Clinicopathological characteristics and treatment outcomes of occult breast cancer: a population-based study

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Abstract

Background: Occult breast cancer (OBC) is a special type of breast cancer. Because of its rarity, clinicopathological information is still insufficient, causing a controversial condition about its treatment recommendation. Thus, we aimed to clarify major clinicopathological information, treatment strategies and prognosis of OBC based on a large population.

Methods: We retrospectively collected adult female OBC population from Surveillance, Epidemiology, and End Results database. We divided the whole cohort into two groups based on surgical treatment in-breast. Descriptive analysis of 18 clinicopathological variables was conducted. Survival analysis was performed based on different clinicopathological factors. Univariate and multivariate Cox regression analysis was performed to identify potential independent predictor for prognosis of OBC.

Results: 1189 OBC patients were in final analysis and most of them were diagnosed as an early-stage carcinoma. Patients received breast-conserving treatment (BCT) was nearly two times of ones received mastectomy. Patients receiving radiotherapy in BCT group were significantly more than patients receiving radiotherapy in mastectomy group (61.76 vs. 50.9%, P < 0.001). After a median follow-up period of 62 months, 5-year and 10-year overall survival (OS) of all subjects was 81.6% and 68.8%, respectively. No significant difference in OS and breast-cancer specific survival (BCSS) was found between mastectomy and local breast-conserving surgery. Older age and larger number of positive lymph nodes causes a worse prognosis whereas radiotherapy brought a better clinical outcome for OBC patients.

Conclusions: OBC has a generally good prognosis. Less-intensive surgery does not negatively impact clinical outcomes of OBC while additional radiotherapy is totally beneficial to prolong OS and BCSS.

Keywords: Occult breast cancer, Surgical treatment, Systemic therapy, Radiotherapy, Survival

Background

Occult breast cancer (OBC) is a special type of breast cancer. It is first reported and described by Halsted as “cancerous axillary glands with non-demonstrable cancer of the mamma” in 1907 [1]. The present definition of OBC is a kind of primary breast cancer diagnosed histologically by biopsy of axillary lymph nodes but without clinical or radiographic finding (mammography and ultrasonography) in the breast itself [2, 3]. The incidence of OBC among all types of breast cancer is about 0.1 to 1% [4].

Because of its rarity and lack of primary focus within the breast, the clinicopathological traits of OBC, including lymph node metastasis, immunohistochemistry...
[hormone status/human epidermal factor receptor-2 (HER-2) status, etc.], is still unclear [5–8]. Moreover, prognosis of OBC is still debatable. 10-year overall survival of OBC in different reports varied from 45% to nearly 70% [9].

The National Comprehensive Cancer Network (NCCN) guidelines of breast disease recommended that patients diagnosed with OBC by magnetic resonance imaging (MRI) be treated in two ways according to nodal condition: (1) for T0N1M0 disease, Breast conserving therapy (BCT) [axillary lymph node dissection (ALND) plus whole breast radiotherapy with or without nodal radiotherapy] or ALND plus mastectomy (modified radical mastectomy, MRM) with or without radiotherapy; (2) for T0N2-3M0 disease, neoadjuvant systemic therapy (chemotherapy, endocrine therapy and targeting therapy) followed by MRM [9, 10].

In our study, we collected the latest edition of population-based data from the Surveillance, Epidemiology, and End Results (SEER) database. The main goal of our study is to further investigate the main clinicopathological features of OBC and acquire the most updated information of association between different types of treatment and prognosis.

Methods

Ethical statement

No patient informed consent is necessary because SEER database is publicly available and all data have been de-identified. We have submitted our application and obtained the approval of usage for the updated data of SEER database.

Data source and study cohort

We conducted a retrospective population-based cohort study using SEER 18 registry research data (Nov 2020 submission). The database included data from 18 population-based cancer registries (2000–2018) and covered approximately 27.8% of US population. Data-retrieving software SEER*STAT software ver. 8.3.9.1 was used to collect finally wanted data. The inclusion criteria include “Female”; age of diagnosis from 18 to 85; year of diagnosis from 2004 through 2018; diagnosis is primary breast cancer; American Joint Committee on Cancer breast staging T is T0 and M is M0; A known number of examined lymph nodes; positive lymph node not less than one (N+). Diagnosis not by histology, male patients, unknown laterality; breast cancer staging not T0, N staging with N0 or Nx, breast cancer with distal metastasis and unknown staging were all excluded.

Clinicopathological variables include age, year of diagnosis, race, marital status, grade, number of examined lymph nodes, number of positive lymph nodes, N staging, surgery types, radiation, chemotherapy, types of systemic therapy, subtypes of breast cancer, estrogen receptor (ER), progesterone receptor (PR), and HER-2. For the reason that HER-2 status was not recorded until 2010, it is not available in patients whose diagnosis were between 2004 and 2009. Subtypes of breast cancer includes Luminal A (ER-positive and/or PR-positive, HER-2 negative), Luminal B (ER-positive and/or PR-positive, HER-2 positive), HER-2 positive (ER and PR-negative, HER-2 positive) and triple negative (ER negative, PR negative and HER-2 negative).

Study endpoints and definition

In our study, OS served as primary outcome. It was defined as from the date of diagnosis to the date of death, no matter if the patient was dead from breast cancer or other reasons. Breast cancer-specific survival (BCSS) was secondary outcome. It was calculated from the day of diagnosis to the date of death caused by breast cancer.

Statistical analysis

For continuous variables, Shapiro tests will be conducted to identify whether they meet the criteria of normal distribution. If so, t-test will be used. If not, Wilcoxon rank sum and signed rank tests will be conducted. For categorical variables, Chi-square test or Fisher’s exact test will be utilized to describe the difference of rate for every clinicopathological variables between two groups. Survival curves were illustrated by the Kaplan–Meier method and the difference in OS and BCSS rate in different groups was identified using log-rank test. Hazard ratio (HR) with 95% confidence intervals (CI) was calculated by Cox proportional hazard regression model to determine the factors significantly related with outcome. Clinicopathological factors with P value < 0.1 in univariate analysis would be selected to be further analyzed in multivariate analysis. Significant association between selected factors and major outcomes was defined as P value of 0.05 or less. All the statistical analyses were two-sided and all the P-value less than 0.05 was set as a significance level except univariate analysis.

The above statistical analysis was conducted by R software version of 4.0.4. Main packages necessary for R program include "survival" (version 3.2-7), "survminer" (version 0.4.8), "ggplot2" (version 3.3.3) and "ggthemes" (version 4.2.4).
Results
Baseline clinicopathological description of OBC cohort
A total of 1189 patients diagnosed as OBC were included in ultimate analysis from 2004 to 2018. Mean age of complete OBC cohort was 59.88 years and the range of age is from 26 through 85. White patients predominated the whole population with a percentage of 79.20% while Asian or Pacific islander accounted for nearly 10%. Majority of OBC patients were married women (n = 699, 58.80%). Ductal carcinoma was the main histological types of OBC. For N staging and the general staging, patients with stage-N1/stage-IIA OBC took nearly two thirds of the whole population (n = 721, 60.60%). Breast-conserving surgery (BCS) were carried out in 120 patients (10.10%) whereas mastectomy was carried out in 422 patients (35.50%). More than half of all patients received radiotherapy and nearly 80% the whole cohort took chemotherapy. For subtypes of OBC, Luminal A subtype was the commonest one (n = 326, 27.40%) while HER-2 positive OBC merely made up of about 6.20% (n = 74) (Table 1).

Comparison of clinicopathological features in different treatment
We extracted OBC patients received either BCT/non-mastectomy [BCS of the breast (n = 120) or no surgical treatment of the breast (n = 628)] or mastectomy into further analysis (Table 2). Totally, 748 women had BCT therapy and 422 patients received mastectomy procedure. No significant difference was in demographic characteristics such as racial composition (P = 0.14) and marital status (P = 0.64). Average age of patients in BCT groups was significantly higher than that in mastectomy group (61.16±11.35 vs. 57.65±11.72, P < 0.001). Speaking of features of OBC, no significant difference was found for tumor grade, laterality between BCT and mastectomy group (P = 0.30 and P = 0.15, respectively). For tumor histology, it was marginally associated with surgical types (P = 0.04). For lymph node stage, majority of patients in BCT group had a relatively early N1 stage (64.30%) whereas proportion of patients in mastectomy group with stages of N2 and N3 were higher than that of patients in BCT group (22.51% vs. 17.51% for N2; 19.43% vs. 16.58% for N3, P < 0.001). A larger proportion of patients in mastectomy group were examined more than 10 lymph nodes (65.40% vs. 52.14%, P < 0.001) while a smaller part of patients in mastectomy group were examined 1-3 lymph nodes (11.61 vs. 17.51, P < 0.001). For number of positive lymph nodes, about half of the patients in both groups had 1–3 positive nodes but a larger proportion of patients in mastectomy group got 4–9 positive nodes (22.04% vs. 15.64%, P < 0.001). More than 60% of the

| Table 1 | Demographic and tumor characteristics |
|-----------------|-----------------|-----------------|
| Characteristic   | Number of patients | Percentage (%) |
| N               | 1189             | 100             |
| Age (year)      |                  |                 |
| < 40            | 54               | 4.54            |
| 40–49           | 176              | 14.80           |
| 50–59           | 348              | 29.27           |
| 60–69           | 343              | 28.85           |
| ≥ 70            | 268              | 22.54           |
| Mean of age (year) | 59.88           |                 |
| Median of age (year, range) | 60.00 (26–85)   |                 |
| Race            |                  |                 |
| White           | 942              | 79.23           |
| Black           | 139              | 11.69           |
| Asian or Pacific Islander | 95  | 7.99        |
| American Indian/Alaska Native | 9  | 0.76        |
| Unknown/other   | 4                | 0.34            |
| Marital status  |                  |                 |
| Not married     | 449              | 37.76           |
| Married         | 699              | 58.79           |
| Unknown         | 41               | 3.45            |
| Grade           |                  |                 |
| I/II            | 65               | 5.47            |
| III             | 223              | 18.76           |
| IV              | 10               | 0.84            |
| Unknown         | 891              | 74.94           |
| Laterality      |                  |                 |
| Right           | 565              | 47.52           |
| Left            | 624              | 52.48           |
| Histology       |                  |                 |
| Ductal carcinoma | 476          | 40.03           |
| Lobular carcinoma | 54           | 4.54            |
| Mixed type      | 25               | 2.10            |
| Other           | 634              | 53.32           |
| N               |                  |                 |
| N1mi            | 31               | 2.61            |
| N1              | 721              | 60.64           |
| N2              | 228              | 19.18           |
| N3              | 209              | 17.58           |
| No. of examined LN |                |                 |
| 1–3             | 182              | 15.31           |
| 4–9             | 177              | 14.89           |
| ≥ 10            | 675              | 56.77           |
| Other/unknown   | 155              | 13.04           |
| No. of positive LN |                |                 |
| 1–3             | 615              | 51.72           |
| 4–9             | 212              | 17.83           |
| ≥ 10            | 148              | 12.45           |
| Other/unknown   | 214              | 18.00           |
| Stage           |                  |                 |
| IB              | 31               | 2.61            |
Table 1 (continued)

| Characteristic                  | Number of patients | Percentage (%) |
|---------------------------------|--------------------|----------------|
| IIA                             | 722                | 60.72          |
| IIIA                            | 228                | 19.18          |
| IIIC                            | 208                | 17.49          |
| Surgery                         |                    |                |
| BCS                             | 120                | 10.09          |
| Mastectomy                      | 422                | 35.49          |
| None/unknown                    | 647                | 54.42          |
| Radiation                       |                    |                |
| Yes                             | 688                | 57.86          |
| None/unknown                    | 501                | 42.13          |
| Chemotherapy                    |                    |                |
| Yes                             | 929                | 78.13          |
| No/unknown                      | 260                | 21.87          |
| Type of systemic therapy        |                    |                |
| Neoadjuvant                     | 118                | 9.92           |
| Adjuvant                        | 583                | 49.03          |
| Neoadjuvant + adjuvant          | 104                | 8.75           |
| Only systemic therapy, no surgery| 28                 | 2.35           |
| Other                           | 190                | 15.98          |
| No/unknown                      | 166                | 13.96          |
| Subtypes                        |                    |                |
| Luminal A                       | 326                | 27.42          |
| Luminal B                       | 111                | 9.34           |
| HER2 positive                   | 74                 | 6.22           |
| Triple negative                 | 148                | 12.45          |
| Unknown                         | 530                | 44.58          |
| ER                              |                    |                |
| Negative                        | 414                | 34.82          |
| Borderline/unknown              | 100                | 8.41           |
| Positive                        | 675                | 56.77          |
| PR                              |                    |                |
| Negative                        | 598                | 50.29          |
| Borderline/unknown              | 126                | 10.60          |
| Positive                        | 465                | 39.11          |
| HER2                            |                    |                |
| Negative                        | 474                | 39.87          |
| Positive                        | 187                | 15.73          |
| Unknown                         | 528                | 44.41          |
| Vital status                    |                    |                |
| Alive                           | 917                | 77.12          |
| Dead                            | 272                | 22.88          |

*BCS* breast-conserving surgery, *MRM* modified radical mastectomy, *RM* radical mastectomy

patients in BCT group were diagnosed as IIA (64.30% vs. 53.55%) OBC while a higher proportion of population in mastectomy group were diagnosed as higher stages of OBC (IIIA: 22.75% vs. 17.51%; IIIC 19.19% vs. 16.58%, \(P < 0.001\)). Rate of Luminal A OBC topped in both BCS groups and mastectomy groups, with 28.61% and 25.12% respectively. HER-2 positive OBC has the lowest rate in both groups (less than 10%). When discussing three immunohistochemistry results apart (ER/PR/HER-2), however, no significant association was found between each of them with surgical procedure (\(P > 0.05\)). Regarding non-surgical management, higher proportion of patients in BCT received radiation compared with that of patients in mastectomy group (61.76% vs. 50.95%, \(P < 0.001\)). Different from radiotherapy, a greater percentage of patients in mastectomy group received chemotherapy than that of patients in BCT group (83.18% vs. 75.67%, \(P = 0.003\)). For patterns of systemic therapy, sequential neoadjuvant and adjuvant therapy were more popular in population from mastectomy group compared with that from BCT group (12.80% vs. 6.55%, \(P < 0.001\)).

**Survival analysis in OBC cohort**

In the whole OBC cohort, the median follow-up duration was 62 months. Totally, 272 people died from all reasons. 168 died because of disease of breast cancer, among which 14 patients received BCS and 53 female received mastectomy. The 5-year and 10-year overall survival of the whole population was 81.60% (95% CI: 79.20–84.10%) and 68.8% (95% CI: 65.30–72.40%), respectively (Fig. 1a). The 5-year and 10-year OBC-specific survival of the whole population was 86.10% (95% CI: 83.90–88.30%) and 79.7% (95% CI: 76.80–82.80%), respectively (Fig. 1b). No matter OS and BCSS for the whole cohort, both of them failed to reach median survival timepoints. And both patients in BCS group and mastectomy group were followed up for a median time of 62 months. For population in BCS group, the 5-year and 10-year OS was 84.50% (95% CI: 77.60–92.10%) and 72.60% (95% CI: 63.30–83.30%) (Fig. 2a); the 5-year and 10-year BCSS was 88.50% (95% CI: 82.30–95.20%) and 84.40% (95% CI: 71.10–92.40%) (Fig. 2b). For mastectomy cohort, the 5-year and 10-year OS was 83.50% (95% CI: 79.60–87.60%) and 71.90% (95% CI: 66.20–78.00%) (Fig. 2a); the 5-year and 10-year BCSS was 87.80% (95% CI: 84.40–91.30%) and 82.00% (95% CI: 77.30–87.00%) (Fig. 2b). The median survival time of OS for BCS group was 12.17 months while median survival time of BCSS for BCS group were not reached (Fig. 2a, b).

Univariate and multivariate COX regression analysis for OS and BCSS were conducted (Tables 3 and 4, respectively). Age, marital status, grade, N staging, number of positive lymph node, stage, radiation, chemotherapy, type of systemic therapy, tumor subtypes, ER and PR were factors significantly associated with OS according to univariate analysis (\(P < 0.10\)) (Table 3). By multivariate analysis, it was found that age, number of positive
| Variables                  | Surgery                      | P-value |
|---------------------------|------------------------------|---------|
|                           | BCT                          | Mastectomy |       |
|                           | N   | Percentage (%) | N   | Percentage (%) |       |
| N                         | 748 | 100            | 422 | 100            | < 0.001 |
| Age                       |     |                |     |                |
| < 40                      | 24  | 3.21           | 29  | 6.87           |         |
| 40–49                     | 91  | 12.17          | 83  | 19.67          |         |
| 50–59                     | 216 | 28.88          | 126 | 29.86          |         |
| 60–69                     | 223 | 29.81          | 114 | 27.01          |         |
| ≥ 70                      | 194 | 25.94          | 70  | 16.59          |         |
| Mean (± SD)               | 61.16±11.35                  | 57.65±11.72 | < 0.001* |
| Race                      |     |                |     |                |
| White                     | 587 | 78.48          | 340 | 80.57          | 0.14**  |
| Black                     | 92  | 12.30          | 45  | 10.66          |         |
| Asian or Pacific Islander | 57  | 7.62           | 36  | 8.53           |         |
| American Indian/Alaska Native | 9  | 1.20           | 0   | 0              |         |
| Unknown/other             | 3   | 0.40           | 1   | 0.24           |         |
| Marital status            |     |                |     |                |
| Not married               | 289 | 34.17          | 153 | 36.3           | 0.64    |
| Married                   | 433 | 61.67          | 256 | 60.7           |         |
| Unknown                   | 26  | 4.17           | 13  | 3.1            |         |
| Grade                     |     |                |     |                |
| I/II                      | 35  | 4.68           | 28  | 6.64           | 0.30    |
| III                       | 135 | 18.05          | 85  | 20.14          |         |
| IV                        | 7   | 0.94           | 2   | 0.47           |         |
| Unknown                   | 571 | 76.34          | 307 | 72.75          |         |
| Laterality                |     |                |     |                |
| Right                     | 342 | 45.72          | 212 | 50.24          | 0.15    |
| Left                      | 406 | 54.28          | 210 | 49.76          |         |
| Histology                 |     |                |     |                |
| Ductal carcinoma          | 277 | 37.03          | 192 | 45.50          | 0.04    |
| Lobular carcinoma         | 37  | 4.95           | 16  | 3.79           |         |
| Mixed type                | 16  | 2.14           | 9   | 2.13           |         |
| Other                     | 418 | 55.88          | 205 | 48.58          |         |
| N                         |     |                |     |                |
| N1mi                      | 12  | 1.60           | 19  | 4.50           | < 0.001 |
| N1                        | 481 | 64.30          | 226 | 53.55          |         |
| N2                        | 131 | 17.51          | 95  | 22.51          |         |
| N3                        | 124 | 16.58          | 82  | 19.43          |         |
| No. of examined LN        |     |                |     |                |
| 1–3                       | 131 | 17.51          | 49  | 11.61          | < 0.001 |
| 4–9                       | 100 | 13.37          | 72  | 17.06          |         |
| ≥ 10                      | 390 | 52.14          | 276 | 65.40          |         |
| Other/Unknown             | 127 | 16.98          | 25  | 5.92           |         |
| No. of positive LN        |     |                |     |                |
| 1–3                       | 376 | 50.27          | 227 | 53.79          | < 0.001 |
| 4–9                       | 117 | 15.64          | 93  | 22.04          |         |
| ≥ 10                      | 86  | 11.50          | 60  | 14.22          |         |
| Other/Unknown             | 169 | 22.59          | 42  | 9.95           |         |
| Stage                     |     |                |     |                | < 0.001 |

Table 2: Basic data of variables in OBC patients with breast-conserving therapy (BCT) and mastectomy.
lymph nodes and radiation were independent predictive factors for OS ($P<0.05$) (Table 4; Fig. 3a–c). For BCSS, age, race, grade, N staging, number of positive lymph node, stage, radiation, chemotherapy, type of systemic therapy, tumor subtypes, ER and PR were selected to enter multivariate analysis ($P<0.10$) (Table 3). In multivariate analysis, independent predictive factors of BCSS included race, number of positive lymph node, radiation and types of systemic therapy ($P<0.05$) (Table 4; Fig. 4a–d). Patients older than 70 has a significant gloomy overall survival than that with age less than 40 (hazard ratio, HR = 2.15, 95% CI = 1.13–4.08). Compared with white OBC patients, Asian/Pacific-island patients tended to get a better BCSS (HR = 0.39, 95% CI = 0.16–0.97, $P=0.04$).
but native Americans had a relatively poor survival (HR = 4.25, 95% CI = 1.01–17.99, P = 0.04). More positive lymph node is associated with both poor OS and BCSS (P < 0.001). Patients receiving radiation tended to get a better prognosis no matter statistical analysis of OS or BCSS (Table 4).

**Discussion**

In our study, we collected nearly 1200 OBC patients for 15 years and the data is the most up-to-date one. We found that OBC was predominated by elderly population. Majority of OBC patients were diagnosed at relative early stage (Stage IIA) and Luminal A type of OBC took up nearly 30% of all subjects. Radiotherapy and chemotherapy were common and important treatments for OBC patients. In this study, we found that older patients tended to receive less-invasive surgical intervention. Patients in mastectomy group were found more involved lymph nodes thus more patients were diagnosed as advanced stage OBC (stage IIIA and IIIC) compared with subjects in BCT group. Patients treated by radiotherapy had a significant difference between two surgical groups, in which more than 60% subjects in BCT group were accepted this therapy but only half of women took radiotherapy in mastectomy groups (P < 0.001). Speaking of survival analysis, the whole OBC cohort generally had optimistic prognosis. 5-year OS and BCSS exceeding 80% and both of the survival analysis did not reach the timepoint of median survival. When the whole cohort was grouped according to Fig. 1 Curves of overall survival (a) and breast cancer-specific survival (b) of the whole cohort of occult breast cancer patients.

**Fig. 2** Curves of overall survival (a) and breast cancer-specific survival (b) of 3 cohorts of patients receiving BCS (pink), mastectomy (green) and no surgery (blue). The dotted line in (a) marked the median overall survival timepoint of patients receiving BCS. BCS breast-conserving surgery.
Table 3  Univariable analysis of OS and BCSS in OBC patients

| Variables                | OS     | BCSS    |
|--------------------------|--------|---------|
|                          | HR     | 95% CI  | P-value | HR     | 95% CI  | P-value |
| Age (year)               |        |         |         |        |         |         |
| < 40                     | 1.05   | 1.03–1.06 | < 0.0001 | 1.03   | 1.02–1.04 | < 0.001 |
| 40–49                    | 0.63   | 0.31–1.31 | 0.22    | 0.82   | 0.34–1.97 | 0.66    |
| 50–59                    | 0.93   | 0.49–1.77 | 0.83    | 0.99   | 0.44–2.20 | 0.98    |
| 60–69                    | 1.14   | 0.60–2.16 | 0.68    | 1.10   | 0.50–2.45 | 0.81    |
| ≥ 70                     | 2.69   | 1.44–5.01 | 0.002   | 2.03   | 0.93–4.46 | 0.08    |
| Race                     |        |         |         |        |         |         |
| White                    | Reference |       | Reference |       |         |         |
| Black                    | 1.30   | 0.93–1.81 | 0.12    | 0.88   | 0.55–1.42 | 0.61    |
| Asian or Pacific Islander | 0.75   | 0.44–1.26 | 0.28    | 0.37   | 0.15–0.89 | 0.03    |
| American Indian/Alaska Native | 1.11   | 0.28–4.49 | 0.88    | 1.78   | 0.44–7.17 | 0.42    |
| Unknown/other            | 8.34 × 10⁻⁷ | INF  | 0.99    | 7.65 × 10⁻⁷ | INF  | 0.99    |
| Marital status           |        |         |         |        |         |         |
| Not married              | Reference |       | Reference |       |         |         |
| Married                  | 0.71   | 0.56–0.91 | 0.007   | 0.77   | 0.56–1.06 | 0.11    |
| Unknown                  | 1.25   | 0.69–2.26 | 0.47    | 1.31   | 0.63–2.72 | 0.47    |
| Grade                    |        |         |         |        |         |         |
| I/II                     | Reference |       | Reference |       |         |         |
| III                      | 2.59   | 1.03–6.54 | 0.04    | 2.59   | 1.03–6.54 | 0.04    |
| IV                       | 0.99   | 0.12–8.52 | 1.00    | 0.99   | 0.12–8.52 | 1.00    |
| Unknown                  | 1.81   | 0.74–4.42 | 0.20    | 1.81   | 0.74–4.42 | 0.20    |
| Laterality               |        |         |         |        |         |         |
| Right                    | Reference |       | Reference |       |         |         |
| Left                     | 1.03   | 0.81–1.31 | 0.79    | 1.11   | 0.82–1.51 | 0.50    |
| Histology                |        |         |         |        |         |         |
| Ductal carcinoma         | Reference |       | Reference |       |         |         |
| Lobular carcinoma        | 0.85   | 0.44–1.62 | 0.61    | 1.24   | 0.59–2.60 | 0.57    |
| Mixed type               | 0.69   | 0.28–1.70 | 0.43    | 0.77   | 0.24–2.47 | 0.67    |
| Other                    | 0.85   | 0.66–1.08 | 0.18    | 1.03   | 0.75–1.43 | 0.84    |
| N                        |        |         |         |        |         |         |
| N1mi                     | Reference |       | Reference |       |         |         |
| N1                       | 2.15   | 0.53–8.70 | 0.28    | 1.01   | 0.32–16.46 | 0.41    |
| N2                       | 2.84   | 0.69–11.67 | 0.15    | 1.01   | 0.64–33.65 | 0.13    |
| N3                       | 4.00   | 0.98–16.32 | 0.05    | 1.01   | 1.04–54.08 | 0.05    |
| No. of positive LN       |        |         |         |        |         |         |
| 1–3                      | Reference |       | Reference |       |         |         |
| 4–9                      | 1.82   | 1.32–2.52 | < 0.001 | 2.77   | 1.79–4.28 | < 0.001 |
| ≥ 10                     | 2.22   | 1.59–3.10 | < 0.001 | 4.42   | 2.91–6.71 | < 0.001 |
| Other/Unknown            | 1.01   | 1.99–3.77 | < 0.001 | 4.09   | 2.67–6.25 | < 0.001 |
| Stage                    |        |         |         |        |         |         |
| IB                       | Reference |       | Reference |       |         |         |
| IIA                      | 2.15   | 0.53–8.70 | 0.28    | 1.01   | 0.32–16.46 | 0.4123  |
| IIIA                     | 2.84   | 0.69–11.63 | 0.15    | 1.01   | 0.63–33.51 | 0.1312  |
| IIIC                     | 4.02   | 0.98–16.40 | 0.05    | 1.01   | 1.04–54.37 | 0.0453  |
| Surgery                  |        |         |         |        |         |         |
| BCS                      | Reference |       | Reference |       |         |         |
| Mastectomy               | 0.82   | 0.53–1.26 | 0.36    | 1.08   | 0.60–1.94 | 0.80    |
| None/Unknown             | 1.13   | 0.76–1.69 | 0.55    | 1.44   | 0.82–2.52 | 0.20    |
types of surgery, both of the 5 and 10-year BCSS in BCS and mastectomy group were higher than 5 and 10-year OS in the same group. However, no significant difference was found no matter in OS or BCSS between BCS and mastectomy group ($P = 0.058$ for OS and $P = 0.14$ for BCSS). For Cox regression analysis, we found that age was an independent predictor for OS and higher age meant a poorer survival. Race served as an independent predictor for BCSS and Asian/Pacific natives has a better clinical outcome while native Americans had a relatively poor survival. Radiotherapy was clinically beneficial to OBC patients, no matter according to OS or BCSS. But no significant benefit was found between survival and systemic therapy. This finding was also supported by the result derived from multivariate analysis of tumor subtypes immunohistochemistry: ER, PR, HER-2 and tumor subtypes were not independent predictors for neither OS or BCSS.

Although NCCN guidelines stated that mastectomy was recommended for OBC patients, the optimal surgical therapy for the ipsilateral breast in OBC has been controversial [14]. According to a meta-analysis collecting 7 qualified studies, no significant difference in overall survival between ALND plus mastectomy and ALND combined with breast radiation [7]. Likewise, in a clinical trial carried on by Rueth's team, no significant survival disparity was found between BCT and mastectomy ($P = 0.7$). No local and distal recurrence occurred within

| Variables                        | OS                      | BCSS                    |
|----------------------------------|-------------------------|-------------------------|
|                                  | HR (95% CI) P-value | HR (95% CI) P-value |
| Radiation                        | Reference              | Reference              |
| None/Unknown                     | Reference              | Reference              |
| Yes                              | 0.66 (0.52–0.84) 0.0007 | 0.70 (0.52–0.95) 0.02   |
| Chemotherapy                     | Reference              | Reference              |
| Yes                              | Reference              | Reference              |
| No/Unknown                       | 0.55 (0.43–0.71) < 0.001 | 0.73 (0.52–1.02) 0.07   |
| Type of systemic therapy         | Reference              | Reference              |
| Neoadjuvant                      | Reference              | Reference              |
| Adjuvant                         | 0.97 (0.61–1.55) 0.91  | 0.92 (0.53–1.60) 0.76   |
| Neoadjuvant + adjuvant           | 0.53 (0.24–1.15) 0.11  | 0.73 (0.32–1.66) 0.45   |
| Only systemic therapy, no surgery| 3.42 (1.71–6.83) 0.0005 | 3.58 (1.61–7.97) 0.002  |
| Other                            | 0.27 (0.37–1.08) 0.09  | 0.52 (0.27–1.04) 0.06   |
| No/Unknown                       | 0.25 (1.01–2.70) 0.04  | 1.39 (0.76–2.53) 0.28   |
| Subtypes                          | Reference              | Reference              |
| Luminal A                        | Reference              | Reference              |
| Luminal B                        | 0.62 (0.30–1.27) 0.19  | 0.69 (0.28–1.66) 0.40   |
| HER2 positive                    | 1.31 (0.70–2.43) 0.40  | 1.80 (0.89–3.64) 0.10   |
| Triple negative                  | 1.63 (1.03–2.57) 0.04  | 2.03 (1.17–3.54) 0.01   |
| Unknown                          | 1.28 (0.91–1.81) 0.16  | 1.52 (0.98–2.35) 0.06   |
| ER                               | Reference              | Reference              |
| Negative                         | Reference              | Reference              |
| Borderline/Unknown               | 1.08 (0.73–1.61) 0.70  | 1.18 (0.73–1.90) 0.50   |
| Positive                         | 0.71 (0.55–0.92) 0.009 | 0.59 (0.43–0.81) 0.001  |
| PR                               | Reference              | Reference              |
| Negative                         | Reference              | Reference              |
| Borderline/Unknown               | 1.08 (0.76–1.56) 0.66  | 1.06 (0.68–1.66) 0.80   |
| Positive                         | 0.78 (0.60–1.01) 0.06  | 0.54 (0.38–0.77) 0.0007 |
| HER2                             | Reference              | Reference              |
| Negative                         | Reference              | Reference              |
| Positive                         | 0.74 (0.46–1.19) 0.21  | 0.85 (0.49–1.47) 0.56   |
| Unknown                          | 1.08 (0.81–1.43) 0.62  | 1.15 (0.81–1.63) 0.43   |

CI confidence interval, ER estrogen receptor, HER-2 human epidermal growth factor receptor-2, N N staging of OBC, PR progesterone receptor
Table 4  Multivariable analysis of OS and BCSS in OBC patients

| Variables                        | OS       |        |        | BCSS     |        |        |
|----------------------------------|----------|--------|--------|----------|--------|--------|
|                                  | HR 95% CI| P-value|        | HR 95% CI| P-value|        |
| Age (year)                       |          |        |        |          |        |        |
| < 40                             | Reference|        |        |          |        |        |
| 40–49                            | 0.57     | 0.27–1.19| 0.13  | 0.64     | 0.26–1.56| 0.32  |
| 50–59                            | 0.82     | 0.43–1.58| 0.56  | 0.82     | 0.36–1.85| 0.64  |
| 60–69                            | 1.04     | 0.55–1.99| 0.90  | 0.97     | 0.43–2.18| 0.93  |
| ≥ 70                             | 2.15     | 1.13–4.08| 0.02  | 1.52     | 0.67–3.41| 0.31  |
| Race                             |          |        |        |          |        |        |
| White                            | Reference|        |        | Reference|        |        |
| Black                            | –        | –      | –      | 0.90     | 0.56–1.47| 0.68  |
| Asian or Pacific Islander        | –        | –      | –      | 0.39     | 0.16–0.97| 0.04  |
| American Indian/Alaska Native   | –        | –      | –      | 4.25     | 1.01–17.99| 0.05  |
| Unknown/other                    | –        | –      | –      | 1.23 × 10⁻⁶| 0-INF | 0.99  |
| Marital status                   |          |        |        |          |        |        |
| Not married                      | Reference|        |        | Reference|        |        |
| Married                          | 0.80     | 0.62–1.02| 0.07  | –        | –      | –      |
| Unknown                          | 1.25     | 0.68–2.31| 0.48  | –        | –      | –      |
| Grade                            |          |        |        |          |        |        |
| I/II                             | Reference|        |        | Reference|        |        |
| III                              | 0.90     | 0.51–1.59| 0.71  | 1.71     | 0.65–4.47| 0.27  |
| IV                               | 0.66     | 0.22–2.04| 0.47  | 0.65     | 0.07–5.73| 0.70  |
| Unknown                          | 0.70     | 0.41–1.19| 0.18  | 1.26     | 0.50–3.16| 0.63  |
| N                                |          |        |        |          |        |        |
| N1mi                             | Reference|        |        | Reference|        |        |
| N1                               | 1.34 × 10¹¹| 0-INF | 0.99  | 1.17 × 10⁻¹³| 0-INF | 1.00  |
| N2                               | 1.72 × 10⁵| 0-INF | 0.99  | 4.04 × 10⁻⁷| 0-INF | 1.00  |
| N3                               | 3.44     | 0.79–14.92| 0.10  | 4.47     | 0.58–34.38| 0.15  |
| No. of positive LN               |          |        |        |          |        |        |
| 1–3                              | Reference|        |        | Reference|        |        |
| 4–9                              | 2.09     | 1.17–3.73| 0.01  | 1.96     | 0.95–4.02| 0.07  |
| ≥ 10                             | 1.53     | 0.86–2.73| 0.15  | 2.28     | 1.16–4.46| 0.02  |
| Other/Unknown                    | 2.47     | 1.76–3.47| < 0.001| 3.26     | 2.07–5.13| < 0.001|
| Stage                            |          |        |        |          |        |        |
| IB                               | Reference|        |        | Reference|        |        |
| IIA                              | 1.39 × 10⁻¹¹| 0-INF | 0.99  | 1.45 × 10⁻¹³| 0-INF | 1.00  |
| IIIA                             | 9.80 × 10⁻⁷| 0-INF | 0.99  | 6.46 × 10⁻⁸| 0-INF | 1.00  |
| IIIC                             | NA       | NA     | NA     | NA       | NA     | NA     |
| Radiation                        |          |        |        |          |        |        |
| None/Unknown                     | Reference|        |        | Reference|        |        |
| Yes                              | 0.68     | 0.52–0.88| 0.003 | 0.63     | 0.45–0.88| 0.007 |
| Chemotherapy                     |          |        |        |          |        |        |
| Yes                              | Reference|        |        | Reference|        |        |
| No/Unknown                       | 0.87     | 0.52–1.44| 0.59  | 1.08     | 0.51–2.28| 0.84  |
| Type of systemic therapy         |          |        |        |          |        |        |
| Neoadjuvant                      | Reference|        |        | Reference|        |        |
| Adjuvant                         | 0.93     | 0.58–1.50| 0.77  | 1.00     | 0.57–1.75| 0.99  |
| Neoadjuvant + adjuvant           | 0.50     | 0.23–1.10| 0.08  | 0.69     | 0.30–1.59| 0.38  |
| Only systemic therapy, no surgery| 1.88     | 0.90–3.90| 0.09  | 2.40     | 1.03–5.60| 0.04  |
| Other                            | 0.55     | 0.32–0.96| 0.04  | 0.46     | 0.23–0.93| 0.03  |
5 years, either [15]. A clinical study based on National Cancer Database collected 190 patients diagnosed from 2004 to 2014 [16]. Treatment strategies included mastectomy alone, radiation alone and mastectomy combined with radiation. No significant difference in OS was found between each two of these three strategies (mastectomy vs. radiation, \(P = 0.650\); mastectomy + radiation vs. mastectomy, \(P = 0.393\); mastectomy vs. radiation, \(P = 0.872\)). These findings are also supported by two retrospective study from China and Korean respectively, suggesting that mastectomy was not more clinically beneficial than BCT [8, 17]. Even some studies found that a less-intensive approach would be beneficial for OBC patient. In another research also based on National Cancer Database, 1231 OBC patients were grouped into MRM ± radiotherapy (N = 592), radiotherapy + ALND (N = 342), ALND alone (N = 106) and no breast surgery (N = 191). They found that patients treated by ALND and radiotherapy have significantly better OS compared with patients received MRM with/without radiotherapy (HR = 0.475, 95% CI 0.306-0.736, \(P = 0.001\)). Multivariate analysis proved that ALND with radiation was an independent protective predictor of OS (HR 0.509, 95% CI 0.321-0.808, \(P = 0.004\)). However, a retrospective study performed by Wang et al. drew an opposite conclusion. Their study included 51 OBC cases from a single center, in which 38 had ALND plus Mastectomy and the other 13 patients had ALND only [18]. 28 of 38 patients having mastectomy had been found the primary tumor in the breast by pathology. Recurrence rate in mastectomy group was 26%, much lower than that in ALND-only group (77%). Patients with mastectomy had a significantly promising disease-free survival and overall survival compared with patients merely received ALND (\(P < 0.001\)). Hence, this study drew a conclusion that mastectomy based on ALND is necessary for OBC patients.

For radiotherapy, we found that radiotherapy is clinically beneficial for OBC. This finding is in line with majority of previous clinical research. A study from the UK collected 29 OBC patients across more than 25 years. Median follow-up time was 44 months. Amongst, 16 patients got local radiotherapy and 13 patients did not receive local radiation. Local recurrence rate was 12.50% in radiation group while 69% of patients in non-radiation group got local recurrence (\(P = 0.02\)). Moreover, radiotherapy could significantly improve relapse-free survival (HR = 0.31, \(P = 0.04\)) and local relapse-free survival (HR = 0.09, \(P = 0.004\)). Overall survival, unfortunately, was not positively impacted by radiotherapy [19]. In 2010, another research conducted by team from UK led by Masinghe reported 53 OBC patients diagnosed from 1974 to 2003. Similar to the above studies, this study was also a mixture of clinical and pathological OBC. All the patients received axillary surgery but only 25 of them (47%) had ALND. 5-year recurrence rate of ipsilateral breast was 16.40% (95% CI 4.30–28.50%) in population receiving radiotherapy, lower than that in non-radiation population (35.80%, 95% confidence interval 7.60–64.10%). Similar results were presented in 10-year ipsilateral relapse rate, where radiotherapy group

### Table 4

| Variables | OS (HR) 95% CI P-value | BCSS (HR) 95% CI P-value |
|-----------|------------------------|--------------------------|
|           |                        |                          |
| No/Unknown | 1.02 0.51–2.06 0.95 | 1.23 0.48–3.17 0.67 |
| Subtypes  |                        |                          |
| Luminal A | Reference              | Reference                |
| Luminal B | 0.63 0.31–1.31 0.22  | 0.65 0.26–1.60 0.35      |
| HER2 positive | 1.10 0.54–2.22 0.79 | 1.31 0.56–3.02 0.53 |
| Triple negative | 1.42 0.81–2.50 0.22 | 1.66 0.81–3.40 0.17 |
| Unknown | 1.53 1.02–2.27 0.04 | 1.64 0.97–2.76 0.06 |
| ER |                        |                          |
| Negative | Reference              | Reference                |
| Borderline/Unknown | 1.13 0.51–2.54 0.76 | 1.63 0.63–4.18 0.31 |
| Positive | 0.78 0.53–1.14 0.20  | 0.87 0.52–1.43 0.57     |
| PR |                        |                          |
| Negative | Reference              | Reference                |
| Borderline/Unknown | 0.85 0.41–1.79 0.68 | 0.72 0.29–1.74 0.46 |
| Positive | 0.99 0.69–1.43 0.98  | 0.78 0.49–1.24 0.30     |

**BCSS** breast cancer-specific survival, **CI** confidence interval, **ER** estrogen receptor, **HR** hazard ratio, **INF** infinite, **N** staging of OBC, **NA** not available, **OS** overall survival, **PR** progesterone receptor
was 23.20% (95% CI 8.90–37.60%) and non-radiotherapy group was 51.90% (95% CI 17.40–86.40%). Furthermore, patients receiving radiotherapy had a significantly higher 5-year and 10-year BCSS rate compared with patients without radiation ($P=0.0073$; 5-year: 72.80% (95% CI 59.10–86.50%) vs. 58.30% (95% CI 30.40–86.20%));
of them got neoadjuvant therapy. Thus, the PCR rate of neoadjuvant therapy was about 60%, which supported the effectiveness of neoadjuvant therapy in the case series above [15]. In the most recent study with the largest sample size, Cohen et.al collected 684 OBC patients and 214 (31.3%) of them received neoadjuvant chemotherapy. PCR was recognized in 55 of 214 (26%) patients took neoadjuvant therapy. In our study, counterintuitively, we found that patients without chemotherapy tended to have a better prognosis, partly because patients administered with chemotherapy had a relatively higher tumor stage. In our study, 21% cases with stage-IIIA OBC and 19% cases with stage-IIIC cases in chemotherapy group patients, whereas both of the stage-IIIA and stage-IIIC OBC patients accounted for 13% in the other group (P=0.002, χ² test). As the number of studies focusing on neoadjuvant chemotherapy was small and the PCR rate varied among these studies by virtue of sample size in huge disparity, it is still debatable whether systemic therapy is beneficial for OBC patients.

In our study, several limitations are necessary to be noticed: (1) For systemic therapy, current database is shortage of specific data such as the chemotherapy formula and dosage of each drug. Thus, we could not get more information about chemotherapy and its relationship with survival. Moreover, data of endocrine therapy is not available in current version of SEER database; (2) SEER database predominately describes clinical characteristic of American citizens including white and black citizens. Data of Asian OBC patients were insufficient so that it is unclear whether the results of this analysis were also generalized to Asian population; (3) Because the data of HER-2 status originates from 2010, it is not available in the cases diagnosed before 2010, which impacted the descriptive results and following analysis about HER-2 status, tumor subtypes as well as their associations with OS and BCSS; (4) For radiation part in SEER database, we did not know the exact number of patients unknown information of radiation and we could not separately summarize number of patients with or without radiation. Hence, some sort of deviation of the survival result might be existed. We hope that more clear information can be retrieved in updated edition of this database.

Conclusion
Majority of OBC patients had a relatively optimistic prognosis. A less-intensive surgical therapy is acceptable for OBC treatment without cost on OS or BCSS. Radiotherapy was beneficial for clinical outcomes of OBC patients. More information of systemic therapy is expected to be obtained to refine the treatment recommendation for OBC.
Abbreviations
ALND: Axillary lymph node dissection; BCS: Breast-conserving surgery; BCT: Breast-conserving therapy; BCSS: Breast-cancer specific survival; CI: Confidence intervals; ER: Estrogen receptor; HER-2: Human epidermal factor receptor-2; HR: Hazard ratio; MR: Magnetic resonance imaging; MRM: Modified radical mastectomy; NCCN: National Comprehensive Cancer Network; OBC: Occult breast cancer; OS: Overall survival; PCR: Pathological complete response; PR: Progesterone receptor; SEER: Surveillance, Epidemiology, and End Results.

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Authors' contributions
ZJZ and XL put forward the idea of this study and ZJZ wrote the manuscript. ZJZ, TZ and YY analyzed and interpreted data of OBC patients. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and integrated are available in Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/). We selected the SEER research plus data, 18 Registries, Nov 2020 Sub (2000–2018) to perform further analysis. Software for data retrieving and integration is SEER* Stat 8.3.9.1, which is successfully downloaded from official website of SEER database (https://seer.cancer.gov/seerstat/).

Declarations
Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declared that they have no competing interests.

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