               | 0.410        |
| No/Unknown               | 92            | 82                | 174               |              |
| Radiation                |               |                   |                   |              |
| Yes                      | 320           | 317               | 637               | 0.945        |
| No                       | 252           | 255               | 507               |              |

OBC, occult breast cancer; non-OBC, non-occult breast cancer; AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; HR, hormone receptor; IQR, interquartile range.

<sup>a</sup> Other includes American Indian/Alaskan native and Asian/Pacific Islander and Unknown.

<sup>b</sup> Not married includes divorced, separated, single (never married), unmarried or domestic partner, and widowed.

<sup>c</sup> The P-value of the Chi-square test was calculated between the OBC and non-OBC groups.

with N1 stage, the presence of N3 was an independent predictor for poor prognosis in OBC cases (HR = 3.955, 95% CI = 2.233–7.006, p < 0.001 for BCSS; HR = 2.799, 95% CI = 1.717–4.563, p < 0.001 for OS, respectively). HER-2-negative occult breast cancer was shown to be associated with a worse OS (HR = 3.466, 95% CI = 1.211–9.808, p = 0.020) but not BCSS. In addition, the lack of radiotherapy was also an independent predictor for worse prognosis in OBC patients (HR = 2.167, 95% CI = 1.306–3.597, p = 0.003 for BCSS; HR = 2.164, 95% CI = 1.414–3.311, p < 0.001 for OS, respectively).

In OBC patients, significant differences in BCSS and OS were observed between the groups stratified by nodal status (Figure 4, Figure 5).
TABLE 4 | Comparison of breast cancer-specific survival (BCSS) and overall survival (OS) between OBC and non-OBC in different nodal status using a multivariate Cox proportional hazard model in the propensity score matched group.

| Nodal status   | BCSS   | OS     |
|----------------|--------|--------|
|                | HR (95% CI) | P      | HR (95% CI) | P      |
| N1             | 0.331  | 0.619  |
| OBC            | 0.785 (0.481–1.280) | 0.005  | 0.903 (0.605–1.349) | 0.018  |
| non-OBC        | Reference |        | Reference |        |
| N2/N3          | 0.019  | 0.013  |
| OBC            | 0.604 (0.397–0.919) | 0.252  | 0.620 (0.425–0.904) | 0.276  |
| non-OBC        | Reference |        | Reference |        |
| N1/N2/N3       | 0.025  | 0.040  |
| OBC            | 0.697 (0.508–0.957) | 0.753 (0.574–0.987) | 0.707  |
| non-OBC        | Reference |        | Reference |        |

OBC, occult breast cancer; non-OBC, non-occult breast cancer; HR, hazard ratio; CI, confidence interval; BCSS, breast cancer-specific survival; OS, overall survival.

**P-value** was adjusted by a multivariate Cox proportional hazard regression model including age, race, marital status, year of diagnosis, grade, mastectomy or not, ER status, PR status, HER-2 status, chemotherapy, and radiation. Bold type indicates significance.

TABLE 5 | Comparison of breast cancer-specific survival (BCSS) and overall survival (OS) between OBC and non-OBC in different hormone receptor status using a multivariate Cox proportional hazard model in the propensity score matched group.

| Cohorts    | BCSS   | OS     |
|------------|--------|--------|
|            | HR (95% CI) | P      | HR (95% CI) | P      |
| HR (+)     | 0.005  | 0.181  |
| OBC        | 0.482 (0.290,0.801) | 0.603 (0.397,0.916) | 0.252  |
| non-OBC    | Reference |        | Reference |        |
| HR (-)     | 0.276  |
| OBC        | 0.766 (0.485,1.209) | 0.800 (0.536,1.195) | 0.707  |
| non-OBC    | Reference |        | Reference |        |
| HER-2 (+)  | 0.077  | 0.954  |
| OBC        | 0.751 (0.169,3.345) | 0.751 (0.169,3.345) | 0.802  |
| non-OBC    | Reference |        | Reference |        |
| HER-2 (-)  | 0.968  |
| OBC        | 0.931 (0.533,1.627) | 0.986 (0.597,1.626) | 0.968  |
| non-OBC    | Reference |        | Reference |        |
| TNBC       | 0.919 (0.446,1.891) | 0.919 (0.446,1.891) | 0.811  |
| OBC        | 0.985 (0.461,2.105) | 0.985 (0.524,1.884) | 0.640  |
| non-OBC    | Reference |        | Reference |        |

OBC, occult breast cancer; non-OBC, non-occult breast cancer; HR, hormone receptor; HR, hazard ratio; HER-2, human epidermal growth factor receptor-2; TNBC, triple negative breast cancer; CI, confidence interval; BCSS, breast cancer-specific survival; OS, overall survival.

**P-value** was adjusted by a multivariate Cox proportional hazard regression model. Bold type indicates significance.

DISCUSSION

OBC is a rare type of breast cancer. Only few studies have ever evaluated the different clinicopathological characteristics and prognostic factors between OBC and non-OBC patients due to the rarity of these cases. The prognosis of OBC up to now is also controversial. Some studies reported a similar outcome or even worse prognosis for OBC patients compared with non-OBC patients (11, 14, 15). However, in a former study based on SEER database, Ge and colleagues also revealed a survival advantage for OBC patients by using propensity score analysis (13). The other SEER-based study by Johnson et al. (16) assessed the effect of local therapy and other clinical variables on risk of breast cancer-specific mortality in OBC patients. However, these two SEER-based studies mainly focused on the importance of local regional treatment (type of surgery or radiation) in OBC. The clinicopathological characteristics and prognostic factors between OBC and non-OBC patients in different tumor stages and molecular subtypes have not been fully elucidated. Therefore, we conducted this historical cohort study based on SEER database with newest data from 2004 to 2015 and utilize with propensity matching score method, aiming to better demonstrate the different clinicopathological characteristics, and prognostic factors (especially the nodal status and molecular subtypes) between OBC and non-OBC patients.

Totally, 572 cases of OBC and 117,217 cases of non-OBC were selected in this study. Compared with non-OBC patients, the OBC patients appeared to have a higher proportion of older age, N3 stage, ER-negative, PR-negative, and HER2-positive tumors. Additionally, the OBC patients were more likely to receive mastectomy and chemotherapy, with most of these findings were similar to the previous studies (7, 10, 12, 18).

Collectively for all selected cases in our study, multivariate analysis indicated a better survival in overall OBC patients compared with overall non-OBC patients. For patients with N1 or N2 stage, the OBC patients also demonstrated a better prognosis than non-OBC patients. While for patients with N3 stage, no statistical survival differences were observed between OBC and non-OBC patients.

Furthermore, the statistical method of propensity matching score was also conducted in this study to reduce selective bias and minimize the impact of confounding factors. 1144 patients included 572 cases in each subgroup were identified in 1:1 propensity score matched study. No factors differed significantly between OBC and non-OBC patients for matched groups. Compared to overall patients with non-OBC in matched
FIGURE 1 | Kaplan–Meier curves of breast cancer-specific survival (BCSS) (A) and overall survival (OS) (B) based on two groups of propensity score matched patients.

FIGURE 2 | Kaplan–Meier curves of breast cancer-specific survival (BCSS) (A) and overall survival (OS) (B) based on two groups of propensity score matched N2/N3 patients.

FIGURE 3 | Kaplan–Meier curves of breast cancer-specific survival (BCSS) (A) and overall survival (OS) (B) based on two groups of propensity score matched HR-positive patients.
TABLE 6 | Multivariate Cox proportional hazard model of breast cancer-specific survival (BCSS) and overall survival (OS) of OBC patients.

| Variables   | BCSS       | OS        |
|-------------|------------|-----------|
|             | HR (95% CI)| P<sup>a</sup> | HR (95% CI) | P<sup>a</sup> |
| Nodal status|            |           |            |
| 1–3         | Reference  |           | Reference  |           |
| 4–9         | 1.761 (0.910–3.407) | 0.093 | 1.502 (0.868–2.600) | 0.146 |
| >9          | 3.955 (2.233–7.008) | <0.001 | 2.799 (1.717–4.563) | <0.001 |
| ER status   |            |           |            |
| Positive    | Reference  |           | Reference  |           |
| Negative    | 1.552 (0.816–2.954) | 0.181 | 1.329 (0.780–2.266) | 0.295 |
| Others      | 4.485 (1.146–17.556) | 0.031 | 2.932 (0.803–10.707) | 0.104 |
| PR status   |            |           |            |
| Positive    | Reference  |           | Reference  |           |
| Negative    | 2.048 (0.961–4.408) | 0.067 | 1.658 (0.909–3.023) | 0.099 |
| Others      | 1.067 (0.231–4.919) | 0.934 | 0.895 (0.230–3.481) | 0.873 |
| HER-2 status|            |           |            |
| Positive    | Reference  |           | Reference  |           |
| Negative    | 2.662 (0.916–7.732) | 0.072 | 3.446 (1.211–9.808) | 0.020 |
| Others      | 1.512 (0.529–4.323) | 0.440 | 2.005 (0.713–5.639) | 0.187 |
| Radiation   |            |           |            |
| Yes         | Reference  |           | Reference  |           |
| No          | 2.167 (1.306–3.597) | 0.003 | 2.164 (1.414–3.311) | <0.001 |

OBC, occult breast cancer; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; HR, hazard ratio.

<sup>a</sup>P-value was adjusted by multivariate Cox proportional hazard regression model including nodal status, ER status, PR status, HER-2 status, radiation. Bold type indicates significance.

FIGURE 4 | Kaplan–Meier curves of breast cancer-specific survival (BCSS) (A) and overall survival (OS) (B) based on nodal status for all occult breast cancer (OBC) patients.

In the cohort of OBC patients, we also sought to investigate the prognostic factors that were related with survival. Univariate Cox regression analysis revealed that AJCC stage, nodal status,
ER, PR, or HER-2 status and radiation status significantly correlated with BCSS and OS. However, results from multivariate Cox regression analysis revealed that N3 nodal stage and lack of radiotherapy were two independent prognostic factors for both BCSS and OS. HER-2 negative status only showed an unfavorable prognosis in OS. Nevertheless, we also observed a tendency with poor prognosis in BCSS for patients with ER/PR or HER-2 negative tumor (HR = 1.552, 95% CI = 0.816–2.954, \( p = 0.181 \), HR = 2.048, 95% CI = 0.951–4.408, \( p = 0.067 \), and HR = 2.662, 95% CI = 0.916–7.732, \( p = 0.072 \), respectively). Similar situations were also observed in patients with N2 stage. Compared to patients with N1 stage, patients with 4–9 lymph nodes positive revealed to have a tendency with poor prognosis in BCSS or OS (HR = 1.761, 95% CI = 0.910–3.407, \( p = 0.093 \), and HR = 1.502, 95% CI = 0.868–2.600, \( p = 0.146 \), respectively). These may partly due to an limited number of breast cancer-specific events which could not provide sufficient statistical power. Moreover, our analysis suggested that chemotherapy did not improve the outcome of OBC patients. Potential explanations might be a selective bias for retrospective study. Those patients who had a favorable prognosis would rather not to receive chemotherapy while those with high probability of relapse would choose to receive chemotherapy. In addition to this, the exact regimens or cycles of the chemotherapy was also not able to be achieved, thereby resulting in limited data for analysis.
The main advantage of this study is a relatively large sample size of OBC patients based on SEER database and the utilization of propensity matching score method to reduce selective bias and minimize the impact of confounding factors. However, several limitations in this study should also be mentioned. Firstly, our study was based on a retrospective cohort. Although the propensity matching score method was used, a number of potential selection biases might still existed. Secondly, some treatment information such as endocrine therapy or anti-HER2 therapy is not available in SEER, while these information were critically essential for the survival outcome for node-positive breast cancer. Thirdly, a lack of central pathology review should be also acknowledged in our study. Additional population-based and multi-institutional studies with larger sample size are warranted.

Up to now, the treatment of OBC almost completely referred to non-OBC. Our study demonstrated that OBC patients had a better outcome compared to non-OBC patients, especially for those with N2/N3 stage or HR-positive tumors. Therefore, de-escalation therapy might be appropriate for selected OBC patients. Nodal status, HER-2 status, and radiation status were three independent prognostic factors for OBC patients. These results not only provided further understanding of OBC but also contributed to clinical practice that clinicians might provide improve clinical management for OBC patients.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

C-GS contributed to conception and design. K-YH, JZ, W-FF, and Y-XL contributed to the development of methodology. K-YH and JZ contributed to acquisition of data and analysis and interpretation of data. K-YH, JZ, Y-XL, and C-GS wrote, reviewed, and/or revised the manuscript. C-GS did study supervision. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/onc.2020.01420/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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