Title Does Definitive Local Therapy Offer Cure in Select HER2+ De Novo Metastatic Breast Cancer Patients Treated with Dual Anti-HER2 Blockade?

Luderve Rosier
University of Florida

Youth Wang
University of Florida

Jihyun Lee
University of Florida

Karen Daily (karen.daily@medicine.ufl.edu)
University of Florida  https://orcid.org/0000-0002-3218-9739

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Abstract

**Purpose:** The role of surgery with curative intent in HER2+ de novo metastatic breast cancer (dnMBC) is uncertain in the era of dual antibody therapy. We sought to determine from existing retrospective data current practice patterns and if an association exists between surgery to the primary tumor and improved survival in HER2+ dnMBC patients treated with dual anti-HER2 blockade, accounting for selection bias.

**Methods:** This study employed data from the National Cancer Database (NCDB) from the years 2013 to 2015. Study inclusion was limited to adult women with HER2+ dnMBC, who received immunotherapy/biologic response modifier drugs (BRM) as a first line treatment. Patients who received both systemic therapy and surgery to the primary breast tumor and patients who received systemic therapy alone were analyzed in two groups. Chi-square test for discrete variables and Wilcox on Rank-Sum test for numeric variables was used to compare the two groups based on patient, tumor, and treatment characteristics. The primary endpoint was overall survival from the time of diagnosis to the time of death.

**Results:** 928 women with HER2+ dnMBC treated with BRM were identified with 43.5% (n= 404) receiving surgery and 56.5% (n= 524) receiving systemic therapy alone. The 3-year overall survival was superior for the surgery group (74.1%, 95% CI 67.9-79.2%) compared to the no surgery group (53.3%; 95% CI 47.6-58.6%). The no surgery group had median overall survival of 39.8 months (95% CI 34.1-44.9), while the surgery group had not yet reached median overall survival.

**Conclusion:** In a group of HER2+ dnMBC patients receiving systemic treatment in the era of dual antibody therapy, patients who underwent surgery had a superior 3-year survival rate than those who did not. There may be a role for HER2+ dnMBC patients with an excellent response to dual HER2 blockade to undergo curative intent local therapy to the primary tumor.

Introduction

Metastatic breast cancer (MBC) can present as recurrence of a previously treated early stage breast cancer or with an intact primary breast tumor at the time of initial diagnosis, commonly called “de novo” MBC (dnMBC). Approximately 5% of MBC cases are dnMBC, which have a better prognosis than the more common recurrent MBC, possibly due to treatment naivety [1]. Current standard of care treatment does not distinguish de novo from recurrent MBC, with both treated with systemic palliative therapy [2].

The value of surgery to the primary tumor in dnMBC has been a longstanding question [2,3]. Nonrandomized retrospective data have shown superior survival for dnMBC patients who undergo surgery [4]. However, because the patients selected to undergo surgery had confounding characteristics of both tumor and patient associated with longer expected survival, the additive value of surgery to systemic therapy has remained uncertain [2]. Despite a lack of evidence clearly establishing benefit, surgery has frequently been performed for selected dnMBC patients. Lane et al [1] demonstrated in a National Cancer Database (NCDB) analysis of 24,015 women with dnMBC that 41.9% of patients
underwent surgery to the primary tumor after systemic therapy. Patients who received surgery were more likely to be earlier in disease progression, younger, have fewer comorbidities, and be treated in an academic institution or comprehensive cancer center.

The Eastern Cooperative Oncology Group has recently reported results of a prospective randomized trial designed to determine if surgery should be offered to dnMBC patients [5]. The E2108 trial randomly assigned dnMBC patients whose disease did not progress with initial systemic therapy to receive local therapy (surgery and/or radiation) or systemic therapy alone. Of 390 patients enrolled between February 2011 and July 2015, 256 underwent randomization to local therapy versus no local therapy in addition to systemic treatment. Of the 125 patients in the local therapy arm, 109 underwent surgery, 87 achieved free surgical margins, and 74 underwent radiotherapy. There was no difference in overall survival between the two randomized groups at 3 years (68.4% with local treatment vs. 67.9% without local treatment, HR 1.09) [1]. These findings in a U.S. population are concordant with those previously reported in an Indian population in which 350 patients were randomized to surgery or not in addition to systemic treatment for dnMBC from February 2005 to January 2013 [6]. There was no difference in overall survival at 2 years (41.9% surgery vs. 43% no surgery) or in median overall survival (19.2 months surgery vs. 20.5 months no surgery). The E2108 trial did not demonstrate a statistically significant difference in overall survival by tumor subtypes including for the 29% of patients whose cancers were HER2+ (n = 79; HR 1.05).

Other prospective randomized trials have been performed to determine the potential benefit of treating dnMBC patients with local therapy followed by systemic therapy versus systemic therapy alone. Results are conflicting. In an Austrian study of 90 dnMBC patients, overall survival favored the non-surgery group by 20 months [7]. Soran et al [8] conducted a similar trial of 274 dnMBC patients in Turkey that demonstrated a 17% improvement in median survival in the surgery group at five years.

While these efforts to define the value of surgery to the primary tumor in dnMBC have been ongoing, systemic therapy advances have significantly improved survival, perhaps most notably in HER2+ disease. The advent of dual anti-HER2 therapy with the addition of Pertuzumab to Trastuzumab has dramatically improved the life expectancy of patients with HER2+ MBC. Prior to Trastuzumab, median survival of HER2+ MBC was less than two years, compared to contemporary median survival of nearly five years with the addition of Pertuzumab [9]. The CLEOPATRA randomized trial of a treatment naïve population (n = 808) has shown that Pertuzumab improves overall survival by approximately 1.5 years. Remarkably, 37% of patients are alive at eight years of follow up and 16% remain free of disease, demonstrating a population of exceptional durable responders to dual anti-HER2 blockade [10].

Patients with dnHER2+ MBC treated with dual HER2 blockade with Trastuzumab and Pertuzumab may represent a patient population who does benefit from surgery to the primary tumor. However, the existing randomized controlled trials are unlikely to answer this question. Pertuzumab was FDA approved in the metastatic setting in 2013 following the first of four total years of enrollment to E2108, so not all HER2+ patients enrolled would have received dual HER2 blockade. In addition, the study’s sample size would not be expected to provide a sufficient number of HER2+ patients to answer this subtype-specific question.
The trial conducted by Badwe et al\textsuperscript{6} from India has previously been criticized in terms of application to a U.S. population due to differences in access to contemporary systemic therapy. The arms were not randomized for HER2 status nor did patients receive HER2-directed therapy.

In an Italian retrospective data set of stage IV HER2\textsuperscript{+} patients, despite similar response rates and progression-free survival with Trastuzumab-based systemic therapy, surgery was associated with prolonged overall survival in the de novo cohort \cite{11}. This work included 331 total patients of whom 23\% or 77 patients had dnMBC. More than half of the dnMBC patients (46/77) underwent surgery to the primary tumor, and these patients had more favorable characteristics. Median survival was 60 months for dnMBC patients who had surgery and 26 months for dnMBC patients who did not undergo surgery (\(p < 0.001\)) correlating to a nearly 70\% reduction in the risk of death.

In this study, we sought retrospective data in the era of dual HER2 blockade with a larger sample size. We suspect that the systemic therapy advances for HER2\textsuperscript{+} breast cancer require a reevaluation of the role of curative intent surgery for patients with dnHER2\textsuperscript{+} MBC. Our question - does definitive local therapy offer cure in select HER2\textsuperscript{+} dnMBC patients treated with dual anti-HER2 blockade? - is timely and shared by others in the field \cite{9,12}.

**Methods**

**Data and patients**

Data for this study was obtained from the National Cancer Database (NCDB). Study inclusion was limited to adult women diagnosed in 2013–2015 with HER2\textsuperscript{+} dnMBC, who received immunotherapy/biologic response modifier drugs (BRM) as a first line treatment. The NCDB classifies both Trastuzumab and Pertuzumab as immunotherapy/BRM drugs. The restricted diagnosis time from 2013 to 2015 coincides with the FDA approval of Pertuzumab and the availability of data on HER2\textsuperscript{+} cancers in the NCDB. Selected patients were analyzed into two groups, those who received systemic therapy along with surgery to the primary breast tumor and those who received systemic therapy alone (surgery vs. non-surgery groups). Patients who did not undergo surgery because of contraindications, because they died before a surgery, or surgery status was unknown were excluded from the study.

**Data analysis plans**

Data on patient demographics, tumor characteristics, treatment regimens, and characteristics of treatment facilities were compared between the surgery and non-surgery groups. The two groups were compared using the Chi-square test for discrete variables and Wilcoxon Rank-Sum test for numeric variables. Multivariable logistic regression models were used to evaluate if there are potential associations between the surgery status and the variables for chemotherapy, tumor grade, hormone therapy, radiation therapy, regional nodes examined, and urban/rural, when adjusted for covariates. The primary endpoint was overall survival from the time of diagnosis to the time of death, patients who are alive at the end of year 2015 or lost to follow-up will be censored. Median overall survival for each group
was calculated using the Kaplan-Meier method and its 95% confidence interval was derived by Greenwood's formula and log-log transformation. Multivariable Cox proportional hazard model was used to calculate hazard ratios for groups as well as confounding factors, including the significant variables from the group comparisons above.

**Results**

935 women with HER2+ dnMBC treated with Immunotherapy/Biologic Response Modifier drugs were identified in the NCDB between 2013 to 2015 (Table 1). Of the 935 women who met the inclusion criteria, 26.7% (n = 250) received surgery alone to the primary tumor, 1.2% (n = 11) underwent radiation alone to the primary tumor, 16.5% (n = 154) received both local treatment modalities, and 54.9% (n = 513) received systemic therapy alone. The median age at diagnosis was 55 years old (Range = 22–90 years). Most patients were White (78.7%), non-Hispanic or non-Spanish (92%), and residents of a metro county (84.1%). The AJCC Clinical T stages of the study population were T1 in 14.7%, T2 in 37.9%, T3 in 17.4%, and T4 in 28.4%. Negative surgical margins were achieved in 86.7% of the patients who underwent surgery. Of the study population, 90.9% received chemotherapy and 39% received hormonal therapy. 62.5% of the tumors had an ER+ status. Most patients treated at an academic/research program received systemic therapy alone (67.4%).

Multivariable Logistic regression model was fitted with surgery vs no surgery as response. Patients treated at other facility types (community cancer programs and integrated network cancer programs) have 2.1 times odds to undergo surgery compared to those treated at an academic/research program (OR 2.1; 95% CI, 1.5–3; P < 0.001). Patients received both surgery and radiation had the youngest median age (median age = 51.5 years). This group also had the greatest proportion of patients with private insurance/managed care (68.2%) and patients living in areas with higher income (50% with median incomes over $63,333.00). Patients with poorly differentiated tumors also have 2.1 times odds to undergo surgery compared to patients with moderately differentiated tumors (OR 2.1; 95% CI 1.4-3; P < 0.001). Patients with clinical T4 disease were also less likely to undergo surgery compared to patients with T1 disease (OR 0.7; 95% CI 0.4–1.3; P = 0.252).
| Variables                     | Total (N = 935) | Yes (N = 407) | No (N = 528) | p-value* |
|-------------------------------|-----------------|---------------|--------------|----------|
| **Age at Diagnosis (grouped)**|                 |               |              |          |
| (40–50]                       | 215 (23)        | 97 (23.8)     | 118 (22.3)   | 0.246    |
| (50–60]                       | 280 (29.9)      | 124 (30.5)    | 156 (29.5)   |          |
| (60–70]                       | 194 (20.7)      | 71 (17.4)     | 123 (23.3)   |          |
| <=40                          | 143 (15.3)      | 69 (17)       | 74 (14)      |          |
| >70                           | 103 (11)        | 46 (11.3)     | 57 (10.8)    |          |
| **Charlson/Deyo Score**       |                 |               |              |          |
| 0                             | 784 (83.9)      | 341 (83.8)    | 443 (83.9)   | 0.948    |
| 1                             | 116 (12.4)      | 51 (12.5)     | 65 (12.3)    |          |
| 2                             | 19 (2)          | 9 (2.2)       | 10 (1.9)     |          |
| >=3                           | 16 (1.7)        | 6 (1.5)       | 10 (1.9)     |          |
| **Chemotherapy**              |                 |               |              |          |
| Administered                  | 850 (90.9)      | 385 (94.6)    | 465 (88.1)   | 0.002    |
| Missing                       | 3 (0.3)         | 0 (0)         | 3 (0.6)      |          |
| Not administered              | 82 (8.8)        | 22 (5.4)      | 60 (11.4)    |          |
| **ER+**                       |                 |               |              |          |
| Missing                       | 6 (0.6)         | 0 (0)         | 6 (1.1)      | 0.094    |
| Negative                      | 345 (36.9)      | 153 (37.6)    | 192 (36.4)   |          |
| Positive                      | 584 (62.5)      | 254 (62.4)    | 330 (62.5)   |          |
| **Facility Location**         |                 |               |              |          |
| Midwest                       | 210 (22.5)      | 90 (22.1)     | 120 (22.7)   | < .001   |
| Missing                       | 130 (13.9)      | 64 (15.7)     | 66 (12.5)    |          |
| Northeast                     | 185 (19.8)      | 52 (12.8)     | 133 (25.2)   |          |
| South                         | 305 (32.6)      | 149 (36.6)    | 156 (29.5)   |          |
|                      | Surgery |
|----------------------|---------|
| West                 | 105 (11.2) | 52 (12.8) | 53 (10) |
| **Facility Type**    |         |
| Academic/Research Program | 331 (35.4) | 103 (25.3) | 228 (43.2) | < .001 |
| Missing              | 130 (13.9) | 64 (15.7) | 66 (12.5) |
| Other                | 474 (50.7) | 240 (59) | 234 (44.3) |
| **Tumor Grade**      |         |
| Missing              | 144 (15.4) | 30 (7.4) | 114 (21.6) | < .001 |
| Moderately differentiated | 253 (27.1) | 96 (23.6) | 157 (29.7) |
| Poorly differentiated | 523 (55.9) | 275 (67.6) | 248 (47) |
| Undifferentiated     | 1 (0.1) | 1 (0.2) | 0 (0) |
| Well differentiated   | 14 (1.5) | 5 (1.2) | 9 (1.7) |
| **Hispanic Origin**  |         |
| Non-Spanish          | 860 (92) | 370 (90.9) | 490 (92.8) | 0.290 |
| Spanish              | 75 (8) | 37 (9.1) | 38 (7.2) |
| **Hormone Therapy**  |         |
| Administered         | 365 (39) | 188 (46.2) | 177 (33.5) | < .001 |
| Missing              | 44 (4.7) | 16 (3.9) | 28 (5.3) |
| Not administered     | 526 (56.3) | 203 (49.9) | 323 (61.2) |
| **Readmission Within 30 Days of Surgical Discharge** |         |
| Missing              | 16 (1.7) | 12 (2.9) | 4 (0.8) | 0.004 |
| No                   | 903 (96.6) | 384 (94.3) | 519 (98.3) |
| Yes                  | 16 (1.7) | 11 (2.7) | 5 (0.9) |
| **Insurance Status** |         |
| Medicaid             | 160 (17.1) | 71 (17.4) | 89 (16.9) | 0.080 |
| Medicare             | 191 (20.4) | 79 (19.4) | 112 (21.2) |
| Missing              | 8 (0.9) | 5 (1.2) | 3 (0.6) |
| Not Insured          | 41 (4.4) | 10 (2.5) | 31 (5.9) |
| Private Insurance/Managed Care | 535 (57.2) | 242 (59.5) | 293 (55.5) |
| Surgery                          |                  |                  |                  |         |
|---------------------------------|------------------|------------------|------------------|---------|
| **Income (2012–2016)**          |                  |                  |                  |         |
| $40,227−50,353                   | 190 (20.3)       | 78 (19.2)        | 112 (21.2)       | 0.253   |
| $50,354−63,332                   | 210 (22.5)       | 97 (23.8)        | 113 (21.4)       |         |
| < $40,227                        | 161 (17.2)       | 59 (14.5)        | 102 (19.3)       |         |
| $63,333−80,000                   | 368 (39.4)       | 170 (41.8)       | 198 (37.5)       |         |
| Missing                          | 6 (0.6)          | 3 (0.7)          | 3 (0.6)          |         |
| **Education (2012–2016)**       |                  |                  |                  |         |
| 10.9−17.5%                      | 223 (23.9)       | 102 (25.1)       | 121 (22.9)       | 0.228   |
| 6.3−10.8%                       | 267 (28.6)       | 108 (26.5)       | 159 (30.1)       |         |
| <6.3%                           | 246 (26.3)       | 119 (29.2)       | 127 (24.1)       |         |
| >=17.6%                         | 193 (20.6)       | 75 (18.4)        | 118 (22.3)       |         |
| Missing                          | 6 (0.6)          | 3 (0.7)          | 3 (0.6)          |         |
| **Primary Site**                |                  |                  |                  |         |
| Axillary tail                    | 2 (0.2)          | 1 (0.2)          | 1 (0.2)          | 0.761   |
| Breast, NOS; multi-focal neoplasm| 229 (24.5)       | 91 (22.4)        | 138 (26.1)       |         |
| Central                          | 41 (4.4)         | 21 (5.2)         | 20 (3.8)         |         |
| LIQ                             | 52 (5.6)         | 22 (5.4)         | 30 (5.7)         |         |
| LOQ                             | 62 (6.6)         | 26 (6.4)         | 36 (6.8)         |         |
| Overlapping lesion               | 221 (23.6)       | 102 (25.1)       | 119 (22.5)       |         |
| UIQ                             | 71 (7.6)         | 35 (8.6)         | 36 (6.8)         |         |
| UOQ                             | 257 (27.5)       | 109 (26.8)       | 148 (28)         |         |
| **Race (Regrouped)**            |                  |                  |                  |         |
| Black                            | 142 (15.2)       | 50 (12.3)        | 92 (17.4)        | 0.162   |
| Missing                          | 6 (0.6)          | 3 (0.7)          | 3 (0.6)          |         |
| Other                            | 51 (5.5)         | 25 (6.1)         | 26 (4.9)         |         |
| White                            | 736 (78.7)       | 329 (80.8)       | 407 (77.1)       |         |
| **Radiation Therapy to the Primary Site** |                  |                  |                  |         |
|                               | Surgery           |
|-------------------------------|-------------------|
| Administered                  | 165 (17.6)        |
| Missing                       | 7 (0.7)           |
| Not administered              | 763 (81.6)        |

**Regional Nodes Examined**

|                               | Surgery           |
|-------------------------------|-------------------|
| Examined                      | 541 (57.9)        |
| Missing                       | 7 (0.7)           |
| No nodes examined             | 387 (41.4)        |

**Surgical Margins**

|                               | Surgery           |
|-------------------------------|-------------------|
| Missing                       | 536 (57.3)        |
| No residual tumor             | 353 (37.8)        |
| Residual tumor                | 46 (4.9)          |

**AJCC Clinical T**

|                               | Surgery           |
|-------------------------------|-------------------|
| Missing                       | 15 (1.6)          |
| c1                            | 137 (14.7)        |
| c2                            | 354 (37.9)        |
| c3                            | 163 (17.4)        |
| c4                            | 266 (28.4)        |

**AJCC Pathologic T**

|                               | Surgery           |
|-------------------------------|-------------------|
| Missing                       | 179 (19.1)        |
| p0                            | 39 (4.2)          |
| p1                            | 103 (11)          |
| p2                            | 140 (15)          |
| p3                            | 45 (4.8)          |
| p4                            | 73 (7.8)          |
| pIS                           | 13 (1.4)          |
| pX                            | 343 (36.7)        |

**Urban/Rural(2013)**

|                               | Surgery           |
|-------------------------------|-------------------|
| Metro                         | 786 (84.1)        |
| Surgery |  |
|---------|---|
| Missing | 25 (2.7) | 8 (2) | 17 (3.2) |
| Rural   | 21 (2.2) | 16 (3.9) | 5 (0.9) |
| Urban   | 103 (11) | 48 (11.8) | 55 (10.4) |

**Year of Diagnosis**

| Year   | 2013 | 2014 | 2015 |
|--------|------|------|------|
| 2013   | 250 (26.7) | 119 (29.2) | 131 (24.8) |
| 2014   | 273 (29.2) | 115 (28.3) | 158 (29.9) |
| 2015   | 412 (44.1) | 173 (42.5) | 239 (45.3) |

**Age at Diagnosis**

| Age   | Median (Min, Max) | Mean (sd) |
|-------|-------------------|-----------|
| Median | 55 (22, 90) | 55 (22, 90) |
| Mean   | 54.3 (13.1) | 54.9 (13.2) |

**Distance to Care (miles)**

| Distance to Care (miles) | Median (Min, Max) | Mean (sd) |
|--------------------------|-------------------|-----------|
| Median (Min, Max)        | 10.3 (0.2, 2009.1) | 31.4 (119.3) |
| Mean (sd)                | 10.4 (0.2, 624) | 22 (43.9) |
|                           | 10 (0.3, 2009.1) | 38.7 (153.5) |

**Day from Dx to Surgery**

| Day from Dx to Surgery | Median (Min, Max) | Mean (sd) |
|------------------------|-------------------|-----------|
| Median (Min, Max)      | 174 (0, 1274) | 167 (151.2) |
| Mean (sd)              | 174 (0, 1274) | 167 (151.2) |

**Surgical Inpatient Stay**

| Surgical Inpatient Stay | Median (Min, Max) | Mean (sd) |
|-------------------------|-------------------|-----------|
| Median (Min, Max)       | 1 (0, 170) | 1.7 (9.2) |
| Mean (sd)               | 1 (0, 170) | 1.7 (9.2) |

*Note: For two group comparisons, P-value for discrete variables, using Chi-Square Test; P-value of numeric variables, using Wilcoxon Rank-Sum test
NA: Not Applicable.*

A Kaplan-Meier Survival Plot was fitted by treatment groups (Fig. 1). The surgery and radiation group had the highest 3-year overall survival rate (79.3%; 95% CI 68.0–87.0%) followed by the surgery alone group (71.1%; 95% CI 63.4–77.5%), systemic therapy alone (54.3%; 95% CI 48.6–59.6%), and radiation therapy alone (14.7%; 95% CI 0.8–46.9%). When grouped into two groups by surgery versus no surgery, the 3-year overall survival was superior for the surgery group (74.1%, 95% CI 67.9–79.2%) compared to the no surgery group (53.3%; 95% CI 47.6–58.6%). The systemic therapy alone group had a median survival of 40 months with a 95% confidence interval of (34.9, 45.5). The radiation therapy group had the lowest
median survival of all 3 treatment groups (18.1 months; 95% CI 7.7–29). The surgery alone and surgery plus radiation groups did not yet reach median survival within our follow-up time frame. When grouping patients into two groups, those receiving surgery and those not receiving surgery, those not receiving surgery had median overall survival of 39.8 months (95% CI 34.1–44.9), and those receiving surgery had not yet reached median overall survival. Multivariable CoxPH model was fitted with OS (Table 2). Patients with pT4 disease had an 8.7 times higher hazard of death compared to pT0 (HR = 8.7; 95% CI 2.1–36.4; p = 0.003). Patients with ER positive status also had a 0.6 times lower hazard of death compared to ER negative status. Patients with higher comorbidity score based on a Charlson/Deyo score of 3 or more had a higher risk of death (HR = 3.1; 95% CI 1.2–7.6; P = 0.016).
### Table 2
Multivariable Cox PH Analysis

| Variable Compare | HR  | Lower CI | Upper CI | P-value |
|------------------|-----|----------|----------|---------|
| Treatment groups |     |          |          |         |
| Surgery vs Radiation | 0.4 | 0.1      | 1.3      | 0.121   |
| Both vs Radiation  | 0.3 | 0.1      | 1.0      | 0.047   |
| None vs Radiation  | 0.6 | 0.2      | 1.7      | 0.314   |
| Age at Diagnosis  |     |          |          |         |
| 1 unit increase   | 1.0 | 1.0      | 1.0      | < .001  |
| Charlson/Deyo Score |      |          |          |         |
| 1 vs 0            | 1.8 | 1.3      | 2.5      | < .001  |
| >=3 vs 0          | 3.1 | 1.2      | 7.6      | 0.016   |
| 2 vs 0            | 1.0 | 0.4      | 2.3      | 0.924   |
| ER+               |     |          |          |         |
| Positive vs Negative | 0.6 | 0.5    | 0.8      | 0.001   |
| Hispanic Origin   |     |          |          |         |
| Spanish vs Non-Spanish | 0.5 | 0.3   | 1.0      | 0.043   |
| AJCC Pathologic T |     |          |          |         |
| p3 vs p0          | 3.5 | 0.7      | 16.2     | 0.114   |
| p2 vs p0          | 5.1 | 1.2      | 21.4     | 0.027   |
| p1 vs p0          | 3.6 | 0.8      | 15.7     | 0.087   |
| pX vs p0          | 5.8 | 1.3      | 25.7     | 0.020   |
| pIS vs p0         | 3.3 | 0.3      | 37.0     | 0.329   |
| p4 vs p0          | 8.7 | 2.1      | 36.4     | 0.003   |

### Discussion

De novo HER2+ MBC is increasingly recognized as a common distinct entity. In a publication including the 6268 dnMBC cases reported to the California Cancer Registry diagnosed 2005–2011, compared to earlier stage disease, there was an enrichment for HER2+ tumors relative to HR+/HER2- in dnMBC [13]. Increased de novo versus recurrent HER2+ MBC over time is seen in HER2+ MBC registries, each
targeting approximately 1000 patient enrollments. RegistHER 2003–2006 had 33% de novo while SystHERs which began in 2012 has 46% de novo. This may be attributable to improved HER2-directed therapy in the (neo)adjuvant setting leading to reduced recurrent HER2 + MBC, more sensitive imaging to identify metastatic disease at presentation, or both [14].

In the era of HER2-directed therapy, HER2 + dnMBC has a favorable prognosis. In two SEER data sets of women diagnosed 2010–2013, the longest survival among dnMBC patients was seen for the HER2+/HR + subtype {15,16}. A data set from NCDB including dnMBC diagnoses from the same period of 2010–2013 also demonstrated HER2+/HR + subtype had better survival than HR+/HER2-. This was despite a less favorable pattern of spread with more visceral and CNS sites of disease for HER2+/HR + and more bone-only disease for HR+/HER2- [17]. In a cohort of 483 dnMBC HER2 + Trastuzumab-treated patients, median OS was 5.5 years. Only 20% of these patients received Pertuzumab, so contemporary outcomes would be expected to be even better. Notably there was a population of exceptional durable responders. Thirteen percent of patients achieved CR on imaging or “NED” status, and this population had 98% overall survival at 10 years [12].

E2108 represents a landmark trial designed to resolve the question of whether surgery to the primary tumor confers a survival advantage in dnMBC. While full publication is awaited, the overall negative results presented at a plenary session of ASCO 2020 have several important limitations in their application to HER2 + dnMBC. The sample size may be insufficient to address subtype specific questions regarding the value of surgery; there were 79 total patients (29% of total) with HER2 + disease. It is not yet reported how many of those received optimal upfront dual anti-HER2 therapy with Trastuzumab and Pertuzumab. If the majority did not receive both Trastuzumab and Pertuzumab, this would compromise the ability to draw conclusions regarding the utility of surgery for Pertuzumab-treated patients.

Like the NCDB study conducted by Lane et al [1] which reported 41.9% of dnMBC patients underwent surgery, we found 43.5% of HER2 + dnMBC patients underwent surgery. In contrast to the work by Lane et al [1], in which academic/research program as site of treatment was associated with a greater likelihood of patients undergoing surgery, we found for the HER2 + dnMBC population that academic/research programs were less likely to be associated with receipt of surgery. These results support the notion that there remains ongoing equipoise on the role of surgery in dnMBC.

Our study demonstrates that HER2 + dnMBC patients who received both surgery and radiation had superior 3-year survival rate than those who received surgery alone, radiation alone, or no local therapy. Patients who received surgery had more than 20% greater chance of being alive at 3 years from diagnosis than those who did not. The small radiation only treatment group likely had an unfavorable outcome due to issues of performance status and comorbidities precluding other treatment modalities and advanced local disease, such that they were recommended palliative radiation. Patients in the surgery with radiation group were also more likely to be younger, have private insurance/managed care, and live in a higher income area. These findings are aligned with previous studies that have reported more favorable patient characteristics for patients selected to undergo surgery [2,3].
There are several limitations of our results. The greatest of these is that it is not possible to know how much of the surgery group patients’ superior survival is due to the favorable characteristics that led to their selection for surgery and how much is due to the surgery itself. We also acknowledge the unexpectedly low reported use of endocrine therapy with 62.5% of tumors ER+ and yet only 39% use of hormonal treatment. This may represent a true underutilization in comparison to standard practice, underreporting to the database, or a combination of the two. Additionally, we have used the surrogate NCDB designation “Immunotherapy/Biologic Response Modifier” to identify patients receiving HER2-directed therapy.

Despite the inherent limitation of a retrospective analysis in which it is not possible to control for biases that influenced whether patients underwent surgery, this study highlights the discrepancies in treatment approaches for HER2+ de novo MBC patients. This work suggests it would be premature to conclude that E2108 has resolved the issue of surgery for all dnMBC patients. There may be additional value for HER2+ patients treated with dual antibody therapy with excellent response to undergo surgery and radiation therapy. These may represent a distinct clinical entity among stage IV breast cancer patients for whom contemporary multimodality therapy can provide cure. Further data from registries such as SystHERs or subtype-specific trials offer the potential to provide greater clarity for patients and clinicians.

Declarations

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Code availability n/a

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References

1. Lane WO, Thomas SM, Blitzblau RC, Plichta J, Rosenberger LH, Fayanju M, Greenup O, R. A (2019) Surgical Resection of the Primary Tumor in Women With De Novo Stage IV Breast Cancer. Annals of Surgery, 537–544
2. Co M, Nga J, Kwonga A (2019) De-novo Metastatic Breast Cancers with or without Primary Tumor Resection- A 10 Year Study. Elsevier

3. Khan SA, Stewart AK, Morrow M (2002) Does aggressive local therapy improve survival in metastatic breast cancer? Surgery

4. Petrelli F, Barni S Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression, Med.Oncol. 29(5) 2012

5. Khan SA, Zhao F, Solin LJ et al. A randomized phase III trial of systemic therapy plus early local therapy versus systemic therapy alone in women with de novo stage IV breast cancer: A trial of the ECOG-ACRIN Research Group (E2108). Presented at: ASCO20 Virtual Scientific Program. J Clin Oncol. 2020;38(suppl):abstr LBA2

6. Badwe R, Hawaldar R, Nair N et al (2015) Loco-regional treatment versus no treatment of the primary tumour in metastatic breast cancer: an open-label randomised controlled trial. The Lancet Oncology 16(13):1380–1388

7. Fitzal F, Bjelic-Radisic V, Knauer M, Steger G, Hubalek M, Balic M,.. . Gnant M (2019) Impact of Breast Surgery in Primary Metastasized Breast Cancer Outcomes of the Prospective Randomized Phase III ABCSG-28 POSYTIVE Trial. Annals of Surgery, 1163–1169

8. Soran A, Ozmen V, Ozbas S et al (2018) Randomized Trial Comparing Resection of Primary Tumor with No Surgery in Stage IV Breast Cancer at Presentation: Protocol MF07-01. Ann Surg Oncol 25(11):3141

9. Lambertini M, Ferriera AR, Di Meglio A, Poggio F, Puglisi F, Sottotetti F, Montemurro F, Poletto E, Bernardo A, Risi E, Dellepaine C (2017) Patterns of care and clinical outcomes of HER2-Positive metastatic breast cancer patients with newly diagnosed stage IV or recurrent disease undergoing first-line trastuzumab-based therapy: A multi-center retrospective cohort study. Clin Breast Cancer 17:601–610.e2

10. Swain SM, Miles D, Kin, Sung-Bae I et al (April 2020) Pertuzumab, Trastuzumab, and Docetaxel for HER2-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomized, placebo-controlled, phase 3 study. The Lancet Oncology. Volume 21. Pages 519–530

11. Rossi V, Nole F, Redana S, at al. Clinical outcome in women with HER2-positive de novo or recurring stage IV breast cancer receiving trastuzumab-based therapy. The Breast. 23(2014):44–49

12. Wong Y, Raghavendra A, Hatzis C et al (2019) Long-Term Survival of De Novo Stage IV Human Epidermal Growth Receptor 2 (HER2) Positive Breast Cancers Treated with HER2-Targeted Therapy. Oncologist 24:313–318

13. Tao L, Chu L, Wang L et al (2016) Occurrence and outcome of de novo metastatic breast cancer by subtype in a large, diverse population. Cancer Causes Control 27:1127–1138

14. Tripathy D, Brufsky A, Cobleigh M et al. Abstract P3-07-14: Increasing proportion of de novo compared with recurrent HER2-positive metastatic breast cancer: Early results from the systemic therapies for HER2-positive metastatic breast cancer registry study. SABCS 2014
15. Howlader N, Cronin K, Kurian A et al. Differences in Breast Cancer Survival by Molecular Subtypes in the United States. Cancer Epidemiology Biomarkers and Prevention. 27(6) June 2018

16. Leone B, Vallejo C, Romero A, Et al. Prognostic impact of metastatic pattern in stage IV breast cancer at initial diagnosis. Breast Cancer Res Treat 161:537–548

17. Press D, Miller M, Liederbach et al (2017) De novo metastasis in breast cancer: occurrence and overall survival stratified by molecular subtype. Clin Exp Metastasis 34:457–465