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Surgical Resection of the Primary Tumor in Women With De Novo Stage IV Breast Cancer:

Contemporary Practice Patterns and Survival Analysis

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Abstract

Objective—We evaluated patterns of surgical care and their association with overall survival among a contemporary cohort of women with stage IV breast cancer.

Background—Surgical resection of the primary tumor remains controversial among women with stage IV breast cancer.

Methods—Women diagnosed with clinical stage IV breast cancer from 2003 to 2012 were identified from the American College of Surgeons National Cancer Database. Those with intact primary tumors who were alive 12 months after diagnosis were categorized by treatment sequence: (1) surgery before systemic therapy, (2) systemic therapy before surgery, and (3) systemic therapy alone. Multivariate logistic regression was used to estimate the association of treatment sequence with surgery type. Overall survival was estimated using multivariate Cox proportional hazards models.

Results—Among 24,015 women, 56.2% (13,505) underwent systemic therapy alone and 43.8% (10,510) underwent surgical resection. Rates of surgery decreased slightly over time (43.1% in 2003 to 41.9% in 2011). Treatment with systemic therapy before surgery was associated with larger tumor size (median 4.5 vs 3.1 cm, $P < 0.001$) and receipt of mastectomy (81.4% vs 52.2%, $P < 0.001$) when compared to those who underwent surgery first. Receipt of surgery, whether before or after systemic therapy (Hazard Ratio, 0.68; 95% confidence interval, 0.62–0.73; Hazard Ratio, 0.56; 95% confidence interval, 0.52–0.61; $P < 0.001$), was independently associated with improved adjusted overall survival when compared to systemic therapy alone.

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Conclusions—Surgical resection of the primary tumor occurs in almost half of women with stage IV breast cancer alive 1 year after diagnosis, and is increasingly occurring after systemic therapy. Coordinated multidisciplinary care remains highly relevant in the setting of metastatic breast cancer, where surgical decisions should be made on an individual basis and may affect survival in select women.

Keywords

breast cancer surgery; metastatic breast cancer; survival

Breast cancer is the most common cancer diagnosis and the second leading cause of cancer-related death among women in the United States. Approximately 5% of breast cancer patients present with metastatic disease at the time of diagnosis.¹ Stage IV breast cancer remains incurable, and survival in this population is driven by the progression of distant disease. Consequently, systemic therapy has remained the cornerstone of treatment, and the role of local therapy remains controversial. The National Comprehensive Cancer Network recommends that surgery of the primary tumor be reserved for women with stage IV breast cancer that have completed systemic therapy with “impending complications, such as skin ulceration, bleeding, fungation, and pain.”² Despite these recommendations, studies have shown that surgical resection of the primary tumor occurs in up to 50% of women with metastatic disease.³

Many large national and single-institution observational studies have suggested that surgical removal of the primary tumor may improve survival among women with stage IV breast cancer.^{3–9} Critics have questioned the quality of these studies, and suggested that this association may be the result of significant bias. This includes the possibility that (1) healthier stage IV patients are offered surgery, while patients with poor projected survival are not (selection bias), (2) stage IV breast cancer patients may include women diagnosed either early by modern imaging (lead time bias) or shortly after surgery (stage migration bias), and (3) surgery may be a surrogate for more aggressive multimodal therapy (treatment facility bias). Retrospective series have therefore been viewed as hypothesis-generating, and the breast oncology community has turned to prospective randomized clinical trials to address these concerns.

Initial reports from prospective studies by Badwe et al¹⁰ and Soran et al¹¹ failed to demonstrate a survival benefit among de novo stage IV breast cancer patients who underwent surgical resection of the primary tumor; however, these findings were criticized for a disproportionate inclusion of patients with advanced metastatic disease, insufficient systemic therapy regimens, and treatment sequences that did not match contemporary practices.¹² In March 2011, the Eastern Cooperative Oncology Group opened a phase III multicenter, prospective, randomized trial (ECOG 2108) to compare surgical resection of the primary tumor to standard therapy in patients with stage IV breast cancer. Results from this trial are expected in June 2025.

Potentially biased observational data and imperfect clinical trials have left uncertainty about the role of surgery in women with metastatic breast cancer in the current age. Thus, we evaluate national patterns of care, and the association of treatment sequence and surgery

with overall survival in a contemporary cohort of women with de novo stage IV breast cancer.

METHODS

Following institutional review board approval, we identified women diagnosed with de novo stage IV breast cancer between 2003 and 2012 from the American College of Surgeons National Cancer Database (NCDB). The NCDB captures approximately 70% of all cancer diagnoses in the United States, including clinical and demographic data from more than 30 million patients in more than 1500 cancer registries.¹³ Women with unavailable treatment sequence data were excluded from the analysis. In order to exclude patients who may have been unresponsive to chemotherapy or had rapidly progressing disease, women who died within the first 12 months after diagnosis or had less than 12 months of follow-up from diagnosis were excluded. Per NCDB reporting requirements, survival data are missing for all patients diagnosed in 2012 (the last year of the associated database), and as a result these patients were also excluded. Subjects were categorized into 3 treatment groups: (1) surgery before systemic therapy, (2) systemic therapy before surgery, and (3) systemic therapy alone. Within the NCDB, stage IV breast cancer is coded according to the American Joint Commission of Cancer designation of clinical M1 disease.¹³ Overall survival was defined as the time from diagnosis to death. Patients who were alive at last follow-up were censored at the date of last follow-up.

Baseline demographic, clinicopathologic, and treatment-level variables were compared across groups. The primary outcome was overall survival. Secondary outcomes included type of surgery, margin involvement, and utilization of radiation therapy (RT). Baseline characteristics and outcomes were compared in an initial univariate analysis using the chi-square test or analysis of variance, as appropriate. The Kaplan-Meier method was used to estimate unadjusted overall survival. A multivariate Cox proportional hazards model was used to estimate the hazard ratios for overall survival. To account for the correlation of patients treated at the same hospital, a robust sandwich covariance estimator was used in all survival models. Multivariate logistic regression models were used to estimate the association of treatment group with receipt of extended/modified radical/radical mastectomy, simple mastectomy, or lumpectomy after adjustment for known covariates. To account for the correlation of patients treated at the same hospital, all logistic models were built in the generalized estimating equations framework with an exchangeable correlation matrix.

To account for women designated as M1 who may have been diagnosed with metastatic breast cancer shortly after surgery and not at diagnosis, a sensitivity analysis was performed using patients designated as both clinical M1 based on the American Joint Committee on Cancer (AJCC) coding, *and* as having documented known metastatic disease by site based on the included NCDB Collaborative Stage Data Set term CS Mets at Dx.¹³ A total of 2499 (10.4%) patients from the original cohort were excluded when these combined criteria were applied.

Only patients with available data for all covariates were included in each model, and effective sample sizes are indicated for each table/figure. No adjustments were made for

multiple comparisons. All statistical analyses were performed in SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patient and Tumor Characteristics

From 2003 to 2011, 24,015 women with stage IV breast cancer met inclusion criteria and were included in the analysis (Fig. 1). Median age was 58 years old [interquartile range (IQR) 49–68 years]. Proportions of clinical T-stage were as follows: T1 was 12.1%, T2 was 26.7%, T3 was 13.8%, T4 was 33.1%, and unknown T-stage was 13.4%. Clinical N-stage was reported as N0 in 20.7%, N1 in 34.5%, N2 in 13.6%, N3 in 12.2%, and unknown in 18.7%. Estrogen-receptor (ER) status was reported as ER+ in 69.3% of patients and ER+ in 20.4% of patients, whereas progesterone-receptor (PR) status was reported as PR+ in 55.5% of patients and PR– in 33.3% of patients. Patient characteristics are summarized in Table 1.

Patterns of Care and Treatment Sequence

Among the cohort of de novo stage IV breast cancer patients alive at 1 year, 56.2% ($n = 13,505$) received systemic therapy alone and 43.8% ($n = 10,510$) underwent surgery of the primary breast tumor. Of those, 19.0% ($n = 4,552$) underwent surgery before systemic therapy and 24.8% ($n = 5,958$) underwent surgery after systemic therapy. During the study interval, patients were more likely to undergo surgery after systemic therapy; these rates increased from 21.4% in 2003 to 24.9% in 2011, while rates of surgery first dropped from 21.7% to 17.0% ($P < 0.001$). Among women undergoing systemic therapy first, the median time from diagnosis to surgery was 6 months compared to 19 days for those undergoing surgery before systemic therapy.

Women undergoing systemic therapy before surgery were younger (median age 55 vs 60; $P < 0.001$), more likely to have private insurance (57.1% vs 47.2%; $P < 0.001$), have clinical T3 or T4 disease (59.1% vs 27.9%; $P < 0.001$) and have ER/PR negative invasive breast cancers (27.6%/41% vs 19.7%/31%; both $P < 0.001$) (Table 1). These women were also more often treated with mastectomy (radical/modified radical/simple) (81.4% vs 52.2%; $P < 0.001$), RT (56.1% vs 39.9%; $P < 0.001$), and chemotherapy (47% vs 38.1%; $P < 0.001$) when compared to women undergoing surgery first. Treatment characteristics are summarized in Table 2.

After multivariable adjustment among women who had surgery, those undergoing systemic therapy before surgery were more likely to have undergone a modified radical/radical mastectomy [odds ratio (OR) 1.46; 95% confidence interval (CI), 1.32–1.61; $P < 0.001$] or a simple mastectomy (OR 1.93; 95% CI, 1.71–2.17; $P < 0.001$) compared to women undergoing surgery first (Table 3). Notably, age less than 40 (OR 1.21, 95% CI, 1.02–1.43; $P = 0.03$), larger tumor size (T4 disease; OR 3.26, 95% CI, 1.28–8.32; $P = 0.01$), and higher rates of clinical node involvement (N3 disease; OR 3.19; 95% CI, 2.69–3.78; $P < 0.001$) were also associated with receipt of modified radical/radical mastectomy.

Survival Analyses

Unadjusted overall survival was greatest in women who underwent surgery after systemic therapy (median: 52.8 months), followed by surgery before systemic therapy (median: 49.4 months) and systemic therapy alone (median: 37.5 months) (log-rank $P < 0.001$) (Fig. 2; Table 4). After adjustment for known covariates including year of diagnosis, age, comorbidity index, clinical T/N stage, ER/PR status, margin status, metastatic site (bony vs other), receipt of RT as part of the primary treatment course, and type of surgery, risk of death was reduced among women undergoing surgery after systemic therapy [Hazard Ratio (HR) 0.56; 95% CI, 0.52–0.61; $P < 0.001$] and surgery before systemic therapy (HR 0.68; 95% CI, 0.62–0.73; $P < 0.001$) when compared to systemic therapy alone (Table 5). Receipt of RT to either the primary and/or metastatic sites had no impact on overall survival (HR 1.01; 95% CI, 0.96–1.05; $P = 0.83$). Of the total cohort, the majority received no RT (59.75%), followed by RT to the breast, chest, or regional lymph nodes (17.89%) and spine (9.19%) and extremity bones including the pelvis (4.36%). In contrast, those with bone-only metastatic disease (HR 0.83; 95% CI, 0.77–0.91), ER+ tumors (HR 0.79; 95% CI, 0.74–0.84), and/or PR+ tumors (HR 0.76; 95% CI, 0.72–0.80) had improved overall survival (all $P < 0.001$).

Based on the results of our sensitivity analysis, 21,516 patients were designated as clinical M1 stage and were indicated as having metastatic disease at diagnosis based on both the cM1 code and the CS Mets at Diagnosis term. Clinicopathologic features were similar to the overall cohort. In this population, median time from diagnosis to surgery was 6.3 months (IQR 4.9–8.0) for women receiving systemic therapy before surgery, and 19 days (IQR 5–34) for women going to surgery first. These data are similar to the overall cohort analysis. Unadjusted survival among patients treated with surgery after systemic therapy (median: 52.2 months), surgery before systemic therapy (46.8 months), and systemic therapy alone (37.4 months, log-rank $P < 0.001$) was also very similar to our prior analysis. Adjusted results were also maintained in this cohort. After adjustment, risk of death was reduced among women undergoing surgery after systemic therapy (HR 0.58; 95% CI, 0.54–0.63; $P < 0.001$) and surgery before systemic therapy (HR 0.72; 95% CI, 0.67–0.79; $P < 0.001$) when compared to systemic therapy alone. Because the results were in agreement, we opted to present only data from the larger cohort.

DISCUSSION

Our study is the largest contemporary analysis to evaluate surgical resection of the primary tumor among women with stage IV breast cancer, and the association of modern treatment with overall survival. On evaluation of 24,015 women with metastatic breast cancer, we identified an overall slightly reduced rate of surgery among stage IV breast cancer patients from 43.1% in 2003 to 41.9% in 2011, with a higher frequency of women undergoing surgery after receipt of systemic therapy in more recent years. Our results demonstrate that among women alive 1 year after a diagnosis of meta-static breast cancer, surgical resection of the primary tumor was associated with improved survival, regardless of treatment sequence. The greatest benefit was seen among stage IV patients with ER+ breast cancer

who underwent surgery after receipt of systemic therapy, regardless of the site of their metastatic disease.

In 2002, Khan et al³ evaluated 16,023 stage IV breast cancer patients diagnosed between 1990 and 1993 from the NCDB, and reported a reduced risk of death (HR = 0.61, 95% CI 0.58–0.65) among the 57.2% (9162) of patients who underwent surgical resection of the primary tumor. These findings questioned the surgical doctrine of reserving resection of the primary breast tumor for palliation alone.

Although other series reported similar results,^{4–7} the benefit of surgical resection itself was questioned. Data from Massachusetts General Hospital, Brigham and Women's Hospital, and Dana Farber Cancer Institute, demonstrated no difference in survival between women diagnosed with metastatic disease before surgery when compared to women treated with systemic therapy alone (median OS of 2.4 vs 2.36 years).⁷ The authors concluded that these findings were related to lead-time bias.⁷ Similarly, in a case-matched study using the National Comprehensive Cancer Network Breast Cancer Outcomes Database, survival was similar between metastatic patients treated nonoperatively and those who underwent surgery first.¹⁴ Collectively, these data suggested that although surgical resection of the primary tumor may be associated with improved survival, the results were potentially confounded by significant bias and varied multimodal therapy.

Prospective registries and randomized clinical trials were designed to address these biases^{10,11}; however, to date, randomized trial data have been criticized for inclusion of a disproportionate number of women with aggressive or advanced metastatic disease, use of nonstandard systemic therapy regimens, or inclusion of women with unconfirmed metastatic sites.¹² The Translational Breast Cancer Research Consortium 013 prospective registry compared women with stage IV breast cancer deemed as responders to chemotherapy; within this population, there was no demonstrated difference in 3-year survival with or without surgery, regardless of tumor subtype.¹⁵ These findings suggest that improved survival may be related entirely to response to systemic therapy, and not at all from resection of the primary breast cancer. The Eastern Cooperative Oncology Group phase III multicenter, prospective, randomized trial (ECOG 2108) will compare standard therapy to surgery after receipt of 32 weeks of systemic therapy for patients with stage IV breast cancer. Results of this trial are expected in June 2025.

In the context of these prior reports, our study showed several important findings. First, despite national guidelines stating that surgery in stage IV breast cancer patients should be reserved for palliation alone, approximately 40% of women underwent surgical resection, consistent with observations from other series.^{5,7,16} From 2003 to 2011, the overall percentage of stage IV breast cancer patients undergoing primary site surgery decreased slightly from 43.1% to 41.9%; however, surgery following systemic therapy increased from 21.4% to 24.9%. Notably, the median time to surgery was 6 months (IQR of 5–8 months). It is unlikely that women undergoing surgery during this time frame required palliative resection, and more likely that, for unknown reasons, surgical resection was included in the care of stage IV patients who were doing well after completion of chemotherapy.

In our study, the majority of patients undergoing surgery after systemic therapy were younger, privately insured, had fewer comorbidities, and underwent treatment at academic or comprehensive cancer centers. Furthermore, among the stage IV breast cancer patients undergoing surgery, those receiving systemic therapy first were more likely to have larger tumor sizes and clinically node-positive disease (T stage 3/4, 59.1% vs 27.9%; N stage 2/3, 30.7% vs 22.8%, both $P < 0.001$). Accordingly, they were also more likely to undergo a modified radical mastectomy than breast conserving surgery, and had lower rates of positive surgical margins compared to women undergoing surgery first ($P < 0.001$). Interestingly, despite unclear evidence that surgery provides a survival benefit to women with metastatic breast cancer, the vast majority who underwent surgery was treated with a more invasive approach.

Our survival analysis demonstrates the greatest survival benefit was seen in women treated with systemic therapy followed by surgery; unadjusted median survival was 52.8 months compared to 37.5 months for those undergoing systemic therapy alone, and 5-year overall survival was 45% compared to 28%. Given that we limited our cohort to women still alive at 12 months after diagnosis, our reported median overall survival is significantly higher than other series.¹⁶ However, our reported effect size of surgery on OS (surgery before systemic therapy: HR 0.68; surgery after systemic therapy: HR 0.56) is similar to modern retrospective series.^{7,16,17}

Prior retrospective series reporting on this topic were criticized for potential bias confounding their results, which we attempted to control for in this study.^{8,9} We included only women who were alive at least 12 months after a diagnosis of stage IV breast cancer, in an attempt to control for early deaths in the systemic therapy alone group, theoretically excluding women with early and rapidly progressing terminal disease. We additionally compared patients by treatment sequence, focusing on the group that underwent surgery after systemic therapy, to better account for stage migration bias and mirror contemporary practice. In addition, our statistical analysis controlled for treatment facility bias, where surgery might be a surrogate for more aggressive multimodal therapy. In attempts to further control for remaining selection bias, we conducted a sensitivity analysis limiting the cohort to only patients with metastatic disease indicated by both a diagnosis of clinical M1 disease and confirmation of known site of metastatic disease, which found similar results.

According to the AJCC staging manual that guides NCDB coding, stage at diagnosis includes imaging and pathologic data collected within 4 months of diagnosis in the absence of disease progression *or* through completion of surgery, whichever is longer. The possibility of upstaging after surgery remains, and could account for our finding that women who went to surgery first did so at a median of 19 days after diagnosis. Unfortunately, outside of independent chart review, there is no way to know definitively if clinical stage IV disease was truly determined before surgical resection or in the early postoperative period. However, concerns about this selection bias leading to falsely improved outcomes after surgery are not supported by our findings. On the contrary, we found that women who went to surgery first had poorer overall survival despite having smaller tumors with clinically negative lymph nodes than those who received systemic therapy before surgery. Thus, selection bias resulting from postoperative upstaging does not entirely explain improved survival in

women who underwent surgery after systemic therapy. Despite this, it is critical that we acknowledge the potential of remaining selection bias within this large observational study. Importantly, women who underwent surgery, either before or after systemic therapy, may have had unknown metastatic disease and were presumably healthy enough to do so. As a whole, these women likely differed from those who received systemic therapy alone.

Several limitations exist in our study that must be acknowledged. As this is a large database series, our study was limited by the available data. We were unable to determine why women with metastatic breast cancer went to surgery either before or after systemic therapy, and whether this was for palliation, local progression, or a result of shared decision making between women and their surgeons. This is significant given that surgery is not considered standard of care, and indications for operative intervention were likely varied in this cohort. In addition, we were unable to include Her2 status given that it was only reliably coded in the NCDB starting with patients diagnosed in 2010. This lack of data limits our ability to draw conclusions regarding differences among subgroups of women undergoing surgery at different time points, or changes in the incidence of surgery at the primary site over time.

Our study provides an evaluation of current trends among women with stage IV breast cancer, and, among those alive at least 1 year after diagnosis, finds improved survival among women who undergo surgical resection of the primary tumor after systemic therapy. Importantly, surgery continues to be included in the care of approximately 40% of women with stage IV disease, despite national guidelines recommending that surgery be offered for palliation alone. Modern systemic therapy has resulted in improved survival over time (20 months in 1988–1993 to 25 months in 1999–2003) to as high as 33 to 55 months,^{18,19} and thus local control may become increasingly important in the management of patients with distant metastatic disease. Our findings may aid in framing changes to current national practice patterns that will ultimately depend on the result of the ECOG 2108 trial. Until then, it remains important that women with metastatic breast cancer are offered coordinated multidisciplinary care, which may influence the treatment and overall survival of this population. Ultimately, surgical engagement in the contemporary care of these women remains highly relevant.

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FIGURE 1.
Consort diagram for patient selection.

FIGURE 2.
Kaplan-Meier curve for overall survival (N = 24015).

TABLE 1

Patient Characteristics

	Treatment Sequence			P
	All Patients (N = 24015)	Surgery Following Systemic Therapy (N = 5958)	Surgery Prior to Systemic Therapy (N = 4552)	
Age, yr				<0.001
<40	1920 (8%)	709 (11.9%)	284 (6.2%)	927 (6.9%)
40–60	11741 (48.9%)	3332 (55.9%)	2061 (45.3%)	6348 (47%)
>60	10354 (43.1%)	1917 (32.2%)	2207 (48.5%)	6230 (46.1%)
Median (IQR)	58 (49–68)	55 (46–63)	60 (50–71)	59 (50–69)
Race				<0.001
White	18856 (78.5%)	4675 (78.5%)	3702 (81.3%)	10479 (77.6%)
Black	4104 (17.1%)	1002 (16.8%)	674 (14.8%)	2428 (18%)
Other	797 (3.3%)	224 (3.8%)	135 (3%)	438 (3.2%)
Insurance status				<0.001
Private	11445 (47.7%)	3400 (57.1%)	2149 (47.2%)	5896 (43.7%)
Government	10553 (43.9%)	2153 (36.1%)	2179 (47.9%)	6221 (46.1%)
None	1358 (5.7%)	307 (5.2%)	155 (3.4%)	896 (6.6%)
Facility type				<0.001
Academic	8291 (34.5%)	1797 (30.2%)	1142 (25.1%)	5352 (39.6%)
Community	2855 (11.9%)	697 (11.7%)	726 (15.9%)	1432 (10.6%)
Comprehensive	12841 (53.5%)	3457 (58%)	2680 (58.9%)	6704 (49.6%)
Other	28 (0.1%)	7 (0.1%)	4 (0.1%)	17 (0.1%)
Charlson/Deyo score				<0.001
0	20640 (85.9%)	5241 (88%)	3756 (82.5%)	11643 (86.2%)
1	2704 (11.3%)	603 (10.1%)	642 (14.1%)	1459 (10.8%)
2	671 (2.8%)	114 (1.9%)	154 (3.4%)	403 (3%)
Clinical T-stage				<0.001
0	125 (0.5%)	13 (0.2%)	20 (0.4%)	92 (0.7%)
1	2910 (12.1%)	482 (8.1%)	926 (20.3%)	1502 (11.1%)
2	6423 (26.7%)	1455 (24.4%)	1678 (36.9%)	3290 (24.4%)
3	3312 (13.8%)	1049 (17.6%)	506 (11.1%)	1757 (13%)

	Treatment Sequence				<i>P</i>
	All Patients (N = 24015)	Surgery Following Systemic Therapy (N = 5958)	Surgery Prior to Systemic Therapy (N = 4552)	Systemic Therapy Alone (N = 13,505)	
4	7959 (33.1%)	2474 (41.5%)	766 (16.8%)	4719 (34.9%)	<0.001
X	3209 (13.4%)	467 (7.8%)	642 (14.1%)	2100 (15.5%)	
Clinical N-stage					
0	4978 (20.7%)	1008 (16.9%)	1371 (30.1%)	2599 (19.2%)	
1	8288 (34.5%)	2304 (38.7%)	1174 (25.8%)	4810 (35.6%)	
2	3261 (13.6%)	997 (16.7%)	549 (12.1%)	1715 (12.7%)	<0.001
3	2924 (12.2%)	835 (14%)	488 (10.7%)	1601 (11.9%)	
X	4482 (18.7%)	795 (13.3%)	956 (21%)	2731 (20.2%)	
ER status					
ER+	16649 (69.3%)	3780 (63.4%)	3185 (70%)	9684 (71.7%)	
ER–	4911 (20.4%)	1647 (27.6%)	896 (19.7%)	2368 (17.5%)	<0.001
PR status					
PR+	13327 (55.5%)	2943 (49.4%)	2648 (58.2%)	7736 (57.3%)	
PR–	8002 (33.3%)	2441 (41%)	1410 (31%)	4151 (30.7%)	

Data presented as N (%) unless otherwise specified. Percentages may not add up to 100 due to rounding or missing values. *P* value for Chi-squared test for categorical variables, and analysis of variance (ANOVA) for continuous variables.

TABLE 2

Treatment Characteristics

	Treatment Sequence			P
	All Patients (N = 24016)	Surgery After Systemic Therapy (N = 5958)	Surgery Before Systemic Therapy (N = 4552)	
Time to surgery (Days)				
Median (IQR)	116 (22 – 197)	187 (146 – 239)	19 (6 – 35)	<0.001
Type of surgery *				<0.001
Radical/extended Radical mastectomy	211 (2%)	146 (2.5%)	65 (1.4%)	
Modified radical mastectomy	4537 (43.2%)	3038 (51%)	1499 (32.9%)	
Simple mastectomy	2478 (23.6%)	1665 (27.9%)	813 (17.9%)	
Partial mastectomy	3138 (29.9%)	1028 (17.3%)	2110 (46.4%)	
Margin status *				<0.001
Negative	8021 (76.3%)	4872 (81.8%)	3149 (69.2%)	
Positive	2044 (19.4%)	881 (14.8%)	1163 (25.5%)	
Metastatic site				0.09
Bone only	3187 (13.3%)	838 (14.1%)	580 (12.7%)	
Other	20828 (86.7%)	5120 (85.9%)	3972 (87.3%)	
Treatment with any radiation				<0.001
No	14352 (59.8%)	2542 (42.7%)	2687 (59%)	
Yes	9391 (39.1%)	3345 (56.1%)	1816 (39.9%)	
Time to systemic therapy, days				
Median (IQR)	30 (16–52)	26 (15–40)	58 (37–87)	<0.001
Type of systemic therapy				<0.001
Chemotherapy only	9811 (40.9%)	2799 (47%)	1733 (38.1%)	
Endocrine only	7562 (31.5%)	728 (12.2%)	1696 (37.3%)	
Both	6642 (27.7%)	2431 (40.8%)	1123 (24.7%)	

Data presented as N (%) unless otherwise specified. Percentages may not add up to 100 due to rounding or missing values.

P value for Chi-squared test for categorical variables, and analysis of variance (ANOVA) for continuous variables.

* Type of surgery, time to surgery, hospital length of stay, and margin status values include only patients who had surgery.

TABLE 3Logistic Model Predicting Type of Surgery (N = 9267)^{*,†}

Outcome (a)		OR (95% CI)	P	Overall P
Modified/extended/radical mastectomy	Treatment sequence			<0.001
	Surgery before systemic therapy	REF		
	Surgery following systemic therapy	1.458 (1.323, 1.607)	<0.001	
Outcome (b)		OR (95% CI)	P	Overall P
Simple mastectomy	Treatment sequence			<0.001
	Surgery before systemic therapy	REF		
	Surgery after systemic therapy	1.928 (1.712, 2.17)	<0.001	
Outcome (c)		OR (95% CI)	P	Overall P
Partial mastectomy	Treatment sequence			<0.001
	Surgery before systemic therapy	REF		
	Surgery after systemic therapy	0.352 (0.315, 0.394)	<0.001	

* All models adjusted for year of diagnosis, age, Charlson/Deyo score, clinical N-stage, clinical T-stage, ER status, PR status, and metastatic site.

† Only patients who had surgery were included in this model.

TABLE 4

5-Year, 10-Year, and Overall Survival by Treatment Type

Treatment Sequence	Total	Deaths (%)	5-Year OS Rate (95% CI)	10-Year OS Rate (95% CI)	Median OS (95% CI)	Log-Rank <i>P</i>
Surgery after systemic therapy	5958	2798 (47%)	0.445 (0.429, 0.461)	0.202 (0.172, 0.233)	52.8 mo (50.6, 54.2)	<0.001
Surgery before systemic therapy	4552	2387 (52%)	0.411 (0.393, 0.428)	0.144 (0.113, 0.179)	49.4 mo (47.4, 51.6)	
Systemic therapy alone	13,505	8320 (62%)	0.275 (0.265, 0.284)	0.085 (0.071, 0.100)	37.5 mo (36.8, 38.2)	
Total	24,015	13,505 (56%)	*	*	42.6 mo (42.0, 43.1)	

* 5 and 10-year total cohort OS rates were not calculated.

TABLE 5

Adjusted Multivariate Overall Survival Model (N = 20,513)

Outcome	HR (95% CI)	P	Overall P
Overall survival			
Treatment sequence			<0.001
Systemic therapy alone	REF		
Surgery after systemic therapy	0.564 (0.524, 0.607)	<0.001	
Surgery before systemic therapy	0.675 (0.623, 0.732)	<0.001	
Year of diagnosis	0.997 (0.985, 1.008)	0.58	0.58
Age (yr)			<0.001
>60	REF		
40–60	0.843 (0.807, 0.881)	<0.001	
<40	0.776 (0.715, 0.842)	<0.001	
Charlson/Deyo score			<0.001
0	REF		
1	1.226 (1.152, 1.304)	<0.001	
2	1.465 (1.331, 1.613)	<0.001	
Clinical N stage			<0.001
0	REF		
1	1.083 (1.025, 1.145)	0.005	
2	1.231 (1.15, 1.318)	<0.001	
3	1.125 (1.047, 1.208)	0.001	
X	1.14 (1.065, 1.219)	<0.001	
Clinical T stage			<0.001
0	REF		
1	1.29 (0.926, 1.797)	0.13	
2	1.385 (1.002, 1.914)	0.05	
3	1.534 (1.107, 2.127)	0.01	
4	1.61 (1.162, 2.231)	0.004	
X	1.439 (1.035, 2)	0.03	
ER-status			<0.001
ER–	REF		
ER+	0.789 (0.741, 0.839)	<0.001	
PR-status			<0.001
PR–	REF		
PR+	0.755 (0.718, 0.795)	<0.001	
Margin status*			<0.001
Negative	REF		
Positive	1.415 (1.306, 1.533)	<0.001	
Metastatic site			<0.001
Other	REF		
Bone only	0.834 (0.768, 0.905)	<0.001	
Treatment with radiation			0.83

Outcome	HR (95% CI)	P	Overall P
No	REF		
Yes	1.005 (0.961, 1.05)	0.83	
Surgery type			<0.001
No surgery	REF		
Radical/extended radical mastectomy	0.949 (0.762, 1.181)	0.64	
Modified radical mastectomy	1.017 (0.939, 1.102)	0.67	
Partial mastectomy	0.821 (0.75, 0.899)	<0.001	

* A level of no surgery for margin status was included to allow for patients who did not have assessable margins to stay in the model, but this level was excluded after modeling due to it being accounted for within the surgery type variable.