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Breast Cancer

# Early and Locally Advanced Metaplastic Breast Cancer: Presentation and Survival by Receptor Status in Surveillance, Epidemiology, and End Results (SEER) 2010–2014

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*Disclosures of potential conflicts of interest may be found at the end of this article.*

**Key Words.** Metaplastic • Breast cancer • Human epidermal growth receptor 2 positive • Survival • Receptor subtype • Surveillance, Epidemiology, and End Results

## Abstract

***Background.*** Metaplastic breast cancer (MBC) is a rare disease subtype characterized by an aggressive clinical course. MBC is commonly triple negative (TN), although hormone receptor (HR) positive and human epidermal growth receptor 2 (HER2) positive cases do occur. Previous studies have reported similar outcomes for MBC with regard to HR status. Less is known about outcomes for HER2 positive MBC.

***Materials and Methods.*** Surveillance, Epidemiology, and End Results Program data were used to identify women diagnosed 2010–2014 with MBC or invasive ductal carcinoma (IDC). Kaplan-Meier curves estimated overall survival (OS) and multivariate Cox models were fitted. For survival analyses, only first cancers were included, and 2014 diagnoses were excluded to allow for sufficient follow-up.

***Results.*** Our MBC sample included 1,516 women. Relative to women with IDC, women with MBC were more likely to be older (63 vs. 61 years), black (16.0% vs. 11.1%), and present with stage III disease (15.6% vs. 10.8%). HER2 positive and HER2 negative/HR positive MBC tumors represented 5.2% and 23.0% of cases. For MBC overall, 3-year OS was greatest for women with HER2 positive MBC (91.8%), relative to women with TN (75.4%) and HER2 negative/HR positive MBC (77.1%). This difference was more pronounced for stage III MBC, for which 3-year OS was 92.9%, 47.1%, and 42.2% for women with HER2 positive, TN, and HER2 negative/HR positive MBC, respectively. A multivariate Cox model of MBC demonstrated that HER2 positive tumors (relative to TN) were associated with improved survival (hazard ratio = 0.32, 95% confidence interval [CI] 0.13–0.79). In a second Cox model of exclusively HER2 positive tumors, OS did not differ between MBC and IDC disease subtypes (hazard ratio = 1.16, 95% CI 0.48–2.81).

***Conclusion.*** In this contemporary, population-based study of women with MBC, HER2 but not HR status was associated with improved survival. Survival was similar between HER2 positive MBC and HER2 positive IDC. This suggests HER2 positive MBC is responsive to HER2-directed therapy, a finding that may offer insights for additional therapeutic approaches to MBC. ***The Oncologist*** 2018;23:481–488

**Implications for Practice:** This population-based study reports recent outcomes, by receptor status, for women with metaplastic breast cancer. Survival in metaplastic breast cancer is not impacted by hormone receptor status. To the authors' knowledge, this is the first report indicating that women with human epidermal growth receptor 2 (HER2) positive metaplastic breast cancer have survival superior to women with HER2 negative metaplastic breast cancer and survival similar to women with HER2 positive invasive ductal carcinoma. This information can be used for counseling patients diagnosed with metaplastic breast cancer. Further understanding of HER2 positive metaplastic breast cancer could offer insights for the development of therapeutic approaches to metaplastic breast cancer more broadly.

## Introduction

Metaplastic breast cancer (MBC) is a rare subtype of breast cancer, representing approximately 0.2%–2.0% of breast cancer diagnoses, and is generally associated with poor outcomes. Metaplastic breast cancer is an overarching term for a group of breast tumors that demonstrate differentiation of the neoplastic cells toward epithelial or mesenchymal components, or a

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mixture of these. As such, components of MBC tumors demonstrate histologies less common in breast cancer, including squamous, spindle cell, chondroid, or osseous, admixed with adenocarcinoma. The World Health Organization, which has recognized MBC as a distinct breast cancer subtype since 2000, classifies these tumors as pure epithelial type or mixed epithelial/mesenchymal type metaplastic breast cancer [1].

Metaplastic breast cancer tumors are often larger at presentation, less likely to involve regional axillary lymph nodes, and of higher grade than breast tumors with more common histologies [2, 3]. These tumors also have a propensity to metastasize to distant sites by hematogenous rather than lymphatic spread [4]. A recent case control study demonstrated that patients with stage I–III MBC had significantly worse 5-year disease-specific survival compared with patients with invasive ductal carcinoma (IDC) of the breast (78% vs. 93%, $p < .0001$) [2]. MBC is currently treated similarly to IDC, although multiple studies have shown that MBC is less sensitive to conventional cytotoxic chemotherapy in both the neoadjuvant and adjuvant settings [5–8]. In the metastatic setting, median survival is less than 1 year [9], and in a series of 27 patients with advanced MBC only a single partial response was seen among 10 different chemotherapy regimens [10].

MBC tumors are most commonly triple negative (TN) breast cancer, although hormone receptor (HR) positive and human epidermal growth receptor 2 (HER2) positive MBC cancers do occur [11]. A population-based analysis has demonstrated no difference in 5-year survival between HR positive and HR negative MBC cases [12]. This was in contrast with invasive ductal and lobular carcinomas of the breast, where survival for HR positive cases was better than for HR negative cases [12]. Several small reports have shown that treatment with antiestrogen therapy does not influence disease-free and overall survival outcomes in HR positive MBC [6, 7, 13]. These studies did not account for tumor HER2 receptor status, and less is known about presentations and outcomes of HER2 positive MBC. This is a particularly significant gap given the availability and use of HER2-directed therapy. Further, an understanding of MBC responsiveness to HER2-targeted therapy might suggest a vulnerability of this refractory disease to antibody derived and other targeted treatments. In this context, we conducted a population-based analysis to understand both clinical and pathologic characteristics, as well as survival outcomes, for women diagnosed from 2010 to 2014 with MBC.

## Materials and Methods

### Data Source

The database from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program was queried to construct our study cohort. For over 40 years, the SEER Program has collected information on all incident cancers occurring within defined geographical areas. These catchment areas currently include 18 registries and represent about 28% of the U.S. population [14]. SEER data, primarily collected from hospitals, include information on patient demographics, cancer diagnosis, tumor characteristics, first course of surgical treatment, and follow-up for vital status. Information regarding tumor subtype for breast cancers (HR and HER2 status) has been released by SEER since 2010. Use of these data for this project was considered not human subjects research by the University of Iowa's Institutional Review Board.

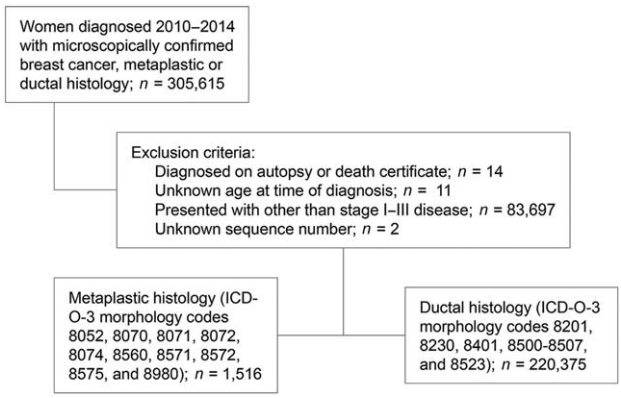


**Figure 1.** Flow diagram for creation of study cohort.
Abbreviation: ICD-O-3, International Classification of Diseases for Oncology, third edition.

### Study Population

Our study cohort included women diagnosed 2010–2014 with microscopically confirmed MBC (Fig. 1). Patients were excluded if they were diagnosed on autopsy or death certificate, presented with other than stage I–III disease, or were of unknown age at time of diagnosis or sequence number. Women presenting with stage IV disease were excluded given their markedly different survival outcomes relative to women with stage I–III MBC [6, 7] and the generally different therapeutic approach, palliative instead of curative, associated with presentation with metastatic disease. Tumors with metaplastic histology were identified with the following International Classification of Diseases for Oncology, third edition (ICD-O-3) morphology codes: 8052, 8070, 8071, 8072, 8074, 8560, 8571, 8572, 8575, and 8980. The following variables were defined for the cohort: age at diagnosis (less than 50, 50 and older); American Joint Committee on Cancer 7th edition stage (I, II, III); grade (1–2: well or moderately differentiated, 3–4: poorly or undifferentiated); race, as defined by SEER (white, black, other, unknown); three mutually exclusive subtypes for those with known receptor status (HER2 positive, TN, HER2 negative/HR positive) and unknown subtype; histology grouping (adenocarcinoma, squamous, adenosquamous, carcinosarcoma, metaplastic not otherwise specified [NOS]); sequence number (first and only cancer, first of multiple cancers, not first cancer); surgical treatment (none, breast-conserving surgery, mastectomy); and year of diagnosis. A cohort of IDC was also created for a comparison group. Ductal carcinomas were identified with the following ICD-O-3 morphology codes: 8201, 8230, 8401, 8500–8507, and 8523 [15]. The remaining inclusion and exclusion criteria were applied to this cohort as well.

### Statistical Analysis

Descriptive statistics were used to compare patient and tumor characteristics across MBC and IDC. Pearson chi-square tests were used to test independence in the distribution of categorical variables by histology. Logistic regression was also used to describe differences in distributions and calculate odds ratios. Kaplan-Meier curves estimated 3-year overall survival, by histology, stage, and subtype. These estimates of overall survival

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**Table 1.** Patient and tumor characteristics of MBC and IDC diagnosed in Surveillance, Epidemiology, and End Results

| Characteristics | MBC, *n* (%) | IDC, *n* (%) | *p* value[a] |
|---|---|---|---|
| Sample size | 1,516 | 220,375 | |
| Age at diagnosis, median (IQR) | 63 (53–74) | 61 (51–71) | |
| <50 | 277 (18.3) | 46,945 (21.3) | .004 |
| 50+ | 1,239 (81.7) | 173,430 (78.7) | |
| Race | | | |
| White | 1,159 (76.5) | 173,656 (78.8) | <.001 |
| Black | 242 (16.0) | 24,400 (11.1) | |
| Other | 109 (7.2) | 20,910 (9.5) | |
| Unknown | 6 (0.4) | 1,409 (0.6) | |
| Histology | | | |
| Adenocarcinoma | 32 (2.1) | 0 (0) | <.001 |
| Squamous | 113 (7.5) | 0 (0) | |
| Adenosquamous | 67 (4.4) | 0 (0) | |
| Carcinosarcoma | 69 (4.6) | 0 (0) | |
| Metaplastic NOS | 1,235 (81.5) | 0 (0) | |
| Ductal | 0 (0) | 220,375 (100) | |
| Subtype | | | |
| HER2 positive | 79 (5.2) | 33,323 (15.1) | <.001 |
| TN | 972 (64.1) | 26,326 (12.0) | |
| HER2 negative/HR positive | 349 (23.0) | 146,864 (66.6) | |
| Unknown | 116 (7.7) | 13,862 (6.3) | |
| Grade | | | |
| Grade 1, 2 | 286 (18.9) | 136,733 (62.1) | <.001 |
| Grade 3, 4 | 1,037 (68.4) | 76,047 (34.5) | |
| Unknown | 193 (12.7) | 7,595 (3.5) | |
| Stage (AJCC 7th) | | | |
| Stage I | 386 (25.5) | 122,372 (55.5) | <.001 |
| Stage II | 894 (59.0) | 74,146 (33.7) | |
| Stage III | 236 (15.6) | 23,857 (10.8) | |
| Sequence number | | | |
| First and only cancer | 1,104 (72.8) | 167,071 (75.8) | .006 |
| First of multiple cancers | 113 (7.5) | 12,839 (5.8) | |
| Not first cancer | 299 (19.7) | 40,465 (18.4) | |
| Surgery | | | |
| None | 69 (4.6) | 9,473 (4.3) | <.001 |
| Lumpectomy | 585 (38.6) | 119,719 (54.3) | |
| Mastectomy | 861 (56.8) | 90,794 (41.2) | |
| Unknown | 1 (0.1) | 389 (0.2) | |
| Year of diagnosis | | | |
| 2010 | 264 (17.4) | 41,356 (18.8) | .669 |
| 2011 | 313 (20.7) | 43,365 (19.7) | |
| 2012 | 307 (20.3) | 44,398 (20.2) | |
| 2013 | 310 (20.5) | 45,448 (20.6) | |
| 2014 | 322 (21.2) | 45,808 (20.8) | |

[a]*p* value from Pearson's chi-square test of independence.

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; HER2, human epidermal growth receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; MBC, metaplastic breast cancer; NOS, not otherwise specified; TN, triple negative.

were not further adjusted. Log-rank tests were used to compare survival across subtypes. Multivariate Cox proportional hazards models were also fitted for individuals with complete information. Variables to be included in these models were selected based on clinical experience, existing literature, and availability of information in SEER data. Purposeful selection,

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**Table 2.** Three-year OS for first breast cancers diagnosed 2010–2013, by histology, stage, and subtype[a]

| Type | Full sample, *n* (OS) | HER2 positive, *n* (OS) | TN, *n* (OS) | HER2 negative/ HR positive, *n* (OS) | *p* value[b] |
|---|---|---|---|---|---|
| MBC | | | | | |
| Stage I–III | 872 (76.7%) | 47 (91.8%) | 601 (75.4%) | 224 (77.1%) | .025 |
| Stage I | | 10 (100.0%) | 136 (91.4%) | 59 (92.8%) | .413 |
| Stage II | | 23 (88.6%) | 374 (76.4%) | 121 (83.4%) | .239 |
| Stage III | | 14 (92.9%) | 91 (47.1%) | 44 (42.2%) | .011 |
| IDC | | | | | |
| Stage I–III | 133,612 (92.4%) | 22,056 (92.5%) | 17,344 (83.8%) | 94,212 (94.0%) | .276 |
| Stage I | | 8,950 (96.3%) | 6,540 (93.6%) | 55,325 (96.6%) | .983 |
| Stage II | | 9,061 (92.9%) | 7,989 (85.0%) | 29,937 (92.4%) | <.001 |
| Stage III | | 4,045 (83.6%) | 2,815 (58.4%) | 8,950 (83.7%) | <.001 |

[a]Sample only includes those with known stage and subtype; estimated overall survival is unadjusted.
[b]Log-rank test of Kaplan-Meier survival curve (comparing HER2 positive with other two subtypes).
Abbreviations: HER2, human epidermal growth receptor 2; HR, hormone receptor; IDC, invasive ductal carcinoma; MBC, metaplastic breast cancer; OS, overall survival; TN, triple negative.

along with backwards and forwards stepwise selection of variables, were conducted as ad hoc analyses, to confirm our choice of variables. The proportional hazards assumption was tested on the basis of Schoenfeld residuals and goodness of fit assessed using Cox-Snell residuals. One Cox model included only MBC, to assess the association between subtype and survival. The second Cox model included HER2 positive cases of MBC and IDC, to assess factors associated with survival in HER2 positive breast cancer. Additionally, for this Cox model, a propensity-score-matched sample was created as a robustness check (supplemental online Table 1). For all survival analyses, women with prior malignancies were excluded, along with those diagnosed in 2014 (to ensure adequate follow-up). All tests were two-sided, and analyses were conducted using STATA MP, version 12.0 (StataCorp LP, College Station, TX).

## Results

### Demographic and Clinical Characteristics

The study cohort included 1,516 women diagnosed with MBC and 220,375 women diagnosed with IDC from 2010 to 2014 (Table 1). Relative to women with IDC, women with MBC were older, with a median age of 63 versus 61 (interquartile range 53–74 and 51–71, respectively, $p < .001$ from nonparametric equality-of-medians test), and more likely to be black (16.0% vs. 11.1%, $p < .001$). The most common reported histology was metaplastic NOS (81.5%), with squamous (7.5%), adenosquamous (2.1%), and carcinosarcoma (4.6%) making up the majority of the other reported histologies. The majority of the MBC tumors ($n = 972$, 64.1%) were TN. HER2 positive tumors and HER2 negative/HR positive tumors represented 79 (5.2%) and 349 (23.0%) cases, respectively, with 116 (7.7%) having unknown receptor status. MBC tumors were more often high grade than IDC tumors (68.4% vs. 34.5%, $p < .001$). Women presenting with MBC were also more likely to have stage III disease than those with IDC (15.6% vs. 10.8%, odds ratio [OR] = 1.52, 95% confidence interval [CI] 1.32–1.75, $p < .001$, logistic regression). Mastectomy, as opposed to lumpectomy or no surgery, was undertaken more often for women with MBC (56.8% vs. 41.2%, $p < .001$). For each stage of disease, mastectomy was undertaken more frequently in MBC than in IDC, with this difference being largest for women with stage II and III disease (stage I: 34.9% vs .31.2% [OR = 1.18, 95% CI 0.94–1.47, $p = .146$]; stage II: 60.9% vs. 47.8% [OR = 1.70, 95% CI 1.48–1.96, $p < .001$); stage III: 81.0% vs. 70.3% [OR = 1.80, 95% CI 1.27–2.54, $p = .001$), all logistic regression). HER2 positive MBC tumors appeared more likely to present as stage III disease, as opposed to stages I or II disease, than either TN or HER2 negative/HR positive MBC tumors (OR = 1.58, 95% CI 0.91–2.76, $p = .106$, logistic regression), although this was not statistically significant at the 5% level.

### Overall Survival

For women presenting with early stage or locally advanced MBC, 3-year overall survival (OS) was 76.7%, compared with 92.4% for those with IDC ($p < .001$; Table 2). For women with MBC, 3-year OS was significantly greater for those with HER2 positive disease than for those with TN or HER2 negative/HR positive disease (91.8% vs. 75.4% vs 77.1%, $p = .025$, comparing HER2 positive with others; Table 2). No significant difference was seen between HER2 positive MBC and other MBC subtypes for stage I and stage II MBC, although the direction was toward improved survival for the HER2 positive cohort. For stage III MBC breast cancers, 3-year overall survival was significantly improved for women with HER2 positive tumors: 92.9% for HER2 positive, 47.1% for TN, and 42.2% for HER2 negative/HR positive ($p = .011$; Fig. 2). Overall survival for women with TN MBC did not differ from those with HER negative/HR positive MBC (overall, 75.4% vs. 77.1%, $p = .516$; stage I, 91.4% vs. 92.8%, $p = .836$; stage II, 76.4% vs. 83.4%, $p = .096$; stage III, 47.1% vs. 42.2%, $p = .974$).

For IDC, 3-year OS differed by stage between the three receptor-based subtypes. For stage I disease, all three groups had comparable OS (96.3%, 93.6%, and 96.6%, $p = .983$). For stages II and III IDC, 3-year OS for TN IDC (85.0% and 58.4%) was inferior to HER2 positive IDC (92.9% and 83.6%, $p < .001$ for both stage II and stage III disease) and HER2 negative/HR positive IDC (92.4% and 83.7%, $p < .001$ for both stage II and III disease).

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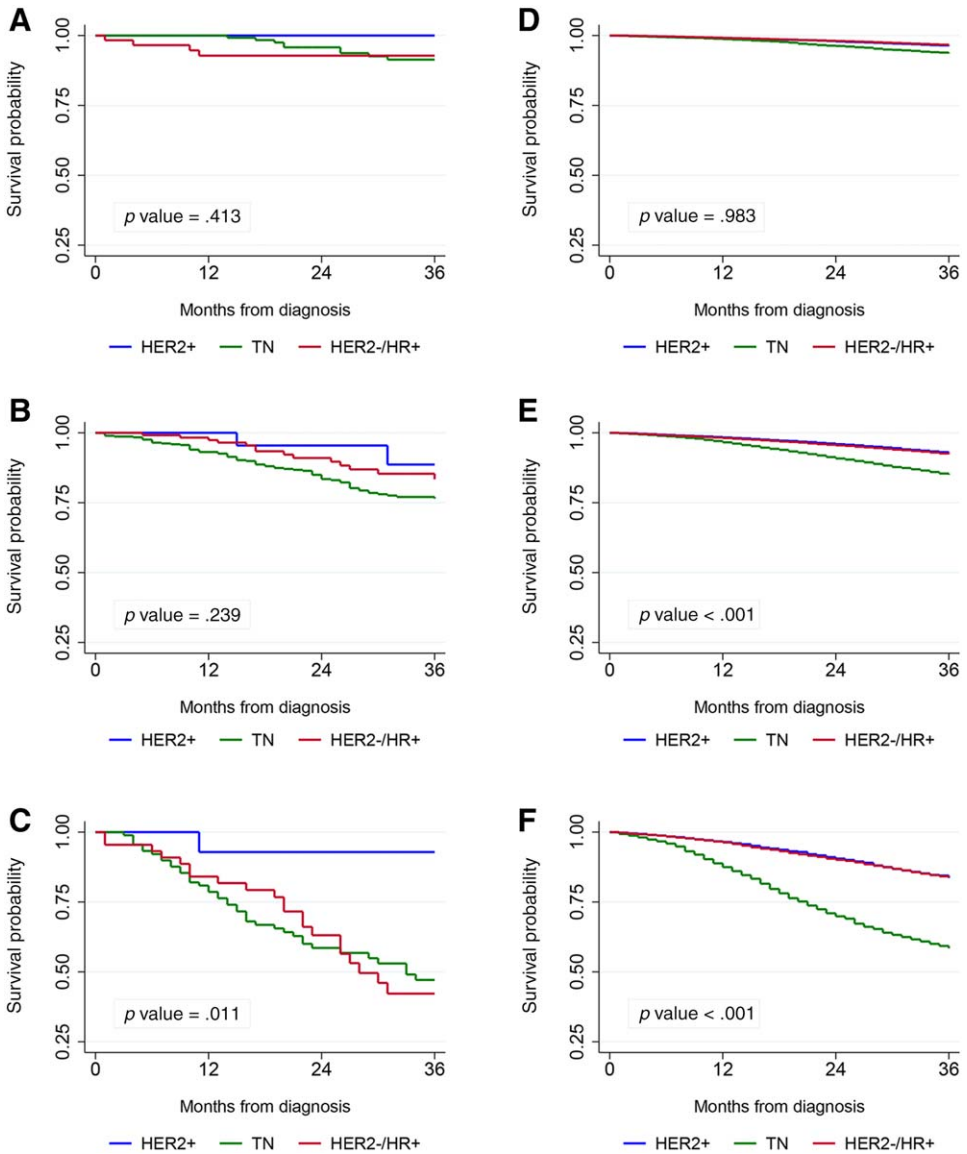


**Figure 2.** Three-year overall survival stratified by histology and stage with log-rank tests comparing all three subtypes. **(A)**: MBC, stage I. **(B)**: MBC, stage II. **(C)**: MBC, stage III. **(D)**: IDC, stage I. **(E)**: IDC, stage II. **(F)**: IDC, stage III.

Abbreviations: HER2+, human epidermal growth receptor 2 positive; HER2−, human epidermal growth receptor 2 negative; HR+, hormone receptor positive; IDC, invasive ductal carcinoma; MBC, metaplastic breast cancer; TN, triple negative.

### Multivariate Cox Proportional Hazards Model

A Cox model demonstrated that improved survival for stage I–III MBC was associated with having a HER2 positive tumor, younger age, lower stage at presentation, and receipt of surgery (Table 3). For HER2 negative MBC, HR status did not impact survival (hazard ratio = 0.72, 95% CI 0.49–1.06, $p = .094$ for HER2 negative/HR positive MBC, compared with triple negative MBC). White and black women, as defined by SEER, had comparable outcomes in this Cox model, although women of "other" races had significantly increased risk. Among those who underwent surgery, women who had a mastectomy had inferior 3-year OS (hazard ratio = 2.00, 95% CI 1.31–3.06), compared with those who had breast-conserving surgery independent of stage at presentation. Including histologic subtypes of MBC in this model (data not shown) demonstrated similar survival across all MBC groups, other than for carcinosarcoma, which, despite small numbers ($n = 62$), had inferior survival (hazard ratio = 2.04, 95% CI 1.14–3.65, $p = .016$). In these analyses, all variables that were significant at the 5% level were similarly so in both the models (with and without histologic subtype). In a Cox model of only HER2 positive MBC and IDC breast cancers, survival did not differ between these histologies (hazard ratio = 1.16, 95% CI 0.48–2.81, $p = .734$; Table 4). Results from a propensity-score-matched sample for this Cox model were similar.

## Discussion

This report on presentations and outcomes of 1,516 women diagnosed with MBC from 2010 to 2014 provides a contemporary study of women with this rare breast cancer. Epidemiologic and clinical characteristics at presentation are similar to those seen in other series, with MBC patients being slightly older and more likely to be black [2, 3]. Hormone receptor status was not associated with survival outcomes; however, HER2 receptor

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**Table 3.** Cox proportional hazards model for metaplastic breast cancer diagnosed 2010–2013[a]

| Characteristics | Hazard ratio | 95% CI | *p* value |
|---|---|---|---|
| Subtype | | | |
| HER2 positive | 0.32 | 0.13–0.79 | .013 |
| TN | ref | | |
| HER2 negative/ HR positive | 0.72 | 0.49–1.06 | .094 |
| Age at diagnosis | | | |
| <50 | ref | | |
| 50+ | 1.72 | 1.11–2.65 | .014 |
| Race | | | |
| White | ref | | |
| Black | 1.08 | 0.70–1.67 | .728 |
| Other | 1.83 | 1.10–3.04 | .02 |
| Grade | | | |
| Grade 1–2 | ref | | |
| Grade 3–4 | 1.48 | 0.89–2.44 | .13 |
| Stage (AJCC 7th) | | | |
| Stage I | ref | | |
| Stage II | 2.31 | 1.23–4.33 | .009 |
| Stage III | 6.11 | 3.12–11.95 | <.001 |
| Surgery | | | |
| None | ref | | |
| Lumpectomy | 0.19 | 0.09–0.38 | <.001 |
| Mastectomy | 0.39 | 0.20–0.73 | .003 |

[a]Sample includes only first cancers and individuals with complete information ($n = 765$).
Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HER2, human epidermal growth receptor 2; HR, hormone receptor; ref, reference; TN, triple negative.

**Table 4.** Cox proportional hazards model for human epidermal growth receptor 2 positive MBC and IDC diagnosed 2010–2013[a]

| Characteristics | Hazard ratio | 95% CI | *p* value |
|---|---|---|---|
| Histology | | | |
| IDC | ref | | |
| MBC | 1.16 | 0.48–2.81 | .734 |
| HR status | | | |
| Positive | ref | | |
| Negative | 1.34 | 1.20–1.49 | <.001 |
| Age at diagnosis | | | |
| <50 | ref | | |
| 50+ | 3.05 | 2.63–3.55 | <.001 |
| Race | | | |
| White | ref | | |
| Black | 1.27 | 1.10–1.46 | .001 |
| Other | 0.64 | 0.52–0.78 | <.001 |
| Grade | | | |
| Grade 1–2 | ref | | |
| Grade 3–4 | 1.23 | 1.10–1.39 | .001 |
| Stage (AJCC 7th) | | | |
| Stage I | ref | | |
| Stage II | 1.66 | 1.44–1.93 | <.001 |
| Stage III | 3.70 | 3.18–4.30 | <.001 |
| Surgery | | | |
| None | ref | | |
| Lumpectomy | 0.19 | 0.16–0.23 | <.001 |
| Mastectomy | 0.24 | 0.21–0.28 | <.001 |

[a]Sample includes only first cancers and individuals with complete information ($n = 21,021$).
Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hormone receptor; IDC, invasive ductal carcinoma; MBC, metaplastic breast cancer; ref, reference; TN, triple negative.

status was associated with improved survival outcomes for women who presented with HER2 positive MBC. Survival for HER2 positive MBC matched that seen for HER2 positive IDC and identifies a subset of women with MBC with favorable outcomes. The finding that the subset of women with carcinosarcoma had inferior survival, relative to women with other histologic subtypes of MBC, is consistent with earlier work describing poor outcomes and lack of response to systemic therapy in this group [6, 16], although this is to the authors' knowledge the largest recent series to directly compare outcomes for carcinosarcoma with other MBC histologic subtypes.

Although this analysis offers some clarity for a subset of MBC cases, the disease overall remains rare, heterogeneous, and complex. Molecular subtyping reveals that MBC tumors frequently display basal-like or claudin-low phenotypes and frequently have TP53 mutations [17–20]. Gene-expression profiling performed in small series has demonstrated some potentially targetable gene mutations largely in the setting of multiple co-mutations [11, 21, 22], and a definitive molecular signature of MBC has not been identified. Although given frequent concurrent genetic and epigenetic alterations in MBC, the likelihood of overwhelming benefit from targeted signaling pathway approaches may be limited [23].

Clinical trials in MBC have largely been small, single institution, and single arm. Previous work has suggested benefit to small subsets of patients, with one series reporting response for three patients when treated with sarcoma-like ifosfamide containing chemotherapy regimens [6]. Among the largest studies is recent work assessing the efficacy of combined mammalian target of rapamycin inhibition (temsirolimus), bevacizumab, and liposomal doxorubicin in 52 women with metastatic MCB, which showed a complete or partial response in 21% of patients with no survival benefit yet demonstrated [24].

Several lines of evidence suggest that immune therapy might be active in this aggressive breast cancer. A phase 1b trial has recently shown evidence of activity of pembrolizumab in heavily treated TN breast cancer [25]. A study that recently profiled 75 MBC tumors demonstrated significantly higher programmed death-ligand 1 expression (46%) in MBC compared with other breast cancer subtypes: HR positive (6%), HER2 positive (6%), triple negative breast cancer (TNBC) not otherwise specified (9%) [22]. This same review reported that tumor infiltrating lymphocytes varied greatly in MBC tumors. MBC tumors

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are also generally characterized by a high mutational burden and genomic instability [23], which has been associated with response to immune therapy in other solid tumors [26–30]. MBC tumors, by definition, also harbor the potential for epithelial to mesenchymal transition and have markers associated with this and relatedly with stem cells [31]. These features likely endow MBC with self-renewal capabilities and underlie resistance mechanisms that circumvent traditional treatments [32]. Growing evidence suggests that tumors with stem cell or stem-cell-like features may be particularly adept at immune evasion and, in turn, vulnerable to immune-modulating therapies [33, 34].

Although a clear limitation of SEER data is that specific systemic therapy is not reported, the overall survival outcomes of HER2 positive MBC paralleling those of HER2 positive IDC (relative to TN breast cancer) suggest that MBC is responsive to HER2-directed therapy. A postulated mechanism of HER2-targeted monoclonal antibodies is engagement of the innate and adaptive immune systems [35]. As such, the present work would provide support for evaluation of immune approaches to MBC.

Limitations to this work include all those inherent in the study of large observational datasets. Although SEER has strict categorization guidelines, some of the women could have been inappropriately grouped. One other recent study has identified women with HER2 positive MBC [11]. In this single-institution series, 5 (20%) of the women with MBC had HER2 positive tumors, supporting that this a rare, but real, biologic entity. The group of women with HER2 positive MBC represent a small subset of a rare tumor type. The small portion of women with HER2 positive MBC (5.2%) in this analysis, relative to the other subgroups, limits interpretation of results. Further, subanalyses within the HER2 positive cohort are limited by small numbers. However, with a large national registry, we identified a large enough group of these women to find significant trends. In this most recent version of SEER, radiation therapy was not included. However, running the survival analysis with 2010–2012 data and including radiation therapy as a variable did not change results or conclusions (data not shown). Metaplastic breast cancers are, by definition, heterogeneous. One might expect heterogeneity within individual tumors with regard to levels of HER2 expression. A subject of further study should be to understand if the improvements shown here are related to treatment with HER2-directed therapy and if this treatment is effective even if the entire tumor does not overexpress this transmembrane receptor.

## Conclusion

This report offers insights into presentation and survival outcomes for a recent cohort of women presenting with early stage and locally advanced MBC in the era of neoadjuvant and adjuvant HER2-directed therapy. We identify, for the first time to our knowledge, a significant subset of women with MBC with markedly improved survival outcomes. These outcomes match those of women with HER2 positive IDC. Future work should tie these outcomes to the treatment that was delivered. These findings might offer suggestions on how to approach MBC more broadly, as we strive to alter the natural history of what remains a poor prognosis breast cancer subtype.

## Author Contributions

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## Disclosures

The authors indicated no financial relationships.

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