Evaluating the Effectiveness of Neoadjuvant Chemotherapy in Reducing Mastectomy for Women With Breast Cancer

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Abstract

Background: Neoadjuvant chemotherapy in breast cancer reduced mastectomy rates by 7% to 13% in randomized trials. However, the differential effects for women with different stages, receptor subtypes, and ages are unknown. We compared mastectomy rates in women who did vs did not receive neoadjuvant chemotherapy in 18 patient subgroups. The main objective was to quantify the potential benefit from neoadjuvant chemotherapy in reducing mastectomy rates for each subgroup.

Methods: Our retrospective analysis used data from the National Cancer Data Base, which includes approximately 70% of incident cancers across the United States. Absolute risk reductions for mastectomy were determined for 18 subgroups of clinical stage, receptor subtype, and age group. In each subgroup, propensity score weighting balanced measured covariates between women treated with vs without neoadjuvant chemotherapy.

Results: A total of 55,709 patients were analyzed. In clinical stage IIA disease, only patients with human epidermal growth factor receptor 2 (HER2)-positive tumors had reduced mastectomy rates associated with neoadjuvant chemotherapy (age < 60 years, 12%; age ≥ 60 years, 12.6%). For stage IIB cancers, neoadjuvant chemotherapy was associated with an absolute reduction in mastectomy rates of 5.9% in women younger than age 60 years with hormone receptor-positive/HER2- disease, 8.2% to 10.7% for triple-negative disease, and 11.7% to 17.4% for HER2+ disease. For stage IIIA, the reductions in mastectomy rates ranged from 6.6% to 15.9%.

Conclusions: In an analysis of patients treated across the United States, we found that neoadjuvant chemotherapy was associated with a reduction in mastectomy rates to a similar magnitude overall as shown in randomized trials, but this benefit varied widely by patient subgroup. This study provides novel information to help women make informed decisions regarding treatment.
consideration of neoadjuvant therapy for women with clinical stage IIA–IIIA cancers who desire breast conservation but are ineligible due to tumor size (4). The benefit in terms of absolute reduction in mastectomy rates from neoadjuvant chemotherapy likely differs by tumor stage, receptor type, and patient age. For example, the ability of neoadjuvant chemotherapy to reduce a need for mastectomy is likely larger for a woman with stage IIA, human epidermal growth factor receptor 2 (HER2)–positive breast cancer compared with one with stage IIB, hormone receptor (HR)–positive disease. When a woman is deciding whether to receive neoadjuvant chemotherapy, knowing the relative magnitude of benefit based on her specific stage, receptor subtype, and age can help with making an informed decision. However, these data do not exist, and the aforementioned randomized trials report reductions in the rates of mastectomy for the overall group but not the more specific rates in patient subgroups. It is also unlikely that there will be future randomized trials specifically comparing neoadjuvant vs adjuvant chemotherapy for each patient stage, receptor subtype, and age subgroup to answer this question.

Therefore, to address this clinically relevant knowledge gap, we undertook this study using the National Cancer Data Base (NCDB) to compare mastectomy rates in women who received vs did not receive neoadjuvant chemotherapy, stratified by clinical stage, tumor receptor subtype, and patient age. The NCDB includes approximately 70% of all incident cancers across the United States with patients, patient care, and outcomes broadly representative of breast cancer patients in this country.

Methods

Data Source

The NCDB is administered jointly by the American College of Surgeons’ Commission on Cancer (CoC) and the American Cancer Society (5). All CoC-accredited institutions report data using standardized coding definitions as detailed by the CoC’s Facility Oncology Registry Data Standards. The NCDB contains data on patient demographics, facility characteristics, county-level socioeconomic characteristics, cancer diagnosis and tumor characteristics, and first course of treatment. The type of primary breast cancer surgery is classified in the NCDB based on standardized Surveillance, Epidemiology and End Results (SEER) site-specific surgery primary site codes (6).

Patient Cohort

In this study, we searched the NCDB for women with incident breast cancers diagnosed from 2010 to 2012 (Figure 1). This study focused on women with clinical stage IIA (T2N0 only), IIB, and IIIA (T3N1 only) disease because these are the specific stages that the NCCN guidelines consider eligible for neoadjuvant chemotherapy if a patient desires breast conservation but is not eligible due to tumor size (4). Women with prior cancer diagnoses or missing data for stage, receipt of systemic therapy, or primary surgery were excluded. Women who received neoadjuvant endocrine therapy alone were also excluded (1% of patients) so that this analysis could focus on the comparison of patients who did vs did not receive neoadjuvant chemotherapy. The study sample was limited to women with common histologies for breast cancer (International Classification of Diseases for Oncology [3rd edition] histology codes 8500-8508 and 8520-

Excluded (No.) Included (No.)

114 753 No prior cancer diagnosis 527 973
24 136 At least part of treatment or decision-making performed at reporting facility 503 837
4627 Females only 499 210
44 804 Histology ductal, lobular, mixed ductal and lobular 454 406
366 500 Include only clinical stage IIA (T2N0), IIB, IIIA (T3N1) 87 906
3790 Patients must have undergone surgery 84 116
14 270 Receipt of systemic therapy/surgery sequence is known, and exclude neoadjuvant endocrine-only treatment. 69 846
14 137 Complete data for covariates 55 709

Figure 1. Selection of cases and exclusion (flow diagram).

8524). This resulted in an analytic sample of 55 709 patients (Figure 1).

Ascertainment of Neoadjuvant Chemotherapy

The NCDB contains data on the time from diagnosis to initiation of chemotherapy and surgery. We classified patients as having received neoadjuvant chemotherapy if their time from diagnosis to initiation of chemotherapy was less than the time from diagnosis to surgery.

Ascertainment of Surgery Type

Type of surgery was ascertained based on standardized SEER codes for breast cancer–specific surgery. Codes classified as breast conserving surgery were 20–24. Codes classified as mastectomy were 30, 40–74, and 80. Patients who underwent local tumor destruction only (code 19), underwent a surgery of unknown type (codes 90 and 99), or who did not have surgery (code 0) were not included in the final data set.

Ascertainment of Covariates

Potential confounders collected by the NCDB and measured before or at the time of neoadjuvant therapy include tumor receptor subtype, clinical American Joint Committee on Cancer stage, tumor grade from biopsy, year of diagnosis, age, race, medical insurance status, zip code education, zip code median income, Charlson/Deyo Comorbidity Score, rurality, facility type, and facility location.

Statistical Analysis

The overall goal of this study was to compare the mastectomy rates in women who received vs did not receive neoadjuvant
chemotherapy and to conduct this analysis separately for each patient subgroup based on stage, receptor subtype, and age. Age 60 years was chosen for stratification because it is a clinically sensible boundary between older and younger patients, and it is also close to the national median age of breast cancer diagnosis. To balance measured confounders in each subgroup among women who received vs did not receive neoadjuvant chemotherapy, we constructed separate propensity score (PS) models using multivariable logistic regression to estimate the probability that each patient received neoadjuvant chemotherapy. This resulted in 18 PS models (all combinations for three stage groups, three receptor subgroups, and two age groups). These models included known confounders and predictors of mastectomy receipt, including all variables in Table 1. To control for measured confounders, we balanced the covariates across treatment groups using standardized mortality ratio (SMR) weighting, assigning a weight of 1 for patients treated with neoadjuvant chemotherapy and a weight of the propensity odds \([PS/(1-PS)]\) for patients who did not receive neoadjuvant chemotherapy and a weight of the propensity odds \([PS/(1-PS)]\) for patients who did not receive neoadjuvant chemotherapy with the same covariate distribution as that observed in patients who received neoadjuvant chemotherapy (7,8). Covariate balance was evaluated using standardized absolute mean difference (SAMD); adequate balance was considered at an SAMD of less than 0.1 (Supplementary Tables 1–18) (9). Due to small sample sizes in the stage IIIA subgroups, only race, insurance, and facility type were included in the PS models. This resulted in residual confounding for some variables across treatment groups, and binomial regression was then used to control for the few variables that were still unbalanced (Supplementary Tables 5, 6, 11, 12, 17, and 18, available online). Crude and weighted proportions of patients undergoing mastectomy were reported for women who received vs did not receive neoadjuvant chemotherapy with the same covariate distribution as that observed in patients who received neoadjuvant chemotherapy (7,8). Covariate balance was evaluated using standardized absolute mean difference (SAMD); adequate balance was considered at an SAMD of less than 0.1 (Supplementary Tables 1–18) (9). Due to small sample sizes in the stage IIIA subgroups, only race, insurance, and facility type were included in the PS models. 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This resulted in residual confounding for some variables across treatment groups, and binomial regression was then used to control for the few variables that were still unbalanced (Supplementary Tables 5, 6, 11, 12, 17, and 18, available online).
data had baseline characteristics similar to the final analysis sample (Supplementary Table 1), except that excluded patients were older and more had Medicare insurance. Overall, 69% to 77% of women were Caucasian and 67% to 70% were treated in community cancer centers. The numbers of patients with stage IIA, IIB, and IIIA cancers were 35,598 (64%), 16,056 (29%), and 4,055 (7%), respectively. After propensity score adjustment, patient characteristics among those who received vs did not receive neoadjuvant chemotherapy were not different in any patient subgroup among patients with stage IIA or IIB disease (details are shown in Supplementary Tables 2–5, 8–11, and 14–17, available online). Due to smaller sample sizes, subgroups of patients with stage IIIA disease had some remaining imbalances in covariates after propensity score weighting (details are shown in Supplementary Tables 6, 7, 12, 13, and 19, available online); this was further accounted for using multivariable modeling.

Mastectomy rates were calculated separately among women who received vs did not receive neoadjuvant chemotherapy in each of the 18 subgroups (3 stages × 3 receptor subtypes × 2 age subgroups). These results are summarized in Table 2. Both crude and propensity score–weighted rates were reported, and they differed minimally (<3% absolute change in results after propensity adjustment for all groups), suggesting that stratification controlled much of the measured confounding for the association between neoadjuvant chemotherapy and mastectomy (Table 2).

Among patients with clinical stage IIA disease, only patients with HER2-positive tumors appeared to benefit from neoadjuvant chemotherapy in reducing mastectomy rates (age < 60 years, mastectomy 47.5% vs 59.5% without neoadjuvant chemotherapy, *P* < .001; age ≥ 60 years, 39.2% vs 51.8%, *P* = .001). For visual presentation, the absolute reduction in mastectomy rates was calculated separately among women who received vs did not receive neoadjuvant chemotherapy in each of the 18 subgroups (3 stages × 3 receptor subtypes × 2 age subgroups). These results are summarized in Table 2. Both crude and propensity score–weighted rates were reported, and they differed minimally (<3% absolute change in results after propensity adjustment for all groups), suggesting that stratification controlled much of the measured confounding for the association between neoadjuvant chemotherapy and mastectomy (Table 2).

| Table 2. Proportion of patients who underwent mastectomy by neoadjuvant chemotherapy receipt before and after propensity score weighing, stratified by stage, IHC subtype, and age group |
|---------------------------------|--------|--------|--------|--------|--------|--------|
|                                 | Unweighted | Weighted |        |
|                                 | Neoadjuvant chemotherapy, % | No neoadjuvant chemotherapy, % | Neoadjuvant chemotherapy, % | No neoadjuvant chemotherapy, % | * | P   |
| Stage IIA                       |        |        |        |        |        |        |
| HR+/HER2-                       |        |        |        |        |        |        |
| < 60                            | 778/1461 (53.3)† | 5798/10,532 (55.1) | 53.3 | 55.5 | .23 |
| ≥ 60                            | 240/485 (49.5) | 5399/11,053 (48.8) | 51.5 | 49.5 | .53 |
| HER2+                           |        |        |        |        |        |        |
| < 60                            | 456/959 (47.5) | 1502/2575 (58.3) | 47.5 | 59.5 | <.001 |
| ≥ 60                            | 130/332 (39.2) | 983/1840 (53.4) | 39.2 | 51.8 | .001 |
| Triple-negative                 |        |        |        |        |        |        |
| < 60                            | 616/1319 (46.7) | 1437/3021 (47.6) | 46.7 | 49.2 | .20 |
| ≥ 60                            | 136/382 (35.6) | 697/1639 (42.5) | 35.6 | 41.5 | .09 |
| Stage IIB                       |        |        |        |        |        |        |
| HR+/HER2-                       |        |        |        |        |        |        |
| < 60                            | 1534/2239 (68.5) | 2465/3303 (74.6) | 68.5 | 74.4 | <.001 |
| ≥ 60                            | 490/777 (63.1) | 1966/2885 (68.1) | 63.1 | 65.6 | .29 |
| HER2+                           |        |        |        |        |        |        |
| < 60                            | 896/1454 (61.6) | 795/1102 (72.1) | 61.6 | 73.3 | <.001 |
| ≥ 60                            | 234/427 (54.8) | 484/667 (72.6) | 54.8 | 72.2 | <.001 |
| Triple-negative                 |        |        |        |        |        |        |
| < 60                            | 806/1374 (58.7) | 621/935 (66.4) | 58.7 | 66.8 | <.001 |
| ≥ 60                            | 193/379 (50.9) | 323/514 (62.8) | 50.9 | 61.6 | .003 |
| Stage IIIA                      |        |        |        |        |        |        |
| HR+/HER2-                       |        |        |        |        |        |        |
| < 60                            | 864/1020 (84.7) | 451/487 (92.6) | 84.7 | 92.6 | <.001 (not controlled) |
| ≥ 60                            | 258/300 (86.0) | 311/339 (91.7) | 86.0 | 90.9 | .06 (not controlled)† |
| HER2+                           |        |        |        |        |        |        |
| < 60                            | 536/643 (83.4) | 150/164 (91.5) | 83.4 | 91.4 | <.001 (not controlled) |
| ≥ 60                            | 116/158 (73.4) | 83/96 (86.5) | 73.4 | 86.7 | <.001 (not controlled)† |
| Triple-negative                 |        |        |        |        |        |        |
| < 60                            | 414/538 (77.0) | 101/118 (85.6) | 77.0 | 87.1 | <.001 (not controlled) |
| ≥ 60                            | 99/136 (72.8) | 49/56 (87.5) | 72.8 | 88.7 | <.001 (not controlled)† |

| *By convention, the group treated with neoadjuvant chemotherapy has propensity weight of 1. covs = covariates; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PR = progesterone receptor. |
| †Due to small sample sizes, only race, insurance, and facility type were included in the propensity score models for stage 3A. Binomial regression was then used to control for the few variables that were still unbalanced. |
| ‡Ratios represent the number of women who had mastectomy divided by all patients in the specific subgroup. |
rates among women who received vs did not receive neoadjuvant chemotherapy, with 95% confidence intervals, is presented in Figure 2. Therefore, for clinical stage IIA and HER2-positive breast cancer, neoadjuvant chemotherapy was associated with an absolute reduction in mastectomy of 12.0% for women younger than age 60 years and 12.6% for women age 60 years or older. For women with clinical stage IIB and IIIA breast cancers, neoadjuvant chemotherapy was associated with decreased mastectomy rates in almost all patient subgroups, but the magnitude of effect differed dramatically (Table 2 and Figure 2). Patients with HER2-positive or triple-negative cancers appeared to have greater magnitudes of benefit from neoadjuvant chemotherapy than patients with HR+/HER2- disease. More specifically, for patients with clinical stage IIB cancers, neoadjuvant chemotherapy was associated with a reduction in mastectomy rates of 5.9% in younger women with HR+/HER2- disease, 8.2% to 10.7% in women with triple-negative disease, and 11.7% to 17.4% in women with HER2-positive disease. For clinical stage IIIA cancers, the reductions in mastectomy rates were 6.6% (HR+/HER2- age < 60 years), 10.6% to 15.9% (triple-negative), and 8.0% to 10.6% (HER2-positive), respectively.

Discussion

For women with early-stage breast cancers, randomized trial data showed that neoadjuvant chemotherapy was associated with a 7% to 13% absolute reduction in mastectomy rates among all women enrolled in the trials (included stage T1c-T4b N0-1 and all ages and receptor subtypes) (1,2). These trials were not large enough to perform subgroup analyses to better assess the magnitude of benefit by patient stage, receptor subtype, and age. Therefore, we undertook this analysis using a large and representative cancer registry of patients from across the United States to fill this current knowledge gap. Specifically, we compared the mastectomy rates of patients who received vs did not receive neoadjuvant chemotherapy in 18 subgroups based on stage, receptor subtype, and patient age.

While the ideal study design to assess the potential benefit of neoadjuvant chemotherapy would be randomized trials, it is unlikely that randomized trials will be performed separately to answer this question for each of the 18 patient subgroups to assess the magnitude of benefit in each based on patient characteristics. Lacking randomized trial data, we used the best alternative approach—utilizing data from a large cancer registry to analyze more than 55,000 contemporary (2010–2012) patients—but we acknowledge that there are important potential limitations with this approach. Most notably, there can be imbalances between the comparison groups including disease characteristics and patient and physician preferences regarding breast conservation, as well as unknown information in the NCDB including chemotherapy type and duration. Additionally, it is unknown what proportion of patients initially attempted breast conservation but required a mastectomy due to positive or close margins. We utilized sophisticated analytic methods for observational data including stratification and propensity score weighting to minimize confounding of measured characteristics, but we recognize that residual confounding, especially in unmeasured variables, is possible. This study is an example of utilizing big data to learn from more patients than those enrolled in clinical trials. Were a randomized trial to be performed, the population of patients with HR+/HER2- could be further studied; based on our results, the benefit of neoadjuvant chemotherapy for reducing mastectomy rates in this subgroup is most uncertain.

Despite these potential limitations, our results have face validity. The observed reductions in the rates of mastectomy associated with neoadjuvant chemotherapy were consistent with those reported from the prospective randomized trials NSABP B-18 (7%) and EORTC 10902 (13%). In addition, the demonstrated differences in rates of mastectomy reduction by different patient subgroups are consistent with known differences in tumor sensitivity to chemotherapy. Specifically, we found that neoadjuvant chemotherapy was not associated with lower mastectomy rates in several patient groups: stage IIA HR+/HER2-, stage IIB HR+/HER2- age 60 years or older, and stage IIIA HR+/HER2- age 60 years or older. The reduced benefit of neoadjuvant chemotherapy for patients with HR+/HER2- cancer observed in this study corroborates findings in the
phase II trial ACOSOG Z1071, which showed that the HR+/HER2- subtype is associated with relatively low rates of pathologic complete response and breast conservation (10). For the other patient subgroups, neoadjuvant chemotherapy was associated with absolute reductions in mastectomy rates ranging between 5.9% and 17.4%. While physicians have known that different types of breast cancers respond differently to chemotherapy, to our knowledge, this study is the first to provide numbers to associate this knowledge with mastectomy rates with vs without neoadjuvant chemotherapy.

Figure 3. Propensity score weighted relative risk reduction of mastectomy with 95% confidence intervals by receptor subtype and age group for (A) stage IIA (T2N0 only), (B) stage IIB, and (C) stage IIIA (T3N1 only). Relative risks are calculated from rates of mastectomy in patients treated with vs without neoadjuvant chemotherapy in each subgroup. Relative risk of less than 1 means that neoadjuvant chemotherapy was associated with a reduced mastectomy rate. HER2 = human epidermal growth factor receptor 2; HR = hormone receptor.
We recognize that there may be other benefits to neoadjuvant chemotherapy that can contribute to a patient’s decision. Neoadjuvant chemotherapy has not been shown to improve overall survival compared with adjuvant chemotherapy (1,2), but giving chemotherapy prior to surgery may allow in vivo assessment of tumor response to systemic therapy. From a patient’s perspective, though, knowing the potential reduction in the mastectomy rate is likely one of the most important factors in this decision.

Results from this study may represent conservative estimates of the potential benefit from neoadjuvant chemotherapy in reducing mastectomy rates. We suspect that women who were able to have breast conserving surgeries without neoadjuvant treatment would likely have received surgery right away, while women who clinically may have needed neoadjuvant chemotherapy in order to have breast conserving surgery would be more likely to be in the neoadjuvant chemotherapy group. Thus, even though our analysis was stratified by clinical stage, women in the neoadjuvant chemotherapy group may have had larger tumors than women who did not receive neoadjuvant chemotherapy within each stage subgroup. If true, this would bias the results in terms of mastectomy rates against the neoadjuvant chemotherapy group, thus making our results conservative estimates of treatment benefit.

There are several important strengths of this study. The large sample size of the NCDB allowed for detailed analyses to be performed for 18 different patient subgroups. There are no other prospective or retrospective data to inform patients on the relative effectiveness of neoadjuvant chemotherapy based on patients’ age group, tumor receptor subtype, and stage. These variables are important predictors of body image concerns, chemosensitivity, and breast conservation eligibility, respectively (4,10,11); they may modify the mastectomy risk reduction of neoadjuvant chemotherapy. Additionally, the patient cohort used in this study reflects more than 1400 cancer centers across the United States and allows these results to be more generalizable than those from clinical trials that often select for younger and healthier patients (12).

The absolute reduction in mastectomy rates associated with the use of neoadjuvant chemotherapy varied widely among patients based on clinical stage, receptor subtype, and age. Overall, we found that mastectomy reduction associated with neoadjuvant chemotherapy was greatest among patients with HER2-positive disease, and also with most subgroups of patients with triple-negative disease. In contrast, older patients with HR+/HER2- disease had less benefit comparatively. These data fill a knowledge gap and provide currently unavailable information that physicians can share with their patients when individualizing neoadjuvant treatment decisions. Because increasing the probability of breast conservation is one important consideration in the decision-making process regarding neoadjuvant chemotherapy for early breast cancer, the data provided in this study can further help patients make an informed decision.

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Dr. Chen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: All authors. Analysis and interpretation of data: All authors. Drafting of the manuscript: Mohiuddin, Chen. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Deal, Lund. Study supervision: Chen.

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