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Surgical Outcomes for Mastectomy Patients Receiving Neoadjuvant Chemotherapy

A Propensity-Matched Analysis

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Objective: To evaluate the risk of neoadjuvant chemotherapy for surgical morbidity after mastectomy with or without reconstruction using 1:1 matching.

Background: Postoperative surgical complications remain a potentially preventable event for breast cancer patients undergoing mastectomy. Neoadjuvant chemotherapy is among variables identified as contributory to risk, but it has not been rigorously evaluated as a principal causal influence.

Methods: Data from American College of Surgeons National Surgical Quality Improvement Program (2006–2012) were used to identify females with invasive breast cancer undergoing planned mastectomy. Surgical cases categorized as clean and undergoing no secondary procedures unrelated to mastectomy were included. A 1:1 matched propensity analysis was performed using neoadjuvant chemotherapy within 30 days of surgery as treatment. A total of 12 preoperative variables were used with additional procedure matching: bilateral mastectomy, nodal surgery, tissue, and/or implant. Outcomes examined were 4 wound occurrences, sepsis, and unplanned return to the operating room.

Results: We identified 31,130 patient procedures with 2488 (7.5%) receiving chemotherapy. We matched 2411 cases, with probability of treatment being 0.005 to 0.470 in both cohorts. Superficial wound complication was the most common wound event, 2.24% in neoadjuvant-treated versus 2.45% in those that were not ($P = 0.627$). The rate of return to the operating room was 5.7% in the neoadjuvant group versus 5.2% in those that were not ($P = 0.445$). The rate of sepsis was 0.37% in the neoadjuvant group versus 0.46% in those that were not ($P = 0.654$).

Conclusions: This large, matched cohort study, controlled for preoperative risk factors and most importantly for the surgical procedure performed, demonstrates that breast cancer patients receiving neoadjuvant chemotherapy have no increased risk for surgical morbidity.

Keywords: breast cancer, immediate breast reconstruction, mastectomy, neoadjuvant chemotherapy, outcomes research, propensity analysis, surgical morbidity

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LEARNING OBJECTIVES

1. Compare and evaluate propensity scoring analysis with matching in the evaluation of neoadjuvant chemotherapy within 30 days of mastectomy for invasive breast cancer and its effect on surgical postoperative complications, specifically wound occurrences, sepsis, and unplanned return to the operating room
2. Summarize the indications and advantages of neoadjuvant chemotherapy in invasive breast cancer.
3. Identify various risk factors for surgical postoperative complications which can be incorporated into the model for analysis using propensity scoring with matching.

The two main objectives of breast cancer surgery are to stage the cancer and to provide local control. Crucial surgical considerations in achieving these objectives include type of surgery, timing, risks, and prevention of complications. As both medical and surgical treatment of breast cancer has evolved over the past few decades, therapeutic options have greatly expanded. One such example is the increased use of chemotherapy given before surgery, termed neoadjuvant chemotherapy.[1,2] Although the hope that neoadjuvant chemotherapy would improve survival compared with adjuvant chemotherapy has not been realized in all situations, it is clear that neoadjuvant chemotherapy significantly improves the ability to perform breast-conserving surgery (BCS) in borderline resectable cases and is absolutely indicated for inflammatory and many unresectable breast cancers.[3–10] Furthermore, it has recently been shown that survival is worse in some types of breast cancer, notably estrogen receptor/progesterone receptor /human epidermal growth factor receptor-negative tumors, if initiation of adjuvant chemotherapy is delayed, making neoadjuvant therapy more appropriate in these cases.[11] Finally, a favorable response to systemic chemotherapy, especially in patients obtaining a pathologic complete response, is a valuable prognostic marker and has led to the further use of neoadjuvant chemotherapy, initially in clinical trials and currently as standard of care.[12–14]

The effect of neoadjuvant chemotherapy on infection and other postoperative complications after breast surgery is not well-defined. Even without considering the use of neoadjuvant chemotherapy, complication rates are variable. For example, a 2012 meta-analysis found rates of surgical site infection (SSI) after

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any type of breast surgery ranging between 1% and 30%, with the wide range dependent on variables such as the definition of SSI, type of surgery, and perioperative therapy.[15]

There is a low likelihood that a randomized controlled trial (RCT) will be undertaken to define the true added risk for surgical morbidity or specifically delineate the postoperative complications related to neoadjuvant chemotherapy in breast cancer patients. However, outcomes research is increasingly seen as confirmation of the end results of health treatments and services. We therefore undertook an observational cohort study of data from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP). The goal was to determine whether neoadjuvant chemotherapy affects the risk of wound occurrences (including SSIs), sepsis, or an unplanned return to the operating room, in matched cohorts of women who had a mastectomy for invasive breast cancer. Unlike other studies, we included only women who had undergone mastectomy for invasive cancer and employed propensity score matching analysis rather than regression methods.

METHODS

The ACS-NSQIP is a national outcome-based and risk-adjusted program.[16] There are 135 variables collected, including preoperative risk factors, intraoperative variables, and postoperative morbidity and mortality up to 30 days. A full description of ACS-NSQIP is available online.[17] The NSQIP partner members can request patient user files (PUF) that include data from all participating centers. Approval was obtained from the Institutional Review Board (#51559).

Study Population

The ACS-NSQIP database was used to identify elective mastectomy with or without nodal procedures and with or without immediate breast reconstruction, using the Current Procedural Terminology (CPT) codes (Supplementary Table A, http://links.lww.com/SLA/B28) and included data from years 2006 to 2012. Inclusion criteria consisted of the following: female sex; clean surgical wound class; International Disease Classification, 9th Revision diagnosis of invasive breast neoplasm (174.0–174.9, 196.3, 198.2, 198.81, 238.3, 239.3, V10.3), coded or as a discharge diagnosis related to the postoperative diagnosis.

Exclusions were carried out in stepwise fashion, consisting of the following criteria: preoperative diagnosis of sepsis or wound infection; pneumonia or wound infection present at time of surgery; disseminated cancer; presence of central nervous system tumors; or those undergoing a procedure unrelated to the mastectomy, nodal, or reconstructive operation at the time of surgery; and those cases in which any of the examined variables were not recorded (NULL) (Fig. 1). Three data values were edited or deleted: age listed as 90+ in NSQIP was considered age of 90; hospital lengths of stay $\geq$365 were deleted (assuming code error); and women >50 years were considered not to be pregnant where the pregnancy variable was NULL.

A total of 56,483 patients were initially identified via CPT codes. Of these, 33,130 patients met inclusion criteria (Fig. 1). The majority of exclusions were for diagnoses other than invasive breast neoplasm [eg, ductal carcinoma in situ (DCIS)] and those cases for which the chemotherapy variable was not collected. A large number of excluded cases were for surgical wound classification as other than clean. After these exclusions, an additional 699 cases were excluded when an unrelated surgical procedure was performed, ranging from gynecologic to orthopedic. After accounting for exclusions (n = 23,353), a total of 2488 patients (7.51% of the data set) received neoadjuvant chemotherapy and 30,642 patients did not.

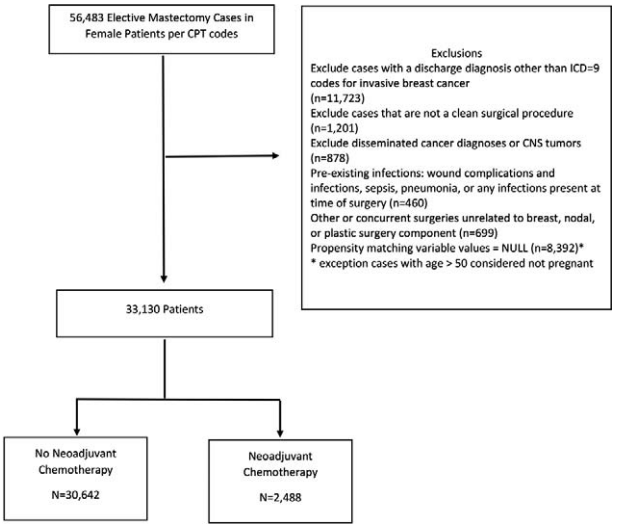

FIGURE 1. Algorithm for selection of dataset groups by neoadjuvant chemotherapy use.

For purposes of this analysis, we considered the NSQIP chemotherapy variable equal to neoadjuvant chemotherapy as defined within the user guide (dated October 2013) (Supplementary Table B, http://links.lww.com/SLA/B28). The database collects information regarding the principal or index operative procedure, and additionally identifies up to 10 ''other'' procedures and up to 10 ''concurrent'' procedures.

Covariates

We included NSQIP demographic and clinical variables (n = 12) for evaluating the risk: age; body mass index (BMI); race; surgery year; type of diabetes (insulin/noninsulin); steroids; dialysis; presence of renal failure; history of transfusion; smoking; preoperative radiation therapy; and pregnancy.[39] Surgical procedural variables included American Society of Anesthesiologists (ASA) status score and surgery types using CPT codes. The surgery types were further grouped as unilateral or bilateral mastectomy; inclusive of a nodal procedure (sentinel and/or axillary node dissection); and inclusion of an immediate reconstruction (implant and/or tissue) procedure. All variables were selected before any analysis of data.

Measured Outcomes

The first outcome is described as a wound occurrence or complication (Supplementary Table B, http://links.lww.com/SLA/B28), using the 4 possible NSQIP wound variables, including superficial SSI; deep incisional SSI; organ space SSI; and wound disruption. These NSQIP definitions are a modification of the centers for disease control and prevention definitions.[18] The 2 other outcomes examined were as follows: sepsis and unplanned reoperation (Supplementary Table B, http://links.lww.com/SLA/B28).

Statistical Analysis

Descriptive statistics were used to characterize demographic and clinical characteristics. Categorical variables are presented by frequencies and proportions, and were compared using the chi-square or Fisher exact test, as appropriate; or using Wilcoxon rank-sum test for ordered categories such as ASA score. Normally distributed continuous variables are expressed as the mean [$\pm$standard deviation (SD)] and were compared using Student *t* test. Continuous variables that do not follow normal distributions are expressed as the median

[interquartile range (IQR)] and were compared using the Wilcoxon rank-sum test.

Since neoadjuvant chemotherapy was not assigned at random, baseline characteristics may have differed among the 2 treatment groups (those receiving chemotherapy vs those not receiving chemotherapy). To account for these differences in baseline characteristics, we first derived propensity scores using a logistic regression model. Propensity score matching is a commonly used method aimed to find a control with similar characteristics to a case, so that any subsequent method to find treatment effect will not be biased toward any treatment option, although the treatment itself may be dependent on the specific patient. Propensity score matching reduces bias caused by imbalanced covariates, such as patient characteristics.[19,20]

After cases were matched 1:1 without replacement using caliper restriction (estimated logits) to the nearest neighbor, the primary outcomes were then regressed on an indicator variable denoting chemotherapy treatment status in a second logistic regression model.

The effect of neoadjuvant chemotherapy as compared with no neoadjuvant chemotherapy was determined using the estimated regression coefficient from the fitted model and is expressed as the odds ratio (OR, or adjusted OR) and the corresponding 95% confidence limits (95% CL). Statistical significance was set at $P < 0.05$,

TABLE 1. Unmatched Cohort by Covariates

	Unmatched Cohort		
	(Mean ± Standard Deviation) or % (n)		
Covariates	**Chemotherapy (n = 2488)**	**No Chemotherapy (n = 30,642)**	***P***
Age	52.25 ± 12.10	59.12 ± 13.54	<0.001
Body mass index	29.00 ± 7.51	28.20 ± 7.40	<0.001
Race			
American Indian–Alaskan Native	0.88 (22)	0.73 (224)	<0.001
Asian Pacific–Nat Hawaiian	4.06 (101)	4.27 (1307)	
Black–African American	12.8 (319)	10.03 (3072)	
Hispanic	1.33 (33)	0.98 (301)	
Unknown	8.88 (221)	9.21 (2821)	
White	72.03 (1792)	74.79 (22,917)	
Year of surgery			
2006	6.35 (158)	6.09 (1867)	<0.001
2007	12.46 (310)	14.17 (4341)	
2008	14.39 (358)	18.73 (5739)	
2009	15.68 (390)	22.32 (6839)	
2010	17.56 (437)	21.1 (6464)	
2011*	19.09 (475)	10.72 (3284)	
2012*	14.47 (360)	6.88 (2108)	
Diabetes			
Insulin	2.97 (74)	3.18 (975)	<0.001
Noninsulin	4.7 (117)	7.79 (2388)	
None	92.32 (2297)	89.02 (27,279)	
Steroids, yes	3.74 (93)	1.31 (401)	<0.001
Dialysis, yes	0.04 (1)	0.26 (81)	0.031
Renal failure, yes	0 (0)	0.04 (11)	NA
Transfuse, yes	0.04 (1)	0.05 (15)	1.000
Smoking, yes	15.51 (386)	14.09 (4317)	0.050
Radiotherapy, yes	2.05 (51)	0.33 (101)	<0.001
Pregnancy, yes	0.16 (4)	0.13 (41)	0.579
Surgery-related variables			
ASA class			
1, No disturb	5.91 (147)	5.53 (1693)	0.385
2, Mild disturb	59.24 (1474)	60.47 (18,530)	
3, Severe disturb	33.24 (827)	32.70 (10,021)	
4, Life threat	1.61 (40)	1.3 (398)	
Mastectomy type			
Unilateral	71.62 (1782)	79.59 (24,387)	<0.001
Bilateral	28.38 (706)	20.41 (6255)	
No nodes; no tissue; no implant	18.17 (452)	20.68 (6337)	<0.001
No nodes; no tissue; implant	2.89 (73)	3.66 (1123)	
No nodes; tissue; no implant	0.88 (22)	0.78 (238)	
No nodes; tissue; implant	0.12 (3)	0.57 (174)	
Nodes; no tissue; no implant	42.89 (1067)	46.04 (14,108)	
Nodes; no tissue; implant	22.83 (568)	19.96 (6117)	
Nodes; tissue; no implant	4.9 (122)	3.64 (1115)	
Nodes; tissue; implant	7.27 (181)	4.67 (1430)	

Chemotherapy within 30 days before surgery to no chemotherapy within 30 days before surgery.
*NSQIP variable defined as 90 days before surgery.

and all comparisons were 2-sided. All statistical analyses were performed in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

The mean age of all patients considered for inclusion in the study population was 58.6 years (median 58, range 18–90). The distribution of demographics (according to NSQIP definition of race) for this set of patients included the following: white (74.6%), followed by 10.2% Black or African American. An additional 9.2% had an unknown designation of race, and the remainder were American Indian or Alaskan Native (0.7%); Asian Pacific Islander or Native Hawaiian (4.2%); or Hispanic (1%).

Matching Variables

Prior propensity matching, we evaluated the data according to patient characteristics and surgical procedures performed. Table 1 details this unmatched study population. In this population, the majority of covariates were found to be statistically different. There were no cases in the neoadjuvant chemotherapy group that had renal failure; therefore this variable was dropped from the matching analysis.

Of the 2488 cases that received neoadjuvant chemotherapy, matches were obtained for 2411 patients, for a matching rate of 96.9%. The distributions of propensity scores in the 2 matched groups were almost the same, implying the matching process was successful (Fig. 2). Table 2 details the propensity-matched data. In this population, all covariates were similar, with P values >0.6. Standardized differences were used to assess the pre and postmatching balance of covariates, with a standardized difference of less than 0.0001 to indicate successful balance between groups (Supplementary Table C, http://links.lww.com/SLA/B28).

In the unmatched cohort (Table 1), there was a statistical difference between groups based on unilateral or bilateral mastectomy, which balanced to 28% bilateral mastectomy after matching (Table 2). The surgical procedural variables were further broken into 8 case combinations for procedures in addition to mastectomy, including nodal procedures (sentinel and axillary lymph node dissection) and reconstruction (use of implant and/or tissue). These combinations allowed patients to be closely matched based on the entire operative procedure performed. In the matched cohort (Table 2), over 75% of patients in both groups underwent a nodal procedure, and at least 38% of patients underwent reconstructive procedure with an implant or tissue. The largest subset of patients in the matched cohort involved patients who underwent a mastectomy with a nodal procedure (43.3%) followed by nodal procedure and implant use (22.75%).

Outcomes Results

The primary study outcomes are detailed in Table 3. The rate of superficial incisional SSI was the most common wound occurrence. Those that received neoadjuvant chemotherapy had no increased risk for superficial SSI, with an adjusted OR of 0.912 (95% CL 0.627, 1.325) when compared with those that did not. There was similarly no increased risk between groups for deep incisional SSI, adjusted OR of 1.073 (95% CL 0.517, 2.229); organ space SSI, adjusted OR of 0.600 (95% CL 0.218, 1.654); or wound disruption, adjusted OR of 1.630 (95% CL 0.674, 3.939). There was no difference in the risk for a sepsis occurrence in those receiving neoadjuvant chemotherapy compared with those that did not, with an adjusted OR of 0.817 (95% CL 0.338, 1.976). Lastly, there was no difference in the risk for returning to the OR for those receiving neoadjuvant chemotherapy compared with those that did not, with an adjusted OR of 1.102 (95% CL 0.859, 1.414). The distribution for the 2 outcomes with the highest rates is described according to selected

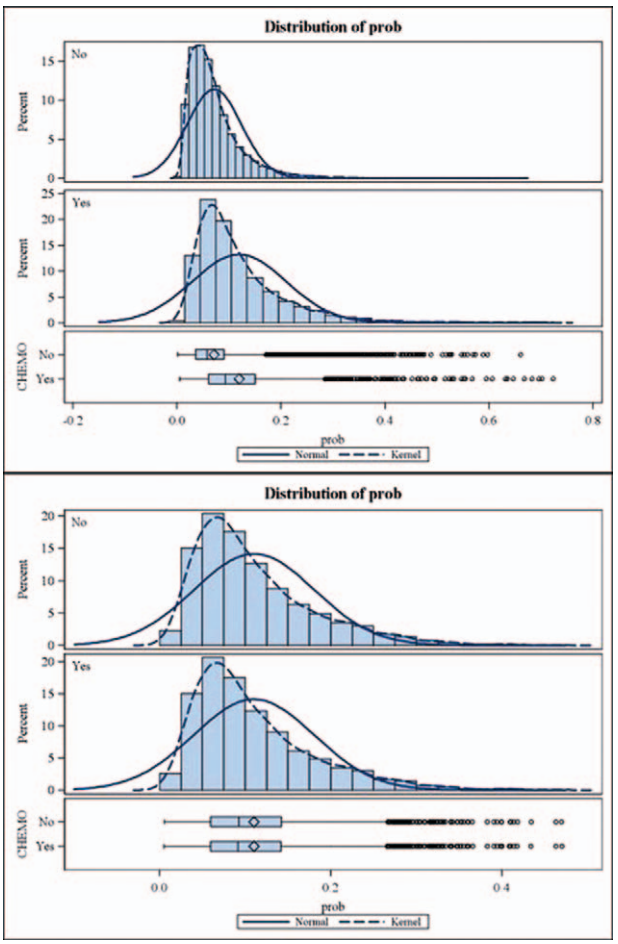

FIGURE 2. Illustration of distribution of probability for receiving chemotherapy before (top figure) and after (lower figure) propensity matching.

reconstruction procedures (Supplementary Table D, http://links.lww.com/SLA/B28).

Table 4 also lists other NSQIP outcome variables by treatment. Although we report that there were no statistical differences, the infrequency of events limits the power and may not prevent a type I error. The median (IQR) total hospital length of stay in days was 1.0 (1.0, 2.0) versus 1.0 (1.0, 2.0) ($P = 0.284$).

Table 5 details preoperative laboratory values for the matched cohort. Values for white blood count and platelets are detailed as continuous variables and further broken into categories for abnormally low, normal, and abnormally high. Reference ranges were obtained from Harrison Principles of Internal Medicine (2012).[21] Laboratory values in patients receiving neoadjuvant chemotherapy were consistent with treatment effect, including lower hematocrit and lower white count and platelet counts. Albumin, creatinine, and blood urea nitrogen were statistically lower in chemotherapy-treated patients, and serum glutamic-oxaloacetic transaminase and alkaline phosphatase were statistically higher in treated patients, although the clinical relevance of these differences is considered trivial.

DISCUSSION

In this 7-year review of NSQIP data in women with invasive breast cancer undergoing mastectomy, with or without nodal

TABLE 2. Matched Cohort by Covariates

	Matched Cohort (Mean ± Standard Deviation) or % (n)		
Covariates	**Chemotherapy (n = 2411)**	**No Chemotherapy (n = 2411)**	***P***
Age	52.59 ± 11.99	52.48 ± 12.18	0.749
Body mass index	28.98 ± 7.44	28.98 ± 8.25	0.999
Race			
American Indian–Alaskan Native	0.75 (18)	0.87 (21)	0.849
Asian Pacific–Nat Hawaiian	4.15 (100)	4.44 (107)	
Black–African American	12.57 (303)	13.23 (319)	
Hispanic	1.29 (31)	1.14 (34)	
Unknown	8.79 (212)	9.37 (226)	
White	72.46 (1747)	70.68 (1704)	
Year of surgery			
2006	6.47 (156)	6.22 (150)	0.749
2007	12.44 (300)	13.56 (327)	
2008	14.81 (357)	13.81 (333)	
2009	16.13 (389)	16.22 (391)	
2010	17.88 (431)	18.54 (447)	
2011*	18.79 (453)	17.67 (426)	
2012*	13.48 (325)	13.98 (337)	
Diabetes			
Insulin	2.94 (71)	3.4 (82)	0.646
Noninsulin	4.77 (115)	4.6 (111)	
None	92.29 (2225)	92.00 (2218)	
Steroids, yes	2.94 (71)	2.99 (72)	0.932
Dialysis, yes	0.04 (1)	0.0 (0)	1.000
Transfuse, yes	0.04 (1)	0.0 (0)	1.000
Smoking, yes	15.43 (372)	15.8 (381)	0.721
Radiotherapy, yes	0.87 (21)	0.91 (22)	0.878
Pregnancy, yes	0.17 (4)	0.17 (4)	1.000
Surgery-related variables			
ASA class			
1, No disturb	6.01 (145)	6.26 (151)	0.823
2, Mild disturb	59.115 (1426)	58.73 (1416)	
3, Severe disturb	33.22 (801)	33.06 (797)	
4, Life threat	1.62 (39)	1.95 (47)	
Mastectomy type			
Unilateral	71.84 (1732)	72.00 (1736)	0.898
Bilateral	28.16 (679)	28.0 (675)	
No nodes; no tissue; no implant	18.42 (444)	18.04 (435)	0.979
No nodes; no tissue; implant	3.03 (73)	3.19 (77)	
No nodes; tissue; no implant	0.91 (22)	0.66 (16)	
No nodes; tissue; implant	0.13 (3)	0.08 (2)	
Nodes; no tissue; no implant	43.05 (1038)	43.55 (1050)	
Nodes; no tissue; implant	22.69 (547)	22.60 (545)	
Nodes; tissue; no implant	4.6 (111)	4.44 (107)	
Nodes; tissue; implant	7.18 (173)	7.42 (179)	

Chemotherapy within 30 days before surgery to no chemotherapy within 30 days before surgery.
*NSQIP variable defined as 90 days before surgery.

procedure and/or reconstruction, patients treated with neoadjuvant chemotherapy within 30 days of surgery showed no increased risk for postoperative surgical wound complications, sepsis, or unplanned return to surgery. Using propensity score matching 1:1, in a population that was designed to minimize variance and reduce the selection bias, the results are relevant to a cross-section of patients.

The modern era of surgery has focused on prevention of postoperative complications, in particular, prevention of infection, because the consequences associated with infection can be profound. Much of the surgical literature is concerned with examining the risk factors associated with this type of morbidity, in the hope that early identification of risk can allow for adaptive or modifications in care. Sustaining any complication, particularly those related to infection, is especially significant in breast cancer patients because it may lead to a delay of adjuvant medical or radiation therapy. In breast cancer surgery, extensive research has been done examining possible risk factors other than neoadjuvant chemotherapy, including obesity, diabetes, smoking, transfusions, mastectomy, operative time, and previous chest irradiation.[15,22–30]

Offering neoadjuvant chemotherapy to selected patients with invasive breast cancer has become more common and now is often an important component of initial management.[10,31–34] In 2012, an International Consensus Conference documented that neoadjuvant chemotherapy could generally be considered for every patient who is a candidate for adjuvant chemotherapy, and also for those patients who desire BCS, but are less than optimal candidates, and patients

TABLE 3. Effect of Neoadjuvant Chemotherapy Within 30 Days of Surgery on Postoperative Surgical Morbidities With Propensity Score Matching

	Chemotherapy	No Chemotherapy			
	% (n)		*P*	Adjusted Odds Ratio	95% CL
Superficial	2.24 (54)	2.45 (59)	0.627	0.912	0.627, 1.325
Deep incisional	0.58 (14)	0.62 (15)	0.849	1.073	0.517, 2.229
Organ space	0.25 (6)	0.41 (10)	0.323	0.600	0.218, 1.654
Wound disruption	0.54 (13)	0.33 (8)	0.278	1.630	0.674, 3.939
Sepsis occurrence	0.37 (9)	0.46 (11)	0.654	0.817	0.338, 1.976
Return to the operating room	5.68 (137)	5.18 (125)	0.445	1.102	0.859, 1.414

with inflammatory or inoperable breast cancer.[35] In 2015, the American Society of Breast Surgeons published practice guidelines for neoadjuvant chemotherapy, noting that this treatment option is an important initial strategy for the management of invasive breast cancer and provides critical information for resectability and surgical management.[36]

Despite the increased number of patients receiving neoadjuvant chemotherapy, optimal timing of surgery after neoadjuvant chemotherapy is not well-defined. Classically, 3 to 6 weeks has been suggested to allow normalization of laboratory values, to permit the patient to regain general well-being, and to allow the patient to recover from the effects of chemotherapy to safely undergo the procedure. However, multiple previous studies have suggested a range of intervals between neoadjuvant chemotherapy and surgery, from 7 days to as long as 4 to 8 weeks when reconstruction is planned.[31,32,37–41]

Overall, the time from the end of neoadjuvant chemotherapy to definitive surgical care is most likely a patient-dependent determination, including immunologic and hematologic variables combined with judgment regarding the level of surgical resection and potential reconstruction. In this study, the exact timing of surgery after neoadjuvant chemotherapy is not known due to database limitations. However, the fact that surgery may have been performed earlier than the aforementioned wait times strengthens the finding that neoadjuvant chemotherapy does not increase risk.

A review of the literature examining the relationship of neoadjuvant chemotherapy to surgical morbidity includes 3 recent papers that used NSQIP datasets. In 2012, Decker et al[29] examined the risk of postoperative wound complications in patients who underwent lumpectomy or mastectomy with or without reconstruction. Using NSQIP data from 2005 to 2010, and including patients with both invasive cancer and DCIS cancer within their dataset, 4.5% received neoadjuvant chemotherapy. Univariate analysis showed neoadjuvant chemotherapy patients had a higher rate of wound dehiscence ($P = 0.009$), but multivariable analysis using an outcome that included all wound complications into a single variable revealed that neoadjuvant chemotherapy was not a risk ($P = 0.9$). They did, however, report a trend in neoadjuvant-treated patients having wound complications in the mastectomy with immediate reconstruction group ($P = 0.06$).

In 2013, Fisher et al[24] examined risk factors for surgical morbidity in immediate breast reconstruction cases to create a tool designed to predict risk for 5 variables: prosthetic or flap loss; unplanned return to the operating room; deep wound infection; superficial SSI; and wound dehiscence. These 5 complications were categorized as "none versus 1 or more." Their NSQIP analysis

TABLE 4. Postoperative Surgical Complications and Hospital Length of Stay Collected by NSQIP

	Matched Cohort		
	% (n)		
Postoperative Variables	**Chemotherapy (n = 2411)**	**No Chemotherapy (n = 2411)**	***P***
Pneumonia	0.2 (6)	0.1 (2)	0.289
Reintubation	0.2 (5)	0.2 (4)	0.754
Pulmonary embolism	0.1 (3)	0.0 (1)	0.625
Failure to wean	0.1 (3)	0.1 (2)	1.000
Renal insufficiency	0.0 (0)	0.2 (4)	0.125
Acute renal failure	0.1 (2)	0.1 (2)	1.000
Urinary tract infection	0.3 (8)	0.7 (17)	0.071
Stroke/cerebrovascular accident	0.0 (0)	0.2 (5)	0.062
Coma	0.0 (1)	0.0 (0)	1.000
Peripheral nerve injury	0.1 (3)	0.0 (0)	0.250
Cardiac arrest	0.1 (2)	0.1 (2)	1.000
Myocardial infarction	0.1 (2)	0.0 (1)	1.000
Transfusion intraop or postop	1.3 (32)	0.9 (21)	0.129
Graft/prosthesis/flap failure	0.6 (15)	0.5 (11)	0.432
Deep vein thrombosis requiring therapy	0.1 (2)	0.2 (6)	0.289
Septic shock	0.0 (1)	0.1 (3)	0.625
	Median (interquartile range)		
Total hospital length of stay	1 (1,2) (n = 2409)	1 (1,2) (n = 2411)	0.284

Results for matched cohort.

TABLE 5. Preoperative Laboratory Values (Nearest to Surgery Date, 0–90 d) for Matched Cohort

	Matched Cohort				
	Median (Interquartile Range) or %				
Covariates	**Chemotherapy**	**n**	**No Chemotherapy**	**n**	***P***
White blood count, K/mm^3	5.7 (4.4, 7.5)	2251	6.62 (5.4, 8.0)	2033	<0.001
Abnormal low (<3.54)	10.5		2.9		<0.001
Normal	75.3		82.7		
Abnormal high (>9.06)	14.2		14.4		
Platelets, K/mm^3	255 (210, 309)	2243	259.5 (217, 308)	2030	0.034
Abnormal low (<165)	8.9		4.1		<0.001
Normal	86.8		92.8		
Abnormal high (>415)	4.3		3.1		
Hematocrit, %	35 (32.7, 37.5)	2275	39.1 (36.7, 41.1)	2093	<0.001
SGOT, U/L	24 (19, 30)	1818	21 (18, 26)	1461	<0.001
Alkaline phosphatase, U/L	78 (63, 98)	1838	72 (59, 89)	1497	<0.001
Albumin, g/dL	4.0 (3.7, 4.3)	1643	4.2 (3.9, 4.4)	1319	<0.001
Creatinine, mg/dL	0.7 (0.6, 0.8)	2124	0.79 (0.7, 0.9)	1930	<0.001
Sodium, mmol/L	140 (138, 141)	2073	140 (138, 141)	1848	0.022
Blood urea nitrogen, mg/dL	12 (10, 15)	2008	13 (11, 17)	1788	<0.001
Bilirubin, mg/dL	0.4 (0.3, 0.6)	1822	0.5 (0.3, 0.6)	1433	<0.001

included patients from years 2005 through 2011, 4.35% of whom received neoadjuvant chemotherapy. Their population was not limited to patients with a breast cancer diagnosis. In univariate analysis, neoadjuvant chemotherapy was not significant ($P = 0.14$). After regression analysis and modeling, which did not include neoadjuvant chemotherapy, the identifiable risk factors for their defined complication variable were as follows: ASA scores of $\geq$3, obesity, and active smoking.

Finally, Abt et al,[27] in 2014, reported on short-term morbidity in patients undergoing mastectomy with or without breast reconstruction. Surgical site morbidity variable was defined as any of the following 5 events: superficial and/or deep SSI; organ space SSI; wound dehiscence; prosthesis or flap failure. A second variable defined as systemic morbidity included 16 possible variables. Review of NSQIP data from 2005 through 2011 found a neoadjuvant chemotherapy rate of 4.74% in a population not limited to those with a breast cancer diagnosis. Using model-wise multivariable logistic regression, they compared neoadjuvant chemotherapy to no neoadjuvant chemotherapy for each surgical procedure and found that neoadjuvant chemotherapy use was independently associated with a lower overall surgical site morbidity in the group undergoing mastectomy without reconstruction. They also found that the odds of systemic morbidity was decreased in the majority of surgical populations receiving neoadjuvant chemotherapy. This result for neoadjuvant therapy being protective for morbidity had the authors calling for further investigation.

Although these prior studies use similar ACS-NSQIP datasets, the methods for analysis and results reported here differ in several major ways. First, we selected only patients with a discharge diagnosis of malignant breast neoplasm, who would be eligible for receiving neoadjuvant chemotherapy. Second, the data we examined were through 2012, and reflected a much higher overall rate of neoadjuvant chemotherapy use at 7.51%, versus 4.35% to 4.74%. Third, a temporal relationship to treatment types was maintained by controlling for the year of surgery and radiotherapy. Fourth, by using propensity matching, proven preoperative risks such as age, ASA score, obesity, and smoking, as well as the surgical procedure performed were taken into account. Finally, the outcome variables we employed were independent of each other and not combined into large groupings. The data also showed that the preoperative laboratory values were consistent with recent chemotherapy, and the lower white count in patients receiving neoadjuvant chemotherapy would ordinarily be expected to contribute to a higher rate of wound infections or sepsis. In comparison to the other studies, one of which reported a trend for higher risk for wound infection and another that reported neoadjuvant chemotherapy as protective, this analysis leaves little doubt as to the results and relationship for neoadjuvant chemotherapy, and risk for surgical morbidity for women who have breast cancer and undertake a significant surgical procedure.

As noted earlier, it is unlikely that a RCT examining the effect of neoadjuvant chemotherapy on surgical morbidity will be done. If a RCT study that examined examined the effect of neoadjuvant chemotherapy on surgical morbidity was performed, the type of chemotherapy and surgical procedures would have to be specified, and patients with various morbidities would likely be excluded. This is often the criticism of a RCT, for which the inclusion criteria are too limiting to be representative of the general population. Propensity analysis, and particularly matching, allows for a wide range of covariates to be considered within the analysis and also allows inclusion of a diverse population, permitting the results to be generalized to a wider population.

There are significant strengths to this observational cohort study, including the use of the ACS-NSQIP dataset which includes a large heterogeneous population pool resembling the general trends of care and coincident outcomes that has been tested and cited in numerous analyses. Additionally, propensity matching, with variables chosen before analysis, provides the ability to control for numerous confounding conditions, and also frequently cited social variables such as age and race. We matched 97% of neoadjuvant chemotherapy cases to others within the same time period matching on the year of surgery. Matching the type of surgical procedures, such as bilateral mastectomy or extensive reconstructive surgery, also indirectly controls for operative time and time in the hospital. Propensity allows inclusion of multiple variables, unlike multivariate regression that is statistically limited to a ratio of outcome events. Further, this analysis included a careful selection process that excluded cases that underwent concurrent gastrointestinal, vascular, orthopaedic, and gynecological procedures unrelated to the planned mastectomy.

Conversely, the limitations of our study are also those inherent to examining data from any large database. The data collected within ACS-NSQIP does not include the type of neoadjuvant chemotherapy or the duration of treatment; rather it is a temporal relationship, denoting that the treatment was received within 30 days before surgery. Employing a 30-day timeframe to database variables and research study outcomes (morbidity or mortality) is common throughout the literature, as an accepted standard. Answering whether neoadjuvant chemotherapy is the principal causal agent for morbidity, for a patient that ends treatment 29 days before surgery as compared with a patient who ends treatment 1 day before surgery, is an unknown. Although the later value used in 2011 and 2012 of 90 days as the definition for receipt of chemotherapy is broad, it likely allowed capture of the majority of patients. The fact that we controlled for the year of surgical treatment would take this definition change into account. As the NSQIP data are geared to surgical outcomes, the use of neoadjuvant chemotherapy is a binary variable that is used for predicting and determining risk for post-operative events rather than as a treatment variable. Lastly, recording the variable for preoperative chemotherapy treatment became optional in 2011, making the rate of neoadjuvant chemotherapy use seem to decline rather than increase. Statistical limitations include issues related to selection bias and unmeasured covariates in propensity analysis and other methods using propensity analysis that may or may not have been preferential for examining large populations.

As the surgical procedures offered to breast cancer patients have evolved, the literature concerning complications and outcomes is an increasingly important source of information for patients, hospitals, and payers alike.[42–47] To assure the best outcomes when considering procedures such as immediate breast reconstruction, or additional surgery such as prophylactic mastectomy, it is crucial to understand the factors that may influence complication rates.[48–50] Planning and timing surgery after neoadjuvant therapy is one of the important elements for consideration.

In conclusion, with the advent and access to pooled and vetted data into large datasets, the field of outcomes research with its use of sophisticated statistical modeling has helped address particular health outcomes to both general and specific populations. This large and well-controlled study of breast cancer patients permits surgeons to counsel their patients that neoadjuvant chemotherapy poses no additional risk for surgical morbidity when mastectomy with or without reconstruction is planned.

REFERENCES

1. Killelea BK, Yang VQ, Mougalian S, et al. Neoadjuvant chemotherapy for breast cancer increases the rate of breast conservation: results from the national cancer database. *J Am Coll Surg*. 2015;220:1063–1069.
2. Mougalian SS, Soulos PR, Killelea BK, et al. Use of neoadjuvant chemotherapy for patients with stage I to III breast cancer in the United States. *Cancer*. 2015;121:2544–2552.
3. Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with breast cancer. *J Clin Oncol*. 1998;16:2672–2685.
4. van der Hage JA, van de Velde JH, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European organization for research and treatment of cancer trial 10902. *J Clin Oncol*. 2001;22:4224–4237.
5. Rouzier R, Mathieu MC, Sideris L, et al. Breast-conserving surgery after neoadjuvant anthracycline-based chemotherapy for large breast tumors. *Cancer*. 2004;101:918–925.
6. Newman LA, Buzdar AU, Singletary E, et al. A prospective trial of preoperative chemotherapy in resectable breast cancer: predictors of breast-conservation therapy feasibility. *Ann Sur*. 2002;9:228–234.
7. Mauriac L, MacGrogan G, Avril A, et al. Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. *Ann Oncol*. 1999;10:47–52.
8. Loible S, von Minckwitz G, Raab G, et al. Surgical procedures after neoadjuvant chemotherapy in operable breast cancer: results of the GEPARDUO trial. *Ann Surg Oncol*. 2006;13:1434–1442.
9. Chen AM, Meric-Bernstam F, Hunt KK, et al. Breast conservation after neoadjuvant chemotherapy: the M.D. Anderson Cancer Center experience. *J Clin Oncol*. 2004;22:2303–2312.
10. Gralow JR, Burstein HJ, Wood W, et al. Preoperative therapy in invasive breast cancer: pathologic assessment and systemic therapy issues in operable disease. *J Clin Oncol*. 2008;26:814–819.
11. Fisher CS, Ma CX, Gillanders WE, et al. Neoadjuvant chemotherapy is associated with improved survival compared with adjuvant chemotherapy in patients with triple-negative breast cancer only after complete pathologic response. *Ann Surg Oncol*. 2012;19:253–258.
12. Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Breast Bowel Project B-18. *J Natl Cancer Inst Monogr*. 2001;30:96–102.
13. Kuerer HM, Singletary E, Buzdar AU, et al. Surgical conservation planning after neoadjuvant chemotherapy for stage II and operable stage II breast carcinoma. *Am J Surg*. 2001;182:601–608.
14. Rouzier R, Extra J-M, Klijanienko J, et al. Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol*. 2002;1:1304–1310.
15. Xue DQ, Qian C, Yang L, et al. Risk factors for surgical site infections after breast surgery: a systemic review and meta-analysis. *EJSO*. 2012;38:375–381.
16. Khuri SF, Daley J, Henderson W, et al. The first national, validated, outcome-based, risk adjusted, and peer-controlled program for the measurement and enhancement of the quality of surgical care. *Ann Surg*. 1998;4:491–507.
17. American College of Surgeons National Quality Improvement Program. Available at: https://www.facs.org/quality-programs/acs-nsqip/program-specifics/participant-use. Accessed December 8, 2015.
18. Mangram AJ, Horan TC, Pearson ML, et al. Guideline for prevention of surgical site infection, 1999. *Infect Control Hosp Epidemiol*. 1999;20:250–278.
19. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res*. 2011;46:399–424.
20. Heinze G, Juni P. An overview of the objectives of and the approaches to propensity score analyses. *Eur Heart J*. 2011;32:1704–1708.
21. Kratz A, Pesce M, Basner RC, et al. Appendix: laboratory values of clinical importance. In: Longo DL, Fauci AS, Kasper DL, eds. *Harrison's Principles of Internal Medicine*. 18th ed., San Francisco: McGraw-Hill Companies, Inc; 2012:3585–3610.
22. El-Tamer MB, Ward M, Schifftner T, et al. Morbidity and mortality following breast cancer surgery in women. *Ann Surg*. 2007;245:665–671.
23. De Blacam C, Ogunleye AA, Monoh AO, et al. High body mass index and smoking predict morbidity in breast cancer surgery. *Ann Surg*. 2012;255:551–555.
24. Fisher JP, Wes AM, Tuggle CT, et al. Risk analysis and stratification of surgical morbidity after immediate breast reconstruction. *J Am Coll Surg*. 2013;217:780–787.
25. Olsen MA, Lefta M, Dietz JR, et al. Risk factors for surgical site infection after major breast operation. *J Am Coll Surg*. 2008;207:326–335.
26. Nguyen TJ, Costa MA, Vidar EN, et al. Effect of immediate reconstruction in postmastectomy surgical site infection. *Ann Surg*. 2012;256:326–333.
27. Abt NB, Flores JM, Baltodano PA, et al. Neoadjuvant chemotherapy and short-term morbidity in patients undergoing mastectomy with and without breast reconstruction. *JAMA Surg*. 2014;149:1068–1076.
28. Mehrara BJ, Santoro TD, Arcilla E, et al. Complications after microvascular breast reconstruction: experience with 1195 flaps. *Breast*. 2005;118:1100–1109.
29. Decker MR, Greenblatt DY, Havlena J, et al. Impact of neoadjuvant chemotherapy on wound complication after breast surgery. *Surg*. 2012;152:382–388.
30. Davis GB, Peric M, Chan LS, et al. Identifying risk factors for surgical site infections in mastectomy patients using the National Surgical Quality Improvement Program database. *Am J Surg*. 2013;205:194–199.
31. Broadwater JR, Edwards MJ, Kuglen C, et al. Mastectomy following preoperative chemotherapy: strict operative criteria control operative morbidity. *Ann Surg*. 1991;213:126–129.
32. Ragaz J, Baird R, Rebbeck P, et al. Neoadjuvant (preoperative) chemotherapy for breast cancer. *Cancer*. 1985;56:719–724.

33. Al-Hilli Z, Boughey JC, Hoskin TL, et al. Increasing use of neoadjuvant treatment for T1 and T2 HER2-positive tumors. *Ann Surg Oncol*. 2015;22:3369–3375.
34. Buchholz TA, Lehman CD, Harris JR, et al. Statement of the science concerning locoregional treatments after preoperative chemotherapy for breast cancer: A National Cancer Institute Conference. *J Clin Oncol*. 2008;26: 791–797.
35. Kaufmann M, von Minckwitz G, Mamounas EP, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol*. 2012;19:1508–1516.
36. Holmes D, Colfry A, Czerniecki B, et al. Performance and practice guideline for the use of neoadjuvant systemic therapy in the management of breast cancer. *Ann Surg Oncol*. 2015;22:3184–3190.
37. von Minckwitz G, Eidtmann H, Rezai M, et al. Neoadjuvant chemotherapy and bevacizumab for HER2-negative breast cancer. *N Engl J Med*. 2012;366:299–309.
38. Bear HD, Tang G, Rastogi P, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. *N Engl J Med*. 2012;366:310–320.
39. Golshan M, Cirrincione MS, Sikov WM, et al. Impact of neoadjuvant chemotherapy in Stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates. *Ann Surg*. 2015;262: 434–439.
40. Narui K, Ishikawa T, Satake T, et al. Outcomes of immediate perforator flap reconstruction after skin-sparing mastectomy following neoadjuvant chemotherapy. *EJSO*. 2015;41:94–99.
41. Golshan M, Garber JE, Gelman R, et al. Does neoadjuvant bevacizumab increase surgical complications in breast surgery? *Ann Surg Oncol*. 2011;18: 733–737.
42. Chow I, Hanwright PJ, Hansen NM, et al. Predictors of 30-day readmission after mastectomy: a multi-institutional analysis of 21,271 patients. *Breast Dis*. 2015;35:221–231.
43. Osman F, Saleh F, Jackson TD, et al. Increased postoperative complications in bilateral mastectomy patients compared to unilateral mastectomy: an analysis of the NSQIP database. *Ann Surg Oncol*. 2013;20: 3212–3217.
44. Jeevan R, Browne JP, Pereira J, et al. Socioeconomic deprivation and inpatient complication rates following mastectomy and breast reconstruction. *BJS*. 2015;102:1064–1070.
45. Al-Hilli Z, Thomsen KM, Habermann EB, et al. Reoperation for complications after lumpectomy and mastectomy for breast cancer from the 2012 National Surgical Quality Improvement Program (NSQIP). *Ann Surg Oncol*. 2015;22:S459–S469.
46. Merchant SJ, Goldstein L, Kruper LL. Patterns and trends in immediate postmastectomy reconstruction in California: complications and unscheduled readmissions. *Plast Reconstr Surg*. 2015;136:10e–19e.
47. Jagsi R, Jiang J, Momah AO, et al. Complications after mastectomy and immediate breast reconstruction for breast cancer. *Ann Surg*. 2016;263: 219–227.
48. Azzawi K, Ismail A, Earl H, et al. Influence of neoadjuvant chemotherapy on outcomes of immediate breast reconstruction. *Plast Reconstruct Surg*. 2010;126:1–11.
49. Mitchem J, Hermann D, Margenthaler JA, et al. Impact of neoadjuvant chemotherapy on the rate of tissue expander/implant loss and progression to successful breast reconstruction following mastectomy. *Am J Surg*. 2008;196:519–522.
50. Hu W, Weeks CM, In H, et al. Impact of neoadjuvant chemotherapy on breast reconstruction. *Cancer*. 2011;117:2833–2841.

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