



Original Research

Metaplastic breast cancer: Treatment and prognosis by molecular subtype

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ABSTRACT

Background: Metaplastic breast cancer (MBC) is a rare and aggressive subtype of breast. However, the effect of molecular subtype on treatment and prognosis of MBC remains unclear.

Patients and methods: The Surveillance, Epidemiology, and End Results database was used to analyze patients with MBC between 2010 and 2016. Molecular subtype was stratified to TN group (ER and PR-/HER2-), HER2 group (ER and PR-/HER2+, ER/PR+ and HER2+), and HR group (ER/PR+ and HER2-). The breast cancer-specific survival (BCSS) differences were estimated using multivariate Cox regression model and Kaplan-Meier curves.

Results: We included 1665 patients with median follow-up time of 27 months (range 0–83 months). 1154 (69.3%), 65 (3.9%), and 446 (26.8%) patients presented in TN group, HER2 group, and HR group, respectively. On multivariate Cox analysis, the prognosis was related to age, tumor size, regional node metastasis, and surgery. Molecular subtype remained no impact on BCSS. Radiotherapy (RT) was associated with better prognosis. Patients cannot benefit from chemotherapy. In Kaplan-Meier curve, triple-negative ($P = 0.047$) and HR-positive ($P = 0.006$) patients receiving RT had a superior BCSS than that not RT. HER2-positive patients cannot benefit from RT. However, adjusted Kaplan-Meier survival model showed that triple-negative ($P = 0.019$) but not HER2-positive ($P = 0.575$) or HR-positive ($P = 0.574$) patients receiving RT had a superior BCSS than that not RT.

Conclusions: Molecular subtype is not associated with the better prognosis of MBC. Patients could benefit from RT. However, triple-negative but not HR-positive or HER2-positive patients have superior survival after receiving RT.

Abbreviations

| | |
|------------|--|
| MBC | Metaplastic breast cancer; |
| RT | Radiotherapy; |
| CT | Chemotherapy; |
| TNBC | Triple-negative breast cancer; |
| SEER | Surveillance, Epidemiology, and End Results; |
| ER | Estrogen receptor; |
| PR | Progesterone receptor; |
| HR | Hormone receptor; |
| HER2 | Human epidermal growth factor receptor 2; |
| ICD-0–3 | International Classification of Diseases for Oncology Version 3. |
| OS | Overall survival; |
| BCSS | Breast cancer-specific survival; |
| DFS | Disease free survival; |
| HRs | Hazard ratios; |
| CI | Confidence interval; |
| TN-MBC | Triple-negative subtype of MBC; |
| Non-TN MBC | MBC without triple-negative subtype; |

IDC Invasive ductal carcinoma, no special type;

Introduction

Metaplastic breast cancer (MBC) is a rare and aggressive subtype accounting for <1% of all breast cancer [1]. Previous studies had reported histologic MBC characterized by either homogenous or mixed components. [2–6] MBC was not identified as a unique pathological type by the World Health Organization until 2000. [7] Since then, as pathologists' understanding of MBC has been improved, the incidence has also increased. [8] However, due to its rarity, the involvement of molecular subtype in treatment and prognosis of MBC is unclear.

Up to now, the role of radiotherapy (RT) in prognosis of MBC remains controversial. Jung et al. [9] pointed out that women with MBC had no benefit from RT. On the other hand, some studies [10–12] showed that RT was associated with better survival of MBC. Dave et al. [13] and Yu et al. [14] agreed with that better outcomes could be observed in patients receiving RT followed breast conservation surgery than that not RT. Additionally, the role of chemotherapy (CT) in prognosis of MBC

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Table 1
Characteristics in MBC patients.

| Variables | TN (n = 1154) | HER2 (n = 65) | HR (n = 446) | p |
|----------------------------|------------------|------------------|-----------------|--------|
| Age (median, range) | 62 (22- 89) | 56 (31-84) | 62 (20-89) | 0.015 |
| Age group | | | | 0.002 |
| ≤ 60 years | 513 (44.5) | 43 (66.2) | 216 (48.4) | |
| > 60 years | 641 (55.5) | 22 (33.8) | 230 (51.6) | |
| Survival months (median) | 26 (0-83) | 28 (0-78) | 28 (0-83) | 0.751 |
| Race (n,%) | | | | 0.020 |
| White | 882 (76.4) | 43 (66.2) | 320 (71.7) | |
| Black | 191 (16.6) | 16 (24.6) | 75 (16.8) | |
| Other | 81 (7.0) | 6 (9.2) | 51 (11.4) | |
| Insurance (n,%) | | | | 0.337# |
| No | 16 (1.4) | 2 (3.1) | 8 (1.8) | |
| Yes | 1138 (98.6) | 63 (96.9) | 438 (98.2) | |
| Grade (n,%) | | | | 0.001# |
| Well differentiated | 53 (4.6) | 0 (0) | 19 (4.3) | |
| Moderately differentiated | 133 (11.5) | 1 (1.5) | 74 (16.6) | |
| Poorly differentiated | 797 (69.1) | 60 (92.3) | 298 (66.8) | |
| Undifferentiated | 35 (3.0) | 1 (1.5) | 11 (2.5) | |
| Unknown | 136 (11.8) | 3 (4.6) | 44 (9.9) | |
| Histology (n,%) | | | | 0.389# |
| Metaplastic carcinoma | 1012 (87.7) | 59 (90.8) | 384 (86.1) | |
| Adenosquamous carcinoma | 46 (4.0) | 1 (1.5) | 25 (5.6) | |
| Carcinosarcoma | 59 (5.1) | 2 (3.1) | 17 (3.8) | |
| Others | 37 (3.2) | 3 (4.6) | 20 (4.5) | |
| Tumor size (n,%) | | | | 0.176 |
| ≤ 10 mm | 70 (6.1) | 6 (9.2) | 30 (6.7) | |
| ≤ 20 mm | 223 (19.3) | 15 (23.1) | 98 (22.0) | |
| ≤ 30 mm | 276 (23.9) | 10 (15.4) | 90 (20.2) | |
| ≤ 40 mm | 171 (14.8) | 11 (16.9) | 80 (17.9) | |
| ≤ 50 mm | 120 (10.4) | 4 (6.2) | 51 (11.4) | |
| > 50 mm | 279 (24.2) | 18 (27.7) | 86 (19.3) | |
| Unknown | 15 (1.3) | 1 (1.5) | 11 (2.5) | |
| Regional node status (n,%) | | | | 0.026# |
| N0 | 951 (82.4) | 45 (69.2) | 347 (77.8) | |
| N1 | 151 (13.1) | 17 (26.2) | 68 (15.2) | |
| N2-3 | 48 (4.2) | 3 (4.6) | 30 (6.7) | |
| Nx | 4 (0.3) | 0 (0) | 1 (0.2) | |
| TNM stage (n,%) | | | | 0.037# |
| I | 261 (22.6) | 19 (29.2) | 109 (24.4) | |
| II | 673 (58.3) | 28 (43.1) | 232 (52.0) | |
| III | 156 (13.5) | 14 (21.5) | 71 (15.9) | |
| IV | 56 (4.9) | 3 (4.6) | 24 (5.4) | |
| Unknown | 8 (0.7) | 1 (1.5) | 10 (2.2) | |
| Chemotherapy (n,%) | | | | 0.003 |
| No | 382 (33.1) | 10 (15.4) | 159 (35.7) | |
| Yes | 772 (66.9) | 55 (84.6) | 287 (64.3) | |
| Radiotherapy (n,%) | | | | 0.231 |
| No | 635 (55.0) | 33 (50.8) | 225 (50.4) | |
| Yes | 519 (45.0) | 32 (49.2) | 221 (49.6) | |
| Surgery (n,%) | | | | 0.689 |
| No | 63 (5.5) | 3 (4.6) | 29 (6.5) | |
| Lumpectomy | 458 (39.7) | 24 (36.9) | 184 (41.3) | |
| Mastectomy | 633 (54.9) | 38 (58.5) | 233 (52.2) | |

MBC = metaplastic breast cancer

= Fisher test.

is also unclear. A relatively consistent observation across many studies suggests that MBC has lower response rates to CT. [9,15-18] However, only a few studies showed that MBC might derive survival benefit from CT. [10,11] RT and CT are routinely used in MBC patients while the outcome remains poor.

MBC has a tendency to present with unique histopathological and molecular characteristics: larger tumor size, less regional axillary node metastasis, poorly differentiated, more commonly triple-negative phenotype [10,19,20]. Additionally, MBC patients had worse outcomes than IDC and triple-negative breast cancer (TNBC) even after receiving comprehensive treatment. [14,21] Nevertheless, in current clinical practice, the treatment strategy of MBC is similar to that of traditional breast cancer according to biomarkers profile [22,23], although the clinical and pathological characteristics of MBC and IDC are different. [14,24] A previous study of the Surveillance, Epidemiology, and End Results (SEER) data from 2000 to 2010 found that hormonal receptor (HR) sta-

tus was not associated improved prognosis in MBC. [25] Another study from Schroeder et al. [20] included 1516 patients showed that human epidermal growth receptor 2 (HER2) but not HR status was associated with improved survival.

The purpose of our study is to compare the clinical process, tumor characteristics and prognosis among different molecular subtypes using the database of the whole population, and evaluate the response of MBC to treatment of traditional breast cancer.

Materials and methods

Patients

Data was retrieved from the SEER database, including all cases of MBC confirmed by pathology and diagnosed between 2010 and 2016. This database collects cancer incidence, demographics and clinicopatho-

logic data, management, and survival data from 18 population-based cancer registries. According to the third edition of International Classification of Diseases for Oncology (ICD-0-3), carcinoma histology was identified to metaplastic cancer with ICD-0-3 codes: 8560, 8562, 8570-8572, 8575, and 8980-8982. [25] 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, with information of known survival time and molecular subtype, stage exception of T0 and Tis. Finally, 1665 patients were enrolled.

Demographics and clinicopathologic features

The demographic parameters included age at diagnosis, race recorded by SEER (white, black, Asian or Pacific Islander, unknown), and insurance status. The clinicopathologic parameters included tumor grade, tumor size (millimeter, mm), regional node status (N0, N1, N2-3, and Nx), TNM-stage, therapy modality (surgery, CT, and RT), and biomarkers profile (estrogen receptor [ER], progesterone receptor [PR], and HER2). According to the SEER recorded, molecular subtype was stratified to three categorical variables: TN group (ER and PR-/HER2-), HER2 group (ER and PR-/HER2+, ER/PR+ and HER2+), and HR group (ER/PR+ and HER2-).

The primary clinical outcome was breast cancer-specific survival (BCSS) which defined from the date of diagnosis to the date of death for breast cancer.

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 neoadjuvant 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.

Statistical analysis

The χ^2 test was carried out to analyze the differences among the three groups. The Cox proportional hazards model was performed to assess the risk factors for BCSS. Hazard ratios (HRs) were shown with 95% confidence intervals (CI). Kaplan-Meier survival analyses were performed to calculate the BCSS rates. All variables with statistically significant difference in the multivariate analysis model were added to further adjusted Kaplan-Meier survival analysis. The adjusted Kaplan-Meier survival estimates for BCSS among subtypes of MBC with or without radiotherapy. All statistical analyses were performed using SPSS statistical software (version 24.0; IBM Corporation, Armonk, NY, USA). R statistical software (version 3.6.1, R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>) conducted an adjusted Kaplan-Meier analysis. A P value < 0.05 was statistically significant.

Results

Patient characteristics

Of the 4672 MBC patients in the SEER registry, our final sample comprised 1665 patients. The characteristics have been recorded in **Table 1**. 1154 (69.3%) of patients were in the TN group, 65 (3.9%) in the HER2 group, and 446 (26.8%) in the HR group.

In the entire cohort, 46.4% of patients were aged ≤ 60 years, with a median age of 62 years (range, 20- 89 years). Most of them were White ($n = 1245$, 74.8%), poor differentiation ($n = 1155$, 69.4%). In patients with available tumor size information, 64.9% were no greater than 40 mm. A total of 389 (23.4%), 933 (56.0%), 241 (14.5%), and 83 (5.0%) of the patients had I, II, III, and IV stage disease, respectively.

Table 2

Univariate analysis of the BCSS in MBC patients.

| | n | 3-year BCSS rate (%) | p |
|---------------------------|------|----------------------|---------|
| Subtype | | | 0.359 |
| TN | 1154 | 78.7 | |
| HER2 | 65 | 87.3 | |
| HR | 446 | 79.6 | |
| Age group | | | 0.029 |
| ≤ 60 years | 772 | 81.2 | |
| > 60 years | 893 | 77.6 | |
| Race | | | 0.023 |
| White | 1245 | 80.8 | |
| Black | 282 | 72.9 | |
| Other | 138 | 77.6 | |
| Insurance | | | 0.946 |
| No | 26 | 74.3 | |
| Yes | 1639 | 79.4 | |
| Grade | | | < 0.001 |
| Well differentiated | 72 | 93.3 | |
| Moderately differentiated | 208 | 87.9 | |
| Poorly differentiated | 1155 | 77.8 | |
| Undifferentiated | 47 | 69.6 | |
| Unknown | 183 | 75.7 | |
| Tumor size | | | < 0.001 |
| ≤ 10 mm | 106 | 98.0 | |
| ≤ 20 mm | 336 | 90.8 | |
| ≤ 30 mm | 376 | 87.5 | |
| ≤ 40 mm | 262 | 85.5 | |
| ≤ 50 mm | 175 | 79.2 | |
| > 50 mm | 383 | 51.7 | |
| Unknown | 27 | 76.4 | |
| Regional node status | | | < 0.001 |
| N0 | 1343 | 82.9 | |
| N1 | 236 | 67.2 | |
| N2-3 | 81 | 57.5 | |
| TNM stage | | | < 0.001 |
| I | 389 | 94.0 | |
| II | 933 | 84.9 | |
| III | 241 | 55.1 | |
| IV | 83 | 16.3 | |
| Unknown | 19 | 93.8 | |
| Chemotherapy | | | 0.393 |
| No | 551 | 79.1 | |
| Yes | 1114 | 79.4 | |
| Radiotherapy | | | 0.001 |
| No | 893 | 75.6 | |
| Yes | 772 | 83.4 | |
| Surgery | | | < 0001 |
| No | 95 | 39.2 | |
| Lumpectomy | 666 | 90.4 | |
| Mastectomy | 904 | 74.8 | |

MBC = metaplastic breast cancer; BCSS = breast cancer-specific survival.

In addition, 1343 (80.7%), 236 (14.2%), and 81 (4.9%) of the patients had N0, N1, N2-3 stage disease, respectively.

Compared with TN group and HR group, HER2 group had a tendency to have younger people, more poorly differentiated tumors, and more regionally metastatic nodes. Furthermore, HER2 group was more likely to be provided with CT. However, no difference in patients receiving surgery and RT was observed among groups. In addition, there was no difference in tumor size among TN group, HER2 group, and HR group.

Survival analysis and prognostic factors

The median follow-up time was 26 months (range 0-83 months), 28 months (range 0-78 months), and 28 months (range 0-83 months) in the TN group, HER2 group, and HR group, respectively. The breast cancer-related death cases were 213 (18.5%) in the TN group, 7 (10.8%) in the HER2 group, and 81 (18.2%) in the HR group.

Table 2 shows the number of events and the 3-year survival rates in three groups. There was no difference in 3-year BCSS rate ($P = 0.359$) among molecular subtypes.

Table 3
Prognostic factors for BCSS in cohort by multivariate analyses.

| Variables | HRs | 95% CI | p |
|---------------------------|--------|--------------|---------|
| Subtype | | | |
| TN | 1.0 | [reference] | |
| HER2 | 0.615 | 0.286–1.320 | 0.212 |
| HR | 0.953 | 0.733–1.239 | 0.719 |
| Age group | | | |
| ≤ 60 years | 1.0 | [reference] | |
| > 60 years | 1.470 | 1.141–1.894 | 0.003 |
| Race | | | |
| White | 1.0 | [reference] | |
| Black | 1.254 | 0.940–1.672 | 0.124 |
| Other | 0.928 | 0.601–1.433 | 0.736 |
| Grade | | | |
| Well differentiated | 1.0 | [reference] | |
| Moderately differentiated | 0.834 | 0.307–2.270 | 0.723 |
| Poorly differentiated | 1.188 | 0.466–3.028 | 0.719 |
| Undifferentiated | 1.617 | 0.552–4.731 | 0.381 |
| Unknown | 1.072 | 0.405–2.839 | 0.889 |
| Tumor size | | | |
| ≤ 10 mm | 1.0 | [reference] | |
| ≤ 20 mm | 2.055 | 0.714–5.908 | 0.182 |
| ≤ 30 mm | 2.658 | 0.949–7.450 | 0.063 |
| ≤ 40 mm | 3.227 | 1.138–9.152 | 0.028 |
| ≤ 50 mm | 3.955 | 1.387–11.279 | 0.010 |
| > 50 mm | 11.592 | 4.244–31.661 | <0.001 |
| Unknown | 2.596 | 0.671–10.037 | 0.167 |
| Regional node status | | | |
| N0 | 1.0 | [reference] | |
| N1 | 1.997 | 1.501–2.657 | < 0.001 |
| N2–3 | 2.302 | 1.583–3.347 | < 0.001 |
| Chemotherapy | | | |
| No | 1.0 | [reference] | |
| Yes | 0.823 | 0.627–1.080 | 0.159 |
| Radiotherapy | | | |
| No | 1.0 | [reference] | |
| Yes | 0.671 | 0.521–0.864 | 0.002 |
| Surgery | | | |
| No | 1.0 | [reference] | |
| Lumpectomy | 0.137 | 0.088–0.215 | <0.001 |
| Mastectomy | 0.193 | 0.135–0.277 | <0.001 |

BCSS = breast cancer-specific survival; HRs = Hazard ratios, CI = confidence interval.

The 3-year BCSS in patients receiving CT and not CT were 79.4% and 79.1%, respectively ($P = 0.393$). On the other hand, patients receiving RT had a better BCSS than that not receiving RT ($P = 0.001$). In addition, the 3-year BCSS rate were progressive decrease in patients with larger tumor size and more regional node involvement

As presented in **Table 3**, prognostic factors for BCSS were analyzed in the multivariate Cox proportional hazards model. Molecular subtypes were not an independent prognostic factor related to better BCSS. In addition, RT was associated with superior prognosis (HRs 0.671; 95% CI, 0.521- 0.864; $P = 0.002$). MBC patients could not benefit from CT (HRs 0.823; 95% CI, 0.627- 1.080; $P = 0.159$). Furthermore, age, tumor size, nodal stage, and surgery were also independent indicators for BCSS. However, race, tumor grade was not related to BCSS.

Adjusted Kaplan-Meier survival analysis

In order to eliminate confounding factors, adjusted Kaplan-Meier survival estimates for BCSS among subtypes of MBC with or without radiotherapy. (**Fig. 1**) When stratified by molecular subtype, RT could improve prognosis in TN ($P = 0.047$) and HR groups ($P = 0.006$), while women receiving RT had not a better survival than that not receiving RT in HER2 group ($P = 0.266$). However, after adjusting, the results were different. RT was significantly associated with better survival in overall cases (adjusted $P = 0.031$) and the TN group (adjusted $P = 0.019$). Patients cannot benefit from RT in HER2 group (adjusted $P = 0.575$) and HR group (adjusted $P = 0.574$).

Discussion

In the current study, we compared the difference of clinical process, tumor characteristics and prognosis among different molecular subtypes, and evaluated the response of tumor with different molecular subtype to treatment of RT and CT. We found that the molecular subtype was not related with better survival. In addition, RT could improve the prognosis of MBC patients with triple-negative but not HR-positive or HER2 positive tumors. While CT was not associated with better prognosis.

MBC without triple-negative (non-TN MBC) is not a common tumor, especially the HER2 phenotype. [20,26] A previous study of SEER data from 2010 to 2014 was performed to compare three subtypes by stratifying by tumor histologic subtype and stage. [20] They recorded that the 3-year overall survival (OS) was significantly improved only in stage III MBC with HER2-positivity. In their study, the sample in stage III was too small ($n = 14$) to convince scholars completely. In our series, 3.9% ($n = 65$) of women were HER2 positive. No difference was observed in prognosis among molecular subtypes. We further explored the role of molecular subtype in patients receiving CT and RT, and found that neither CT nor RT was associated with improved survival in women with HER2 positive. The reasons for this effect could be the facts that, firstly, the research population was different. They excluded patients with distant metastasis; secondly, their SEER ICD-0–3 codes that identified MBC cases were different with most studies [25,27,28]; Thirdly, there might be other uncertain reasons due to their incomplete information of exclusion criteria.

Although triple-negative breast cancer is the most common in MBC, HR-positive MBC also occur. [26] In a study from Wright et al. [25] which included 2338 MBC, they concluded that, contrary to traditional breast cancers, HR positivity did not improve clinical outcomes in MBC. In our study, 26.8% of women expressed HR-positive phenotype. Although HR group was patients with ER/PR positive and HER2 negative in our study and with ER/PR positive (HER2 status unknown) in Wright’s study, our results were consistent with their findings. The reason for this phenomenon could be the incidence of ER/PR positive and HER2 positive MBC (2.2% in our study) was low.

In addition, in a study from He et al. [10], which included 1112 MBC patients diagnosed between 2010 and 2014, the results of Kaplan–Meier analysis showed that RT was associated with improved prognosis in both TN-MBC and non-TN MBC. In addition, in their multivariate analyses model, better prognosis correlated with younger population, smaller tumor size and less lymph node involvement, and receiving surgery. However, our results showed that RT was associated with improved prognosis in TN-MBC while non-TN MBC cannot benefit from RT. One major drawback of their study was that there were no adjustments of other variables in the Kaplan–Meier curves to take the other variables with significant difference in multivariate model into consideration.

In our study, RT was significantly associated with superior prognosis of MBC. While some studies disagree with this finding, other studies showed that there was a significant effect on outcomes. Jung et al. [9] reported patients with MBC had no benefit from RT. On the other hand, He et al. [10] showed RT was related to improvements in OS and BCSS in the multivariate analyses model. However, some authors pointed out that the role of RT in prognosis of MBC was related to types of surgical methods. Dave et al. [13] and Yu et al. [14] found that RT had a benefit for MBC patients undergoing breast conservation surgery but not total mastectomy. Additionally, a few studies illustrated that the role of RT in prognosis was related to clinical characteristics of MBC besides types of surgical methods. Tseng et al. [20] and Carson et al. [29] showed that RT had better survival for MBC patients undergoing breast conservation surgery and those patients undergoing mastectomy combined with tumor size and axillary lymph nodes. Of note, patients diagnosed with IDC can benefit from RT regardless of molecular subtype. However, in the adjusted model, only triple negative patients diagnosed with MBC could benefit from RT.

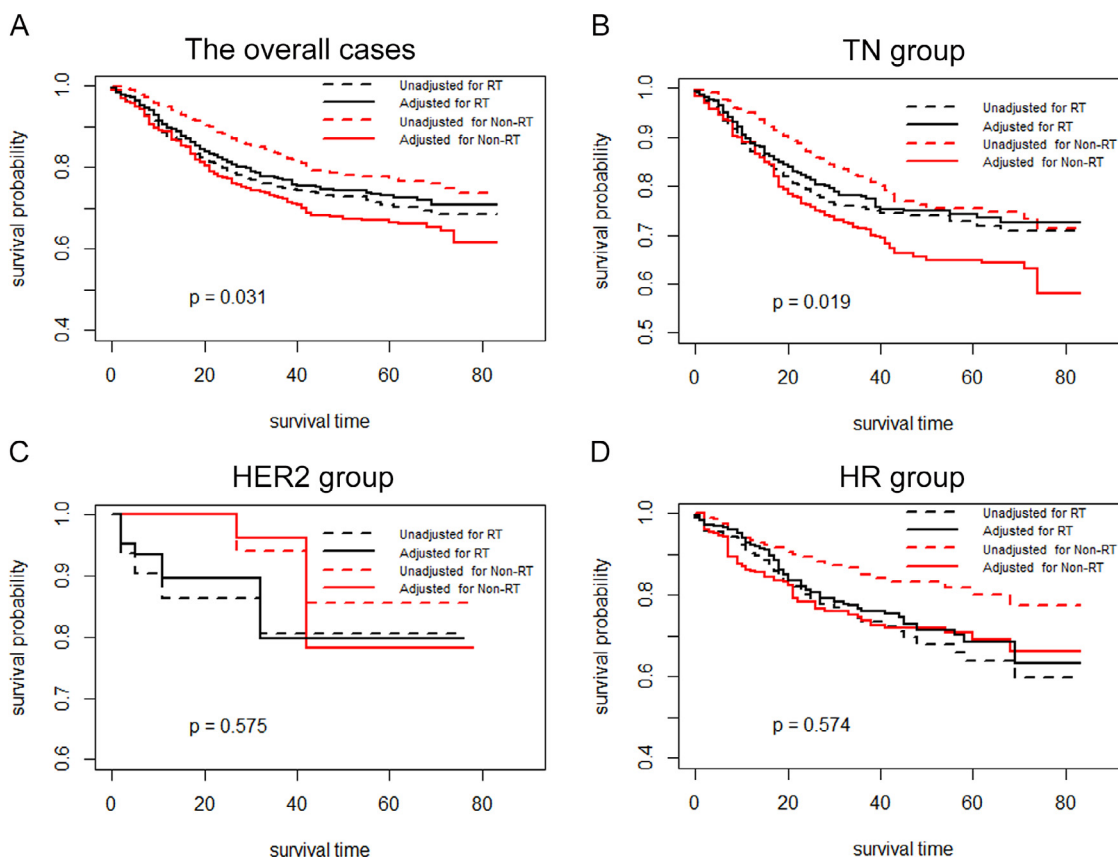


Fig. 1. Adjusted Kaplan-Meier survival estimates for BCSS among subtypes of MBC with or without radiotherapy. RT = radiotherapy. Multivariate Cox regression model includes the following variables: age, tumor size, regional node status, surgery.

The rate of adjuvant CT is quite high (66.9% in TN group, 84.6% in HER2 group, and 64.3% in HR group) in three groups. However, the previous researches showed that the response rate of MBC to CT regimens was relatively low. MBC might be a type of basal breast cancer, characteristic by higher grade and more rapid growth. [29–32] The expression levels of estrogen and progesterone receptor, and HER-2/neu receptor in MBC cells were lower than that of IDC, while the expression levels of Ki-67 and p-53 were higher. [33,34] In MBC patients, DNA repair pathways, such as TOP2A, PTEN, and BRCA1, were downregulation by analyzing genomic profiling. These findings might explain the low incidence of lymph node metastasis, resistance to conventional CT regimens, and sensitivity to radiation therapy.

There were several limitations in our study. Firstly, it was characterized by the observational nature and the possibility of selection bias because of its retrospective study. Secondly, HER2 status could not obtain in the database until 2010. Therefore, the follow-up time is not long. That might be the reason that chemotherapy was not associated with the prognosis of MBC. 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 also has a strength. As far as we know, this is the first detailed study of the impact of molecular subtype on treatment and prognosis of MBC using adjusted Kaplan-Meier survival analysis.

Conclusion

In our study, RT was significantly associated with superior prognosis. In contrast, patients cannot benefit from CT. In addition, molecular subtype is not related with the prognosis of MBC and is not a signifi-

cant role in women receiving CT. Of note, RT correlates with improved survival in triple-negative but not HR-positive or HER2-positive MBC patients.

Ethics statement

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

Supplemental Data: Supplemental materials accompanying this article can be found in the online version at https://widgets.figshare.com/articles/11993307/embed?show_title=1

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tranon.2021.101054.

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