Presentation and Survival by Hormonal Receptor Status in Metaplastic Breast Cancer: A Propensity Score-matched Analysis

Siqin Wang  
Huazhong University of Science and Technology

Jin Hu  
Huazhong University of Science and Technology

yanting Zhang  
Huazhong University of Science and Technology

Jian Shen  
Huazhong University of Science and Technology

Fang Dong  
Wuhan Union Hospital

Ximeng Zhang  
Wuhan Union Hospital

Chong Lu  
Wuhan Union Hospital

Dan Shang (✉️ shangdanwh@163.com)  
Wuhan Union Hospital  https://orcid.org/0000-0002-8755-5409

Research

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Abstract

**Background:** Studies reported the hormonal receptor (HR) status was not associated with survival in metaplastic breast cancer (MBC). In addition, MBC patients cannot benefit from chemotherapy (CT). The present study aimed to evaluate the efficacy of CT on MBC patients with high risk (T1-4N2-3M0 and T4N0-1M0) by propensity-score matching (PSM).

**Methods:** A retrospective study was performed to analyze MBC from the SEER database. Breast cancer-specific survival (BCSS) rates were analyzed using the Kaplan–Meier curve and differences assessed by log-rank tests. Cox proportional hazard models were used to assess BCSS. PSM was used to make 1:1 case-control matching.

**Results:** We identified 3116 patients. The median follow-up time was 44 months (range, 1–321 months). 23.0% of patients were HR-positive. About 62.5% of patients received CT, which seem not to relate to HR status. Recurrence risk had a significant difference between HR-negative and HR-positive groups. In the multivariable Cox proportional hazards regression model, HR status was not associated with a better BCSS. CT had no benefit for MBC. Multivariate analyses after PSM (n=1274) confirmed that both CT and HR status were not associated with prognosis. The Kaplan–Meier curve before PSM showed that HR-negative MBC with intermediate-risk benefited from CT. For HR-positive MBC, patients with intermediate and high risk benefited from CT. However, CT could only benefit for HR-positive MBC with high risk after PSM.

**Conclusion:** PSM analysis showed that CT could only benefit for HR-positive MBC with high risk.

1. **Background**

Metaplastic breast cancer (MBC) is a rare and aggressive form of breast cancer [1, 2] comprising < 1% of all invasive breast cancers [3, 4] The World Health Organization (WHO) identified metaplastic histology as a unique pathological type in 2000.[5] Wargotz et al. divided metaplastic cancer into five categories: carcinosarcoma, matrix-producing carcinoma, spindle cell carcinoma, squamous cell carcinoma, and carcinoma with osteoclastic giant cells.[6–10] Recently, studies had described two categories: carcinoma with squamous metaplasia and with heterologous components.[11]

Of note, in the National Comprehensive Cancer Network (NCCN) breast cancer guidelines, management of MBC is still similar to invasive ductal carcinoma (IDC).[12] However, comparing to breast cancers with more common histology, the MBC is characterized by larger tumor size, less regional node metastasis, and higher tumor grade.[13–15] The pathway of metaplastic cancer metastasis was hematogenous but not lymphatic spread.[16] A previous study found that MBC patients with stage I–III disease had significantly worse 5-year breast cancer-specific survival (BCSS) compared with that of synchronous IDC. [17] Previous studies reported that MBC is chemorefractory, whatever patients received either neoadjuvant or adjuvant settings. [2, 18–20]
Although commonly molecular subtype is the triple-negative phenotype in MBC, hormone receptor (HR) positive and human epidermal growth receptor 2 (HER2) positive tumors do exist.[21] A population-based study reported, HR status was not associated with survival in MBC, which was different from infiltrating ductal and lobular carcinomas.[22] In addition, previous studies had reported that the prognosis of HR-positive patients receiving antiestrogen therapy demonstrated no difference in outcomes with that of no receiving antiestrogen therapy. [19, 20, 23]

Although previous studies had reported the chemotherapy (CT) was not associated with improved survival and HR status was not associated with better survival in MBC, the role of CT is unclear for MBC with different risk of recurrence, especially when considering HR status. The purpose of our study is to compare the prognosis of different HR status, and to evaluate the response of MBC to CT at different risk of recurrence by using the database of the whole population.

2. Materials And Methods

2.1 SEER Database and Patients

Malignant tumors are recorded by diagnosis codes according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3) in the SEER database. It was comprised of open access data from 18 population-based cancer registries in the United States. Patients diagnosed with MBC were confirmed by pathology from 1975 to 2016. In our study, the ICD-O-3 codes included 8560, 8562, 8570–8572, 8575, and 8980–8982. The inclusion criteria were as follows: female, age of at least 18 years, breast cancer as first and the only cancer diagnosis, unilateral breast cancer, diagnosis obtained from histology or cytology confirmation and not from autopsy or death, complete information of known survival time and molecular subtype, stage exception of T0 and Tis and pathological stage I to III tumors. (Fig. 1)

The low-risk group included patients with T1-2N0M0, the intermediate-risk group included patients with stage T1-2N1M0 and T3N0M0 [24], and the high-risk group included patients with stage T1-4N2-3M0 and T4N0-1M0 [25].

2.2 Demographic and clinicopathologic features

The demographic parameters included age at diagnosis, race recorded by SEER (white, black, Asian or Pacific Islander, unknown). The clinicopathologic parameters included tumor grade, histologic subtype, tumor size (T1, T2, T3, and T4), regional lymph node status (N0, N1, N2, and N3), risk stratification (low risk, intermediate risk, high risk), HR status, CT, radiotherapy (RT), local therapies (lumpectomy, mastectomy, and none), and years at diagnosis. The molecular subtype was analyzed as a binary categorical variable: HR-negative (ER- and PR-) group and HR-positive (ER-/PR+, ER+/PR-, ER+/PR+) group. The primary clinical outcome for this series was BCSS from the date of diagnosis to the date of death caused by MBC.
In the SEER database, in cases where ER/PR is reported on more than one tumor specimen, the highest value is recorded. If any sample is positive, record as positive. If neoadjacent therapy is given, record the assay from tumor specimens prior to neoadjuvant therapy. If neoadjuvant therapy is given and there are no ER/PR results from pre-treatment specimens, report the findings from post-treatment specimens. If ER/PR is positive on an in situ specimen and ER/PR is negative on all tested invasive specimens, code ER/PR as negative. If 1% or greater cells stain positive, the test results are considered positive.

2.3 Statistical analysis

The Student t-test and $\chi^2$ test were performed to compare the clinicopathological characteristics between two groups. The BCSS rates were calculated using the Kaplan–Meier model and comparisons were conducted using the log-rank test. The multivariable Cox proportional hazards regression model was performed to assess the risk factors for BCSS. Hazard ratios (HRs) were showed with 95% confidence interval (CI). All statistical analyses used SPSS statistical software (version 24.0; IBM Corporation, Armonk, NY, USA), and $P < 0.05$ was statistically significant.

Stratification by the T stage was performed to PSM. PSM was used to make 1:1 case-control matching. Patients with stage T1 were included to model I with match tolerance 0.001, stage T2 to model II with match tolerance 0.001, stage T3 to model III with match tolerance 0.001, and stage T4 to model IV with match tolerance 0.005. A total of 384 (30.1%), 644 (50.6%), 144 (11.3%), and 102 (8.0%) of the patients were included in the model I, II, III, and IV, respectively. The difference of the short-term clinical outcomes in the Kaplan–Meier model was conducted using the Gehan-Breslow-Wilcoxon test, while the difference of the long-term outcomes using the Log-rank test.

3. Result

3.1 Demographic and Clinical Characteristics

Of the 4672 MBC patients in the SEER registry, our final sample comprised 3116 patients. The demographic and clinical characteristics in the study are shown in Table 1. 23.0% (716/3116) of patients were HR-positive. About 62.5% (1948/3116) of patients received CT, which seem not to relate to HR status ($P = 0.398$). The median age at diagnosis was 61 (range, 22–90 years), and 62 (range, 24–90 years) in the HR-negative group and the HR-positive group, respectively. A total of 757 (24.3%), 1861 (59.7%), and 498 (16.0%) patients had low-risk, intermediate-risk, and high-risk disease, respectively. Recurrence risk had a significant difference between HR-negative and HR-positive groups. The HR-positive group tended to lower tumor grade, smaller tumor size, and less lymph node metastasis.
Table 1
Demographic and clinical characteristics in MBC patients.

| Characteristic                        | Before PSM | After PSM | p   | Before PSM | After PSM | p   |
|---------------------------------------|------------|-----------|-----|------------|-----------|-----|
|                                       | HR-negative | HR-positive | p | HR-negative | HR-positive | p   |
|                                       | n = 2400   | n = 716   |     | n = 637    | n = 637    |     |
| Age (median)                          | 61 (22-90) | 62 (24-90) | 0.761 | 62 (22-90) | 62 (22-90) | 0.875 |
| Follow-up time (median)               | 47 (1-320) | 40 (1-321) | 0.003 | 44 (1-280) | 41 (1-321) | 0.632 |
| Race                                  | 0.023      | 0.850     |     |
| White                                 | 1859 (77.5) | 534 (74.6) |     | 488 (76.6) | 501 (78.6) |     |
| Black                                 | 372 (15.5) | 109 (15.2) |     | 97 (15.2)  | 89 (14.0)  |     |
| Asian or Pacific Islander             | 151 (6.3)  | 61 (8.5)   |     | 47 (7.4)   | 42 (6.6)   |     |
| Other                                 | 18 (0.8)   | 12 (1.7)   |     | 5 (0.8)    | 5 (0.8)    |     |
| Grade                                 | 0.005      | 0.981     |     |
| Well differentiated                   | 88 (3.7)   | 33 (4.6)   |     | 27 (4.2)   | 28 (4.4)   |     |
| Moderately differentiated             | 253 (10.5) | 105 (14.7) |     | 83 (13.0)  | 89 (14.0)  |     |
| Poorly differentiated                 | 1625 (67.7)| 477 (66.6) |     | 442 (69.4) | 433 (68.0) |     |
| Undifferentiated                      | 117 (4.9)  | 24 (3.4)   |     | 19 (3.0)   | 21 (3.3)   |     |
| Unknown                               | 317 (13.2) | 77 (10.8)  |     | 66 (10.4)  | 66 (10.4)  |     |
| Histology                             | 0.005      | 0.561     |     |
| Metaplastic carcinoma                 | 1920 (80.0)| 564 (78.8) |     | 536 (84.1) | 520 (81.6) |     |
| Carcinosarcoma                        | 120 (5.0)  | 20 (2.8)   |     | 17 (2.7)   | 13 (2.0)   |     |
| Adenosquamous carcinoma               | 122 (5.1)  | 55 (7.7)   |     | 38 (6.0)   | 45 (7.1)   |     |
| Adenocarcinoma with squamous metaplasia| 97 (4.0)  | 38 (5.3)   |     | 20 (3.1)   | 26 (4.1)   |     |
| Others                                | 141 (5.9)  | 39 (5.4)   |     | 26 (4.1)   | 33 (5.2)   |     |
| Tumor size                            | 0.023      | 1.000     |     |
| T1    | 636 (26.5) | 216 (30.2) | 192 (30.1) | 192 (30.1) |
|-------|------------|------------|------------|------------|
| T2    | 1206 (50.2) | 347 (48.5) | 322 (50.5) | 322 (50.5) |
| T3    | 390 (16.3) | 93 (13.0)  | 72 (11.3)  | 72 (11.3)  |
| T4    | 168 (7.0)  | 59 (8.2)   | 51 (8.0)   | 51 (8.0)   |

| Regional lymph node status | 0.005 | 0.180 |
|---------------------------|-------|-------|
| N0                        | 1893  | 526  |
|                           | (78.9)| (73.5)| 463 | (72.7) | 493 | (77.4) |
| N1                        | 382   | 128  | 131 |
|                           | (15.9)| (17.9)| (20.6)| 105 | (16.5) |
| N2                        | 78    | 36   | 22  |
|                           | (1.6) | (5.0) | (3.5)| 24  | (3.8) |
| N3                        | 47    | 26   | 21  |
|                           | (2.0) | (3.7) | (3.3)| 15  | (2.4) |

| Risk stratification | 0.024 | 0.865 |
|---------------------|-------|-------|
| Low risk            | 569   | 188   |
|                     | (23.7)| (26.3)| 165 | (25.9)| 173 | (27.2)|
| Intermediate risk   | 1464  | 397   | 370 |
|                     | (61.0)| (55.4)| (58.1)| 366 | (57.5)|
| High risk           | 367   | 131   | 102 |
|                     | (15.3)| (18.3)| (16.0)| 98  | (15.4)|

| Chemotherapy | 0.398 | 0.909 |
|--------------|-------|-------|
| No           | 890   | 278   |
|              | (37.1)| (38.8)| 389 | (61.1)| 387 | (60.8)|
| Yes          | 1510  | 438   | 248 |
|              | (62.9)| (61.2)| (38.9)| 250 | (39.2)|

| Radiotherapy | 0.149 | 0.955 |
|--------------|-------|-------|
| No           | 1307  | 368   |
|              | (54.5)| (51.4)| 337 | (52.9)| 338 | (53.1)|
| Yes          | 1093  | 348   | 300 |
|              | (45.5)| (48.6)| (47.1)| 299 | (46.9)|

| Surgery type | 0.724 | 0.279 |
|--------------|-------|-------|
| Lumpectomy   | 1010  | 307   |
|              | (42.1)| (42.9)| 261 | (41.0)| 284 | (42.8)|
| Mastectomy   | 1244  | 371   | 340 |
|              | (51.8)| (51.8)| (53.4)| 326 | (51.2)|
| None         | 146 (6.1) | 38 (5.3) | 36 (5.7) | 27 (4.2) |
|--------------|-----------|-----------|-----------|-----------|

Abbreviations: MBC= metaplastic breast cancer; HR= Hormonal receptor; PSM= propensity-score matching.

After using age, race, tumor grade, tumor histology, lymph node state, risk stratification, chemotherapy, radiotherapy, and surgery type as covariates, Table 1 showed that no parameters differed in the two groups.

### 3.2 Survival Analyses before PSM

The median follow-up time was 47 months (range, 1–320 months) in the HR-negative group and 40 months (range, 1–321 months) in the HR-positive group. BCSS was 77.3% at 5 years in patients receiving CT versus 75.3% at 5 years in patients not receiving CT (P = 0.411). In the intermediate-risk group, patients receiving CT demonstrated superior BCSS to patients not receiving CT (82.1% at 5 years vs. 72.2% at 5 years, P < 0.001), but not in low-risk or high-risk groups. (Fig. 2)

In multivariate analysis model, the risk of recurrence was significantly associated with worse BCSS (low-risk as reference, intermediate-risk: HRs 1.630; 95% CI, 1.130–2.350; P = 0.009; high-risk: HRs 2.847; 95% CI, 1.870–4.334; P < 0.001). Of note, HR-positive patients seem not to have better BCSS (HRs 1.017; 95% CI, 0.841–1.231; P = 0.860) than HR-negative patients. Patients could not benefit from CT (HRs 1.104; 95% CI, 0.906–1.346; P = 0.326). In addition, race, tumor grade, and tumor histology was not related to better BCSS. However, age, RT, and surgery type were independent indicators for BCSS. (Table 2)
Table 2
Prognostic factors for BCSS in early and locally advanced MBC by multivariate analyses.

| Variables                        | Before PSM          | After PSM           |
|----------------------------------|---------------------|---------------------|
|                                  | HRs (95% CI)        | p                   | HRs (95% CI)        | p                   |
| Age                              | 1.014 (1.007–1.020) | < 0.001             | 1.025 (1.015–1.036) | < 0.001             |
| Race                             |                     |                     |                     |                     |
| White                            | 1.0 [reference]     |                     | 1.0 [reference]     |                     |
| Black                            | 1.100 (0.887–1.365) | 0.384               | 1.180 (0.824–1.690) | 0.366               |
| Asian or Pacific Islander        | 0.905 (0.645–1.271) | 0.565               | 0.900 (0.534–1.518) | 0.693               |
| Other                            | 0.967 (0.472–1.983) | 0.927               | 1.022 (0.251–4.163) | 0.976               |
| Grade                            |                     |                     |                     |                     |
| Well differentiated              | 1.0 [reference]     |                     | 1.0 [reference]     |                     |
| Moderately differentiated        | 0.750 (0.378–1.488) | 0.411               | 1.761 (0.402–7.714) | 0.453               |
| Poorly differentiated            | 1.312 (0.704–2.446) | 0.392               | 3.279 (0.793–13.553)| 0.101               |
| Undifferentiated                 | 2.039 (1.033–4.024) | 0.040               | 4.506 (0.991–20.491)| 0.051               |
| Unknown                          | 1.493 (0.781–2.856) | 0.224               | 4.266 (0.993–18.323)| 0.051               |
| Histology                        |                     |                     |                     |                     |
| Metaplastic carcinoma            | 1.0 [reference]     |                     | 1.0 [reference]     |                     |
| Carcinosarcoma                   | 1.061 (0.731–1.541) | 0.754               | 0.861 (0.367–2.018) | 0.731               |
| Adenosquamous carcinoma          | 0.846 (0.558–1.283) | 0.432               | 1.047 (0.589–1.860) | 0.877               |
| Adenocarcinoma with squamous metaplasia | 0.992 (0.694–1.418) | 0.965               | 1.343 (0.801–2.252) | 0.264               |
| Others                           | 0.812 (0.559–1.180) | 0.275               | 0.843 (0.425–1.670) | 0.624               |
| Risk stratification              |                     |                     |                     |                     |
| Low risk                         | 1.0 [reference]     |                     | 1.0 [reference]     |                     |
Variables & Before PSM & After PSM

| Variables          | HRs (95% CI)     | p     | HRs (95% CI)     | p     |
|--------------------|------------------|-------|------------------|-------|
| Intermediate risk  | 1.630 (1.130–2.350) | 0.009 | 2.747 (1.656–4.556) | <0.001 |
| High risk          | 2.847 (1.870–4.334) | <0.001 | 9.587 (5.597–16.423) | <0.001 |

HR status

| HR status | Before PSM | After PSM |
|-----------|------------|-----------|
| HR(-)     | 1.0 [reference] | 1.0 [reference] |
| HR(+)     | 1.017 (0.841–1.231) | 0.860 | 1.070 (0.829–1.380) | 0.604 |

Chemotherapy

| Chemotherapy | Before PSM | After PSM |
|--------------|------------|-----------|
| Yes          | 1.0 [reference] | 1.0 [reference] |
| No           | 1.104 (0.906–1.346) | 0.326 | 0.893 (0.644–1.237) | 0.495 |

Radiotherapy

| Radiotherapy | Before PSM | After PSM |
|--------------|------------|-----------|
| Yes          | 1.0 [reference] | 1.0 [reference] |
| No           | 1.221 (1.022–1.458) | 0.028 | 0.836 (0.623–1.120) | 0.23 |

Surgery types

| Surgery types | Before PSM | After PSM |
|---------------|------------|-----------|
| Lumpectomy    | 1.0 [reference] | 1.0 [reference] |
| Mastectomy    | 1.242 (1.006–1.534) | 0.044 | 1.647 (1.160–2.338) | 0.005 |
| None          | 1.403 (0.970–2.030) | 0.072 | 2.660 (1.484–4.768) | 0.001 |

MBC = metaplastic breast cancer; BCSS = breast cancer specific survival; AJCC = American Joint Committee on Cancer; HRs = hazard ratios; HR = hormonal receptor; PSM = propensity-score matching.

### 3.3 Survival Analysis after PSM

To analyze the independent prognostic factors for the BCSS, we used the Cox proportional hazards model. Of note, neither HR status (HR-negative as reference, HRs 1.070; 95% CI, 0.829–1.380; P < 0.604) nor CT (receiving CT as reference, HRs 0.893; 95% CI, 0.644–1.237; P < 0.495) was not associated with outcome. The parameters with significant difference related to better prognosis of MBC were age (HRs 1.025; 95% CI, 1.015–1.036; P < 0.001), risk stratification (low-risk as reference, intermediate risk, HRs 2.747; 95% CI, 1.656–4.556; P < 0.001; high-risk, HRs 9.587; 95% CI, 5.597–16.423; P < 0.001), and surgery
types (lumpectomy as reference, mastectomy, HRs 1.647; 95% CI, 1.160–2.338; P < 0.005; None, HRs 2.660; 95% CI, 1.484–4.768; P < 0.001). However, race, tumor grade, tumor histology, and radiotherapy were not associated with better BCSS.

3.4 Subtype analysis for the role of HR status in chemotherapy

We further evaluated the role of HR status in CT under different risk of recurrence. In Kaplan–Meier analysis, when HR status was negative, intermediate-risk patients received CT had superior survival than that not receiving CT (P < 0.001). When HR status was positive, intermediate- and high-risk patients receiving CT had better survival than that without CT (intermediate-risk group, P = 0.027; high-risk group, P = 0.010). For patients within a low-risk group or entire cohort, CT was not associated with better BCSS regardless of HR status. (Fig. 3) In PSM-data set, however, only HR-positive patients with high risk could benefit from CT. Of note, CT might improve the short-term clinical outcomes for patients with intermediate-risk regardless of HR status (HR-negative, the Gehan-Breslow-Wilcoxon test P = 0.047; HR-positive, the Gehan-Breslow-Wilcoxon test P = 0.017).

4. Discussion

In the present study, we examined the effect of CT on the prognosis of MBC patients and explored the role of HR in CT under different risk of recurrence. After propensity score matching and using the variables as covariates considered importantly by some scholars, our results showed that only HR-positive patients with high risk could benefit from CT. Of note, CT might improve the short-term clinical outcomes for patients with intermediate-risk regardless of HR status.

Although the previous study reported MBC had a good survival, they had a small sample and short follow-up period. [26–29] A study reported median survival for metastatic MBC patients was less than 1 year. [30] MBC patients with stage IV have different management and survival outcomes relative to patients with stage I–III. [19, 20] As mentioned above, we excluded MBC patients with distant metastasis.

The proportion of MBC receiving CT ranged from 33 to 86%. [13, 19, 31] On the one hand, patients receiving CT with a wide range may indicate that the effect of CT was not yet certain in MBC patients, although several small, single-institution and the single-arm study showed that CT could improve the prognosis of MBC. [32–34] On the other hand, patients receiving CT with a high rate may be due to their tendency to more common triple-negative phenotype and larger tumor size. [35] There was also another reason that the management strategy of MBC is similar to traditional breast cancer in the NCCN guideline. [12] However, most studies had illustrated that CT might not affect the outcome of MBC. [2, 14, 17, 18] In our study, 62.5% of patients underwent CT but they cannot benefit from it, which was consistent with the previous study. [36, 37] However, in the subtype analysis, only HR-positive patients with high risk could benefit from CT. That has not been appreciated so far. The reason for this effect could be the fact that our research population excluded patients with distant metastasis and follow-up was longer than published studies. Besides this, different risks of recurrence may be also worth considering.
HR-positivity has been considered as a biomarker as a better outcome for traditional breast cancer. However, previously published literature illustrated HR status was not associated with the prognosis of MBC.\[22\] As reporting by Schroeder et al.\[35\], for early and locally advanced MBC patients, HER2 but not HR status was associated with superior survival. In addition, they also found that survival was parallel between HER2-positive MBC and HER2-positive IDC. However, most researchers concluded that survival of MBC patients was the worse carcinoma in traditional breast cancer.\[14, 18, 38\] In many relatively consistent observation studies showed that MBC tended negative biomarkers. [ER, PR, HER2] \[14, 39–41\] Previous studies reported only 0–17% of cases expressed HR-positivity. \[7, 8, 42\] The expression of HR in MBC was uncommon. In the present study, 23.0% of patients were HR-positive cases. HR status was not a significant prognosticator in multivariate analysis, which was consistent with the result of Wright et al. reported. \[22\]

However, Wright et al. only conducted the Kaplan–Meier model and log-rank test without further analysis. In our study, subtype analysis was performed to explore the response of HR status to CT according to risk stratification before and after PSM. We found that patients with low risk cannot benefit from CT regardless of HR status. The reason for this phenomenon could be a smaller tumor size with a low risk of hematogenous metastasis. In addition, patients with intermediate-risk might benefit from CT regardless of HR status. However, patients with high risk benefited from CT only when they expressed HR-positivity. Such an occurrence probably accounts for HR-negative MBC patients with a worse prognosis than triple-negative breast cancer (TNBC).\[14, 18, 37\]

The European Society for Medical Oncology has adopted the statement that MBC patients are recommended to undergo CT from the 2013 St. Gallen consensus statement. The possible reason for this could be the fact that the HR status is commonly negative.\[43, 44\] A clinical overview study from Abouharb et al. \[30\] showed that the role of targeted therapies was a major investigation. Due to different molecular phenotypes, MBC can particularly benefit from these management strategies, as evidenced by Adams’ case report. \[33\] For this aggressive tumor, molecular analysis is important.

51.8% of patients were treated with mastectomy and 42.3% were treated with lumpectomy. Notably, mastectomy is performed more often for patients with MBC, likely due to the presentation with a larger tumor and triple-negative phenotype. However, in multivariate analysis, patients who underwent lumpectomy had better survival than patients who underwent a mastectomy. These data convinced us that breast-conserving therapy is an effective treatment strategy combined with other historical data for MBC patients.\[22\]

There were several limitations to our study. Firstly, it was characterized by the observational nature and the possibility of selection bias because of its retrospective study. Secondly, the SEER database lacks baseline characteristics of MBC patients, including performance status, comorbidities, and socio-economic environment parameters. Thirdly, detailed chemotherapy regimens and radiotherapy information could not be available from the SEER database, so that further case-control study could not
be performed. However, our results will help researchers to understand the role of molecular subtypes in the prognosis of MBC.

Our study has several key strengths. The involvement of CT in the prognosis of MBC is unclear. From our results, when stratified by recurrence risk, the prognosis was improved in MBC patients receiving CT. In addition, although studies had reported that HR status was not related to prognosis, HR status can redefine the role of chemotherapy in the prognosis of MBC.

5. Conclusion

Although HR status had no effect on the prognosis of MBC and CT was not associated with BCSS, HR-positive patients with high risk could benefit from CT. Of note, CT might improve the short-term clinical outcomes for patients with intermediate-risk regardless of HR status. The role of HR status is particularly important for the treatment of early and locally advanced metaplastic cancer of the breast.

List Of Abbreviations

| Abbreviation | Description                           |
|--------------|---------------------------------------|
| BCSS         | Breast cancer-specific survival       |
| CI           | Confidence interval                   |
| CT           | Chemotherapy                          |
| HER2         | Human epidermal growth receptor 2     |
| HR           | Hormone receptor                      |
| HRs          | Hazard ratios                         |
| ICD-O-3      | International Classification of Diseases for Oncology |
| IDC          | Invasive ductal carcinoma             |
| MBC          | Metaplastic breast cancer             |
| NCCN         | National Comprehensive Cancer Network |
| PSM          | Propensity-score matching             |
| RT           | radiotherapy                          |
| TNBC         | Triple-negative breast cancer         |
| WHO          | World Health Organization             |

Declarations

Ethics approval and consent to participate
This study was exempt from the approval processes of the Institutional Review Boards because the SEER database patient information is de-identified.

Consent for publication

All the authors approved the publication of this manuscript.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available in the Figshare.com repository, https://doi.org/10.6084/m9.figshare.11985234.

Competing interests

The authors declare that they have no conflict of interest.

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Author contributions

Siqin Wang and Jin Hu conceived and designed the study. Jin Hu and Yanting Zhang performed data quality control and statistical analyses. Jian Shen provided the functional raw data and Fang Dong and Ximeng Zhang performed the analysis. Cong Lu and Dan Shang drafted the manuscript. All other authors provided samples and data. All authors critically read, commented and approved the manuscript.

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All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Jin Hu and Yanting Zhang. The first draft of the manuscript was written by Jin Hu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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