

## Surgical Management of Breast Cancer in 2010–2011 SEER Registries by Hormone and HER2 Receptor Status

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### ABSTRACT

**Background.** Although locoregional recurrence is known to affect overall survival for operable breast cancer, the impact of receptor status on locoregional control is debated. Currently, hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) status are generally not considered relevant to surgical choice. This study examines recent population-level surgical trends with regard to receptor status.

**Methods.** We used the Surveillance, Epidemiology, and End Results (SEER) data to identify stage I–III female breast cancers diagnosed from 2010 to 2011. Patients were categorized by HR and HER2 receptor status. Univariate and multivariate logistic regressions were used to assess factors associated with undergoing mastectomy and the choice of contralateral prophylactic mastectomy (CPM).

**Results.** The overall mastectomy rate for the 87,504 women diagnosed in 2010–2011 was 43.4%. On multivariate analysis, the odds of receiving mastectomy was greater for HER2-positive disease with either HR-negative or HR-positive status, than for women with HER2-negative/HR-positive disease (odds ratio 1.73 and 1.31, respectively; all  $p$  values  $<0.001$ ). Age, stage, marital status, race, and year of diagnosis also correlated with mastectomy. Triple-negative breast cancer (TNBC) was associated with CPM, while HER2 status was not. The mastectomy rate, which increased overall from 2006 to 2010, has continued to increase for stage III disease but has decreased for stage I disease. Mastectomy rates overall were lower in 2011 than 2010 ( $p = 0.012$ ).

**Conclusions.** HER2-positive disease and TNBC were independent predictors of more extensive surgery in this large, recent, population-based cohort. Although mastectomy rates have continued to increase for stage III disease, mastectomy rates overall were lower in 2011 than in previous years.

Numerous randomized clinical trials have demonstrated the efficacy of breast-conserving surgery (BCS) compared with mastectomy in early-stage breast cancer.<sup>1–6</sup> The 1990 National Cancer Institute consensus statement for early-stage breast cancer states that, given the lower morbidity of BCS it should be considered the treatment of choice for eligible patients, and breast-conservation rate has since been added to the quality measures that cancer institutions report.<sup>7</sup> The decision for BCS or mastectomy depends on a variety of factors, including anatomical and surgical considerations, availability of radiation treatment, and patient preference. However, hormone receptor (HR) and human epidermal growth factor receptor-2 (HER2) status are not considered pertinent to the decision by any guidelines.

Nevertheless, there is debate regarding the role of receptor status in local recurrence after breast-conserving therapy. A meta-analysis of 15 studies examining over 12,000 patients found that patients with HER2-positive or triple-negative breast cancer (TNBC) had a significantly higher risk of local recurrence after BCS than those who had HER2-negative/HR-positive disease.<sup>8</sup> Although the initial large studies comparing mastectomy and BCS failed to show any survival difference related to in-breast tumor recurrence (IBTR), the Early Breast Cancer Trialists' meta-analysis found differences in overall survival at 15 years of follow-up related to the prevention of recurrence by radiation therapy, suggesting that IBTR does play a role in long-term survival. Together, this may lead to the

perception that patients with TNBC and HER2-positive disease have greater benefit from more extensive surgery.<sup>9</sup> A single-institution study of 1194 patients treated in France found a higher mastectomy rate in these patients compared with those with luminal A and B disease, even though IBTR did not differ among the subtypes.<sup>10</sup> This study seeks to evaluate surgical trends for stage I–III breast cancer, utilizing recent, population-based information from the Surveillance, Epidemiology, and End Results (SEER) program database.

## METHODS

### *Study Participants*

Female invasive breast cancer and population data were obtained from SEER. This program includes 18 registries, representing 28 % of the population.<sup>11</sup> Women diagnosed in 2010 or 2011 with stage I–III breast cancer who underwent surgery were included. Breast cancer was the first primary malignancy and was required to be pathologically confirmed. The University of Iowa Institutional Review Board approved this study.

Of 94,176 potentially eligible patients, the following were excluded: individuals diagnosed at autopsy or on death certificate ( $n = 7$ ), men ( $n = 747$ ), and patients who did not receive surgery ( $n = 5300$ ) or whose type of surgery was unknown ( $n = 251$ ). Squamous cell carcinomas, basal cell carcinomas, and sarcomas ( $n = 367$ ) were also excluded.

Women were categorized as receiving BCS (surgery of primary site variable values of 20–24) and mastectomy (surgery of primary site variable values of 30–80). Patients in the HR-positive subgroup were either estrogen receptor (ER)-positive, progesterone receptor (PR)-positive, or both. Those with borderline ER/PR status were considered ER/PR-positive and those with borderline HER2 were categorized as having missing HER2 status. Patients with TNBC were ER-negative, PR-negative, and HER2-negative. Thus, women were categorized into four, mutually exclusive subtypes: HER2-positive/HR-positive, HER2-positive/HR-negative, HER2-negative/HR-positive, and TNBC. HR status was unavailable for 2344 (2.7 %) women, 4653 (5.3 %) women had missing HER2 information, and 2103 women (2.4 %) had borderline HER2. Contralateral prophylactic mastectomy (CPM) and reconstruction were identified by the surgery of primary site variable. Stage was based on the SEER-adjusted American Joint Committee on Cancer (AJCC), 6th edition. We categorized women into six age groups: <40, 40–49, 50–59, 60–69, 70–79, and  $\geq 80$  years. Marital status at the time of diagnosis was categorized into three groups: married, single, and separated. Race was categorized as White,

Black, and other, and women were also categorized as Hispanic or not. Finally, individuals were categorized by year of diagnosis.

### *Statistical Analysis*

Univariate and multivariate logistic regressions were used to assess factors associated with undergoing mastectomy and with electing CPM. Receptor status, age, marital status, race and ethnicity, and year of diagnosis were included in the regressions. Reconstruction was included for the CPM analysis, and missing values were dropped from statistical analyses. All tests were two-tailed and  $p$  values <0.05 were considered statistically significant. Trend analysis of mastectomy and CPM rates included diagnoses from 2001 to 2011, with the same inclusion and exclusion criteria as above. All analyses used STATA version 12.0 (StataCorp LP, College Station, TX, USA).

## RESULTS

In 2010–2011, there were 87,504 women with a first breast cancer who were stage I, II, or III at presentation and who received either BCS or mastectomy (Table 1). The overall mastectomy rate was 43.4 %. Patients with HER2-positive disease and TNBC were more likely to be younger and present at a higher stage than HER2-negative/HR-positive patients.

### *Univariate Analysis*

Univariate analysis by subtype revealed that women with HER2-positive disease, regardless of HR status, and TNBC were significantly more likely to undergo mastectomy than women with HER2-negative/HR-positive tumors (Table 2). Other significant predictors of mastectomy were stage, age, race, marital status, and year of diagnosis.

### *Multivariate Analysis*

On multivariate analysis, subtype remained a significant predictor of mastectomy, although the odds ratios (ORs) were smaller in absolute values than in the univariate analysis (Table 3). ORs of mastectomy for HER2-positive/HR-positive and HER2-positive/HR-negative disease were 1.31 and 1.73, respectively (all  $p$  values <0.001). TNBC was no longer significant at the 5 % level (OR 1.05;  $p = 0.057$ ), and the largest effect size was seen for stage at presentation. Higher-stage disease was associated with a greater likelihood of mastectomy (OR 2.31–8.17; all  $p$  values <0.001)

**TABLE 1** Surgery and breast cancer subtype by disease stage 2010–2011

	<i>N</i> (%)	Median age (years)	Stage I	Stage II	Stage III	<i>p</i> value <sup>a</sup>
Full sample	87,504 (100)	60	51.0 %	36.8 %	12.2 %	
Surgery						
BCS	49,534 (56.6)	62	63.4 % (70.6)	32 % (49.3)	4.7 % (21.7)	<0.001
Mastectomy	37,970 (43.4)	57	34.7 % (29.4)	43.2 % (50.7)	22.1 % (78.3)	
Receptor status						
HER2-positive/HR-positive	8076 (10.0)	57	41.6 % (8.2)	41.6 % (11.1)	16.8 % (13.5)	<0.001
HER2-positive/HR-negative	3516 (4.4)	56	36.7 % (3.1)	40.3 % (4.7)	23.06 % (8.0)	
HER2-negative/HR-positive	59,391 (73.8)	61	54.6 % (80.0)	34.9 % (69.3)	10.5 % (62.9)	
TNBC	9545 (11.9)	57	36.8 % (8.6)	46.9 % (14.9)	16.4 % (15.6)	

Those with missing information not included in the analyses. Column percent reported in parentheses. Percent may not equal 100 due to rounding. *BCS* breast-conserving surgery, *HER2* human epidermal growth factor receptor-2, *HR* hormone receptor, *TNBC* triple-negative breast cancer

<sup>a</sup> *p* value based on Chi square test

compared with stage I breast cancer. Multivariate analysis which included tumor size and nodal involvement, instead of stage, showed similar results, with little or no change in effect size and significance for other covariates (results not shown).

#### *Mastectomy Rates and Contralateral Prophylactic Mastectomy*

Historical trends for surgery by stage and use of CPM are shown in Fig. 1. The overall mastectomy rate decreased from the years 2001–2005, and then increased from the years 2006–2010. In 2011 this rate decreased to 42.8 % compared with 44.0 % in 2010 ( $p < 0.001$ ). For stage I disease, mastectomy rates have decreased since peaking in 2009 (30.2 % in 2009, 29.0 % in 2011;  $p = 0.005$ ). There was no significant change in mastectomy rates between 2009 and 2011 for stage II disease (50.6 % in 2009, 49.8 % in 2011;  $p = 0.165$ ). In contrast, mastectomy rates continue to increase for stage III disease (76.9 % in 2009, 78.8 % in 2011;  $p = 0.015$ ).

The rate of CPM (for those with unilateral disease who received a mastectomy) has increased markedly since 2001 (7.8 % in 2001, 26.6 % in 2011;  $p < 0.001$ ). A greater proportion of TNBC and HER2-positive/HR-positive patients elected CPM than HER2-negative/HR-positive patients (28.1 and 27.3 % vs. 24.9 %;  $p < 0.001$ ). HER2-positive/HR-negative women were no more likely to elect CPM than HER2-negative/HR-positive women. However, on multivariate analysis, HER2 status, regardless of HR status, was not associated with CPM (Table 4). Only women with TNBC remained more likely to elect CPM than HER2-negative/HR-positive patients (OR 1.26;  $p < 0.001$ ). Women who chose reconstruction were more likely to elect CPM (OR 2.62;  $p < 0.001$ ).

## DISCUSSION

This is the most recent population-based analysis demonstrating a difference in surgical management of breast cancer based on HR status and, to our knowledge, is the first large, population-based study to examine HER2 status as a factor. A review of SEER registry data from the years 2000–2008 found both negative ER and PR status to be predictors of mastectomy, and smaller, single-institution studies have found that mastectomy is performed more often for both HR-negative and HER2-positive patients.<sup>10,12</sup>

The interaction between receptor status and IBTR has been the subject of a number of studies, and the findings have been inconsistent. A study of 753 patients found no difference in 5-year locoregional recurrence rates by receptor status in women treated with BCS.<sup>13</sup> Similar findings were reported in a review of 482 patients.<sup>14</sup> Conversely, a study of nearly 3000 patients with over 10-year follow-up found increased IBTR in patients with HER2-positive disease and TNBC.<sup>15</sup> A 2011 report involving 1434 patients treated with breast conservation found a significantly higher rate of IBTR in patients who had HER2-positive disease and TNBC;<sup>16</sup> however, these patients did not receive targeted anti-HER2 therapy. Other studies, in which contemporary therapy was used, have failed to show differences in recurrence.<sup>17,18</sup>

Increasingly, local failure is felt to be a function of more aggressive biology, with multiple retrospective analyses showing no difference in locoregional recurrence after mastectomy or BCS in patients with TNBC.<sup>19,20</sup> In 2014, the Consensus Guideline on Margins for Breast Conserving Surgery addressed this issue, stating “although there is evidence that the risk of IBTR varies by subtype based on the results of many studies, patients with aggressive tumors

**TABLE 2** Univariate analyses of factors predicting mastectomy

	Sample size	% of sample <sup>a</sup>	Mastectomy rate (%)	OR <sup>b</sup>	<i>p</i> value <sup>b</sup>
<b>Subtype</b>					
HER2-positive/HR-positive	8076	10.0	51.8	1.61	<0.001
HER2-positive/HR-negative	3516	4.4	60.5	2.28	<0.001
HER2-negative/HR-positive	59,391	73.8	40.1	Ref	
TNBC	9545	11.9	47.7	1.36	<0.001
<b>Age (years)</b>					
<40	4451	5.1	68.5	2.82	<0.001
40–49	15,742	18.0	52.6	1.43	<0.001
50–59	22,182	25.4	43.6	Ref	
60–69	23,141	26.5	37.1	0.76	<0.001
70–79	14,300	16.3	37.0	0.76	<0.001
≥80	7680	8.8	40.2	0.87	<0.001
<b>Stage</b>					
I	43,670	51.0	29.4	Ref	<0.001
II	31,537	36.8	50.7	2.46	<0.001
III	10,429	12.2	78.3	8.67	<0.001
<b>Marital status</b>					
Married	48,980	59.2	43.5	Ref	
Single	12,255	14.8	46.0	1.11	<0.001
Separated	21,557	26.0	41.9	0.94	<0.001
<b>Race</b>					
White	69,990	80.4	42.6	Ref	
Black	8987	10.3	45.0	1.10	<0.001
Other	8097	9.3	48.9	1.29	<0.001
<b>Hispanic</b>					
No	77,970	90.1	42.9	Ref	
Yes	8558	9.9	48.4	1.25	<0.001
<b>Year of diagnosis</b>					
2010	43,241	49.4	44.0	Ref	
2011	44,263	50.6	42.8	0.95	<0.001

OR odds ratio, *HER2* human epidermal growth factor receptor-2, *HR* hormone receptor, *TNBC* triple-negative breast cancer

<sup>a</sup> Those with missing information not included in that particular analysis

<sup>b</sup> OR of mastectomy (vs. breast-conserving surgery) and *p* value from univariate logistic regression

remain at equally increased risk for local failure irrespective of treatment with mastectomy or BCS, indicating there is no justification for more widely clear margins over no ink on tumor for any BC subtype".<sup>21</sup>

The perception of increased risk for local recurrence is only one of a complex interplay of factors surrounding the surgical decision. Patients with HER2-positive breast cancers are more likely to be younger and present at a higher stage. These clinical characteristics were independently associated with mastectomy in our multivariate analysis, as well as other population-based and single-institution studies.<sup>14,17,22</sup> The effect of stage on mastectomy rate is intuitive as tumor size can have obvious implications on surgical options.

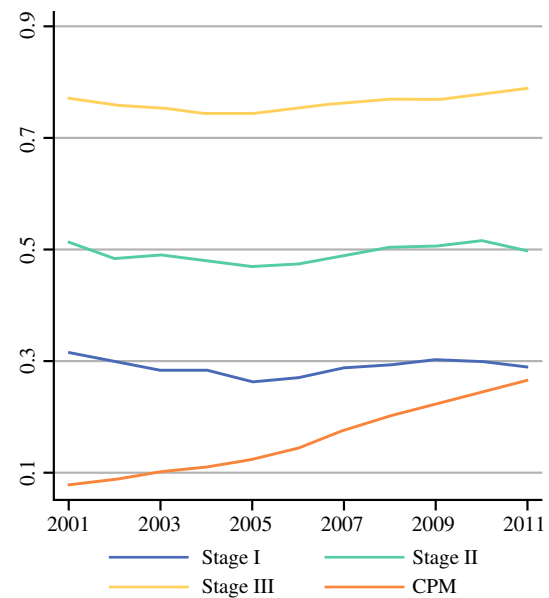
SEER registry data cannot account for variables such as patient choice, adjuvant therapy, genetic testing, family history, breast size, multicentricity, and use of magnetic resonance imaging (MRI). In multiple studies, breast MRI has been shown to be associated with a higher mastectomy rate.<sup>23–25</sup> In one study of 6072 tumors, HER2-positive breast cancer was found to have a 1.6-fold greater incidence of multifocality than luminal A subtypes, although this has not always been replicated in other series.<sup>26,27</sup> TNBC should prompt genetic counseling per National Comprehensive Cancer Network (NCCN) guidelines in patients ≤60 years of age, and genetic testing has also been shown to influence the decision for mastectomy.<sup>28,29</sup>

**TABLE 3** Multivariate model of factors predicting mastectomy

	OR	<i>p</i> value	95 % CI
<b>Subtype</b>			
HER2-positive/HR-positive	1.31	<0.001	1.24–1.38
HER2-positive/HR-negative	1.73	<0.001	1.60–1.87
HER2-negative/HR-positive	Ref		
TNBC	1.05	0.057	1.00–1.10
<b>Age (years)</b>			
<40	2.37	<0.001	2.19–2.56
40–49	1.38	<0.001	1.32–1.45
50–59	Ref		
60–69	0.83	<0.001	0.79–0.87
70–79	0.86	<0.001	0.82–0.91
≥80	0.93	0.034	0.88–0.99
<b>Stage</b>			
I	Ref		
II	2.31	<0.001	2.24–2.39
III	8.17	<0.001	7.73–8.63
<b>Marital status</b>			
Married	Ref		
Single	0.94	0.005	0.89–0.98
Separated	1.02	0.259	0.98–1.06
<b>Race</b>			
White	Ref		
Black	0.91	0.001	0.87–0.96
Other	1.18	<0.001	1.12–1.25
<b>Hispanic</b>			
No	Ref		
Yes	1.05	0.072	1.00–1.11
<b>Year of diagnosis</b>			
2010	Ref		
2011	0.96	0.012	0.93–0.99

OR odds ratio, CI confidence interval, HER2 human epidermal growth factor receptor-2, HR hormone receptor, TNBC triple-negative breast cancer

In this study, CPM was more likely to be performed in women with TNBC. Although the BRCA status of this population was not available, it is likely that more patients with TNBC had a predisposing mutation as there is a known propensity for BRCA1 carriers to develop basal-type breast cancer.<sup>30</sup> A review of SEER registry data from the years 2000–2006 noted that the rates of CPM rose, while the rates of unilateral mastectomy fell, suggesting that in some patients the decision to perform therapeutic mastectomy rather than breast conservation is driven by the desire for CPM.<sup>31</sup> This may enlighten our multivariate results, which found that HER2-positive patients disproportionately elect mastectomy (but not CPM) and that TNBC patients disproportionately elect CPM (but not mastectomy).



**FIG. 1** Proportion of patients receiving mastectomy, by stage, and proportion receiving CPM, 2001–2011. CPM contralateral prophylactic mastectomy

The findings reported here occur in the context of rising mastectomy rates for all breast cancer in recent years. Both the Moffit Cancer Center and the Mayo Clinic have reported on robust databases of over 5000 patients each, noting increases in mastectomy rates after an initial decrease seen prior to 2004.<sup>32,33</sup> A recent review reported an increase in mastectomy rates from 35.6 % in 2005 to 38.4 % in 2008 for SEER patients with T1-2 N0-3 M0 disease.<sup>12</sup> This trend is not seen in Europe. A recent report of 15,369 breast cancer patients from the European Society of Breast Cancer Specialists database demonstrated a decline in mastectomies from 38.1 % in 2005 to 13.1 % in 2010.<sup>34</sup> Our study noted an increase in mastectomy rates overall from 2006 until 2010, with a slight decrease in 2011, suggesting that the mastectomy rate may have plateaued.

## CONCLUSIONS

This large, recent, population-based series elucidates the relative role of HR receptor and HER2 status on the current surgical choices for operable breast cancer. Some women may be receiving more extensive surgery based on the perception of increased risk of future disease, locoregional or distant, without clear evidence of survival benefit. As systemic therapies improve, any benefit to more aggressive surgery may become even less apparent. Further study of the complex interactions involved in surgical decision making, as well as better understanding of the benefits and risks of surgical options, would advance care for women with breast cancer.



**TABLE 4** Multivariate model of factors predicting CPM

	OR	p-value	95 % CI
<b>Subtype</b>			
HER2-positive/HR-positive	1.02	0.624	0.94–1.11
HER2-positive/HR-negative	0.98	0.705	0.87–1.10
HER2-negative/HR-positive	Ref		
TNBC	1.26	<0.001	1.16–1.37
<b>Reconstruction</b>			
No	Ref		
Yes	2.62	<0.001	2.48–2.78
<b>Age</b>			
<40	2.41	<0.001	2.19–2.65
40–49	1.46	<0.001	1.36–1.57
50–59	Ref		
60–69	0.69	<0.001	0.64–0.75
70–79	0.36	<0.001	0.32–0.41
≥80	0.12	<0.001	0.09–0.15
<b>Stage</b>			
I	Ref		
II	0.85	<0.001	0.80–0.91
III	0.81	<0.001	0.75–0.88
<b>Marital status</b>			
Married	Ref		
Single	0.82	<0.001	0.75–0.88
Separated	0.92	0.034	0.86–0.99
<b>Race</b>			
White	Ref		
Black	0.48	<0.001	0.43–0.53
Other	0.46	<0.001	0.41–0.51
<b>Hispanic</b>			
No	Ref		
Yes	0.50	<0.001	0.46–0.55
<b>Year of diagnosis</b>			
2010	Ref		
2011	1.15	<0.001	1.09–1.21

Includes those with unilateral disease who received a mastectomy  
 CPM contralateral prophylactic mastectomy, OR odds ratio, CI confidence interval, HER2 human epidermal growth factor receptor-2, HR hormone receptor, TNBC triple-negative breast cancer

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