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Breast Reconstruction in Inflammatory Breast Cancer: An Analysis of Predictors, Trends, and Survival from the National Cancer Database

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Introduction: Survival for women diagnosed with inflammatory breast cancer (IBC) has improved with advances in multimodal therapy. This study was performed to evaluate trends, predictors, and survival for reconstruction in IBC patients in the United States.

Methods: Women who underwent mastectomy with or without reconstruction for IBC between 2004 and 2016 were included from the National Cancer Database. Predictors for undergoing reconstruction and association with overall survival were determined.

Results: Of 12,544 patients with IBC who underwent mastectomy, 1307 underwent reconstruction. Predictors of reconstruction included younger age, private insurance, higher income, performance of contralateral prophylactic mastectomy, and location within a metropolitan area ($P < 0.001$). The proportion of women having reconstruction for IBC increased from 7.3% to 12.3% from 2004 to 2016. Median unadjusted overall survival was higher in the reconstructive group l [93.7 months, 95% confidence interval (CI) 75.2–117.5] than the nonreconstructive group (68.1 months, 95% CI 65.5–71.7, hazard ratio = 0.79 95% CI 0.72–0.88, $P < 0.001$). With adjustment for covariates, differences in overall mortality were not significant, with hazard ratio of 0.95 (95% CI 0.85–1.06, $P = 0.37$).

Conclusions: Reconstruction rates for IBC are increasing. Women with IBC who undergo reconstruction tend to be younger and are not at the increased risk of all-cause mortality compared to those not having reconstruction. The National Cancer Database does not differentiate immediate from delayed reconstruction. However, the outcomes of immediate reconstruction in carefully selected patients with IBC should be further studied to evaluate its safety. This could impact current guidelines, which are based largely on an expert opinion. *(Plast Reconstr Surg Glob Open 2021;9:e3528; doi: 10.1097/GOX.0000000000003528; Published online 15 April 2021.)*

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INTRODUCTION

Inflammatory breast cancer (IBC) is an aggressive cancer accounting for up to 5% of new breast cancer diagnoses.[1] The presentation can have a wide spectrum, ranging from subtle skin erythema to diffuse breast involvement with skin dimpling and nipple retraction.[2] Treatment usually involves multimodal therapy with neoadjuvant chemotherapy, modified radical mastectomy, and adjuvant radiation.[3,4] IBC is frequently diagnosed at an earlier age and historically has carried a poor prognosis with a median survival of 15 months. However, with newer systemic therapies, outcomes have improved substantially and contemporary 5-year survival rates are reported to be between 40% and 70% with a median survival of 2–4 years.[2,3]

Though reconstruction was traditionally limited in the setting of IBC by diffuse skin involvement, high locoregional recurrence, and poor long-term survival, this

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approach has shifted in recent years with the availability of improved multimodal therapy and better survival outcomes. Previous studies have shown that reconstruction has acceptably low wound complication rates and is not associated with increased recurrence, delay in initiation of adjuvant chemoradiation, or reduced overall or cancer-specific survival.[1,5–7] Current National Comprehensive Cancer Network guidelines propose that delayed reconstruction with autologous tissue is the preferred option for patients with IBC after modified radical mastectomy and radiation.[8] Moreover, the increased rate of prophylactic contralateral mastectomy at the time of initial surgical treatment for IBC has led to additional consideration of reconstruction options at the time of resection to limit symptomatic chest wall imbalance and improve quality of life.[9,10] In this study, we sought to evaluate recent trends, predictors, and outcomes of breast reconstruction among patients in the National Cancer Database (NCDB) undergoing treatment for IBC.

METHODS

Data Source

The NCDB is a nationwide oncology outcomes database that currently captures approximately 70% of all new invasive cancer diagnosis in the United States each year and is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society.[11] The data used in the study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator. Women who underwent mastectomy with or without reconstruction for nonmetastatic IBC (cT4d or pT4d) between 2004 and 2016 were reviewed from the NCDB. The NCDB notably does not capture the timing of reconstruction (ie, immediate versus delayed) for these specific codes. We included patient sociodemographic information, tumor characteristics, and reconstruction status. Patients with unknown stage, metastatic, noninvasive, and bilateral or midline breast cancer and those who underwent breast conserving therapy, subcutaneous mastectomy, extended radical mastectomy, unspecified type of mastectomy, and care outside of their reporting facility were excluded. Additionally, patients with missing time to surgery since diagnosis, those with definitive surgery over 365 days since diagnosis, and those with additional surgery after definitive surgery were excluded from our analyses.

Statistical Analysis

Chi-square analyses and Student *t*-tests were used to determine associations between reconstruction status and sociodemographics, tumor characteristics, and treatment characteristics. The stage was reported using NCDB analytic stage. Due to the large number of variables, we initially selected characteristics associated with reconstruction (using $P < 0.10$) as potential predictors. To reduce multicollinearity, we included sociodemographic factors in a single multivariable logistic model to identify factors independently associated with reconstruction (results not shown). Similarly, we included tumor and treatment characteristics in a single multivariable logistic model to identify independent factors (results not shown). The statistically significant ($P < 0.05$) predictors from these models were included in a final multivariable logistic model, as shown in Table 1. Trends based on reconstruction status were assessed by year of diagnosis. Cochran-Armitage tests were used to assess temporal trends.

The association of reconstruction and overall survival (OS) was examined in those who had been followed at least a year from diagnosis with complete information on timing of additional therapy, which excluded those who did not have follow-up (NCDB PUF data does not include survival for most recent year of dataset, 2016), those with less than 1 year of follow-up (diagnosis in 2015), and those with missing time to medical treatment including chemotherapy, radiation, or hormonal therapy. Survival

Table 1. Logistic Regression Model for Predictors of Reconstruction

Variable	Odds Ratio	95% CI	*P*
Age, y			<0.001
18–39	2.28	1.82–2.86	
40–49	2.12	1.75–2.57	
50–59	1.36	1.13–1.64	
60–69	1.00	(Reference)	
≥70	0.42	0.31–0.58	
Year of diagnosis (continuous,1-y difference)	1.06	1.04–1.08	<0.001
Insurance			<0.001
Private insurance	1.00	(Reference)	
Medicaid	0.63	0.52–0.76	
Medicare	0.70	0.56–0.87	
Other government	0.75	0.43–1.31	
Uninsured	0.59	0.42–0.83	
Unknown	0.87	0.51–1.49	
Income			<0.001
<$38,000	1.00	(Reference)	
$38,000–$47,999	1.04	0.84–1.29	
$48,000–$62,999	1.27	1.03–1.56	
≥$63,000	1.72	1.41–2.10	
Missing	1.84	0.88–3.88	
Urban/rural continuum			<0.001
Large metropolitan	1.00	(Reference)	
Metropolitan	0.63	0.54–0.73	
Urban	0.60	0.44–0.82	
Rural	0.45	0.34–0.60	
Unknown	0.84	0.57–1.23	
Personal cancer history			0.006
First and only cancer	1.00	(Reference)	
First of >1	1.43	1.16–1.77	
Second	0.95	0.76–1.18	
Third or more; unknown	1.25	0.73–2.15	
Stage			0.020
1	1.31	1.06–1.62	
2	1.16	0.90–1.39	
3	1.00	(Reference)	
Contralateral surgery			<0.001
Ipsilateral mastectomy with CPM	2.02	1.78–2.29	
Unilateral mastectomy	1.00	(Reference)	
Initial diagnosis location			0.002
At facility	1.00	(Reference)	
Elsewhere	1.22	1.08–1.38	
Surgery at reporting facility			<0.001
Yes	1.37	1.15–1.62	
No	1.00	(Reference)	
Type of surgery			<0.001
Total mastectomy	1.00	(Reference)	
Modified radical mastectomy	0.68	0.59–0.78	
Radical mastectomy	1.11	0.78–1.57	

time was defined from diagnosis to death from any cause; patients were censored at the time of last contact. The Kaplan-Meier methods were used to construct survival curves and distributions were compared with the log rank test.

Cox proportional hazards regression models were used to examine associations between reconstruction status and overall mortality, with robust standard errors to account for clustering within facility. In a "partial adjustment" model, in addition to reconstruction, covariates included selected patient characteristics including age at diagnosis as a quadratic, race (white, black, Asian, or other) and Charlson score (0, 1, or 2+). In a "full adjustment" model, year of diagnosis, type of insurance, and analytic stage were included as additional covariates, whereas personal history of cancer (first and only, first of more than one, and second or higher) and treatment pattern (chemotherapy and/or radiotherapy and/or hormone therapy) were included as stratification variables because the proportional hazards assumption did not hold for these variables. We used 2 approaches to address immortal time bias, where one treatment group appears to have longer survival because they survived a longer treatment interval. The first was to include only those who received chemotherapy as part of their treatment, using the "full adjustment" model. The second approach was landmark analyses at 6 and 12 months, where patients who did not have at least 6 and 12 months of follow-up from diagnosis (or had died before the 6- or 12-month cutpoint) were excluded from their respective landmark analyses, again using the "full adjustment" model. Analysis was performed using SAS version 9.4.

RESULTS

There were 12,544 NCDB patients in the analytic cohort, including 11,237 (89.6%) patients who did not undergo reconstruction and 1307 (10.4%) who underwent reconstruction. Of the patients who had reconstruction, 491 (37.6%) underwent tissue-based reconstruction, 374 (28.6%) underwent implant-based reconstruction, 142 (10.9%) underwent combined tissue and implant reconstruction, and 300 had an unspecified reconstruction procedure (23.0%). The average age at diagnosis was 56.9 (Table 2). Patients who underwent reconstruction were significantly younger at diagnosis versus the nonreconstructive patients (mean age 50.8 versus 57.2 years, $P < 0.001$). Compared to nonreconstructed patients, a higher proportion of reconstructed patients had private insurance (71.8% versus 51.0%, $P < 0.001$), earned over $63,000 median household income (44.1% versus 28.2%, $P < 0.001$), and lived in large metropolitan areas (65.3% versus 49.2%, $P < 0.001$). Additionally, reconstructive patients had lower Charlson comorbidity scores (Charlson score of 0: 86.2% versus 82.5%, $P < 0.001$). Facility location and type were provided for patients age 40 and over, where reconstruction varied by geographic location ($P < 0.001$) and by type ($P < 0.001$). A greater proportion who underwent surgery lived in the Northeast region compared to nonreconstructive patients (23.3% versus 17.2%). Nearly half of patients underwent surgery at a comprehensive community cancer program (45.3%). However, a greater proportion of reconstructive patients underwent surgery at academic centers (38% versus 30.5%) and at integrated cancer network programs (16.8% versus 12.5%).

A summary of tumor characteristics is listed in Table 3. Overall, stages 1, 2, and 3 were 7%, 11%, and 82% of the analytic cohort, respectively. A higher proportion of patients who underwent reconstruction had a lower stage cancer compared to nonreconstructed patients. Of reconstructive patients, 9.8% and 13.4% had stages 1 and 2 disease, respectively, versus 6.3% and 10.7% of the nonreconstructive patients ($P < 0.001$). Because IBC is considered stage IIIB or IIIC disease, this discrepancy in the stage is related to how IBC is diagnosed, whether clinically or pathologically. IBC diagnosis was based on either clinical and/or pathologic T4d staging, which differed by reconstruction ($P < 0.001$): 71.7% of the reconstructive patients were diagnosed with IBC clinically compared to 66.5% of the nonreconstructive patients. Because the NCDB reports pathologic stage, it is likely that some patients who had clinically diagnosed IBC where reported to have a lower stage based on pathologic diagnosis, which may explain this discrepancy. Reconstructive patients also had a lower burden of nodal disease, with 25.3% having pathologic stage N0 versus 20.4% of nonreconstructed patients, and 28.2% of reconstructed patients having pathologic stage N3 compared to 33.2% of the nonreconstructed patients ($P < 0.001$).

Treatment characteristics are included in Table 4. Compared to nonreconstructed patients, a higher proportion of reconstructed patients underwent contralateral prophylactic mastectomy (CPM) (41.8% versus 21.5%, $P<0.001$), simple mastectomy (29.2% versus 21.2%, $P < 0.001$), and combined treatment with radiation, chemotherapy, and hormonal therapy (42.0% versus 37.0%, $P < 0.001$).

Predictors of Breast Reconstruction

Table 1 represents a summary of the multivariable logistic regression analysis for having breast reconstruction. Predictors of breast reconstruction in IBC included younger age, private insurance, higher median household income, patients residing in large metropolitan areas, CPM, and type of mastectomy (each $P < 0.001$). Additionally, more recent diagnosis was associated with higher odds of reconstruction [OR for a difference of 1 year = 1.06, 95% confidence interval (CI) 1.04–1.08, $P < 0.001$].

Trends in Reconstruction in IBC

Figure 1 charts the proportion of IBC patients who underwent reconstruction over time. The proportion of patients undergoing reconstruction increased from 7.3% in 2004 to 12.3% in 2016 (trend $P < 0.001$). The proportion of patients who underwent reconstruction after simple mastectomy increased from 0.8% to 4.5% (Fig. 2). There was also an increase in the proportion of patients who underwent CPM from 11.7% to 26.3% during the same time period (Fig. 3).

Table 2. Sociodemographics

Variable	Overall, N = 12,544 (%)	No Reconstruction, N = 11,237 (89.6%)	Reconstruction, N = 1307 (10.4%)	*P*
Mean age at diagnosis (y), SD	56.9, 13.2	57.6, 13.2	50.8, 11.2	<0.001
Age at diagnosis (y)				<0.001
18–39	1136 (9.1)	934 (8.3)	202 (15.5)	
40–49	2619 (20.9)	2200 (19.6)	419 (32.1)	
50–59	3739 (29.8)	3334 (29.7)	405 (31.0)	
60–69	2884 (23.0)	2662 (23.7)	222 (17.0)	
≥70	2166 (17.3)	2107 (18.8)	59 (4.5)	
Race				0.29
White	10,152 (80.9)	9097 (81.0)	1055 (80.7)	
Black	1850 (14.7)	1664 (14.8)	186 (14.2)	
Asian	284 (2.3)	254 (2.3)	30 (2.3)	
Other/missing	258 (2.1)	222 (2.0)	36 (2.8)	
Ethnicity				0.16
Hispanic	801 (6.4)	716 (6.4)	85 (6.5)	
Non-Hispanic	11,022 (87.9)	9860 (87.7)	1162 (88.9)	
Unknown	721 (5.7)	661 (5.9)	60 (4.6)	
Charlson score				<0.001
0	10,355 (82.5)	9229 (82.1)	1126 (86.2)	
1	1740 (13.9)	1584 (14.1)	156 (11.9)	
≥2	449 (3.6)	424 (3.8)	25 (1.9)	
Personal cancer history				
First and only cancer	10,104 (80.5)	9037 (80.4)	1067 (81.6)	0.012
First of >1	1013 (8.1)	890 (7.9)	123 (9.4)	
Second	1244 (9.9)	1143 (10.2)	101 (7.7)	
Third or more; unknown	183 (1.5)	167 (1.5)	16 (1.2)	
Type of insurance				<0.001
Medicaid	1569 (12.5)	1432 (12.7)	137 (10.5)	
Medicare	3484 (27.8)	3324 (29.6)	160 (12.2)	
Other government	143 (1.1)	128 (1.1)	15 (1.1)	
Uninsured	521 (4.2)	481 (4.3)	40 (3.1)	
Unknown	162 (1.3)	146 (1.3)	16 (1.2)	
Private	6665 (53.1)	5726 (51.0)	939 (71.8)	
Percentage with high-school education*				<0.001
<7 or unknown	2800 (22.3)	2401 (21.4)	399 (30.5)	
7–12.9	3984 (31.8)	3571 (31.8)	413 (31.6)	
13–20.9	3467 (27.6)	3158 (28.1)	309 (23.6)	
≥21	2293 (18.3)	2107 (18.9)	186 (14.2)	
Income*				<0.001
<$38,000	2309 (18.4)	2154 (19.2)	155 (11.9)	
$38,000–$47,999	2989 (23.8)	2762 (24.6)	227 (17.4)	
$48,000–$62,999	3422 (27.3)	3083 (27.4)	339 (25.9)	
$>63,000	3748 (29.9)	3172 (28.2)	576 (44.1)	
Missing	76 (0.6)	66 (0.6)	10 (0.8)	
Urban/rural continuum				<0.001
Large metropolitan	6382 (50.9)	5529 (49.2)	853 (65.3)	
Metropolitan	3810 (30.4)	3508 (31.2)	302 (23.1)	
Urban	746 (5.9)	696 (6.2)	50 (3.8)	
Rural	1293 (10.3)	1228 (10.9)	65 (5.0)	
Unknown	313 (2.5)	276 (2.5)	37 (2.8)	
Distance from facility (miles)				0.47
<10	6450 (51.4)	5764 (51.3)	686 (52.5)	
21–20	2864 (22.8)	2556 (22.7)	308 (23.6)	
21–40	1748 (13.9)	1577 (14.0)	171 (13.1)	
>40 or unknown	1482 (11.8)	1340 (11.9)	142 (10.9)	
Initial diagnosis location				<0.001
At facility	7307 (58.3)	6623 (58.9)	684 (52.3)	
Elsewhere	5237 (41.7)	4614 (41.1)	623 (47.7)	
Facility geographic location†				<0.001
Northeast	2031 (17.8)	1774 (17.2)	257 (23.3)	
Southern	4365 (38.2)	3987 (38.7)	378 (34.2)	
Midwest	3158 (27.7)	2858 (27.8)	300 (27.2)	
Western	1854 (16.3)	1684 (16.4)	170 (15.4)	
Facility type†				<0.001
Community cancer program	1203 (10.5)	1150 (11.2)	53 (4.8)	
Comprehensive community cancer program	5164 (45.3)	4718 (45.8)	446 (40.4)	
Academic program	3563 (31.2)	3143 (30.5)	420 (38.0)	
Integrated network cancer	1478 (13)	1292 (12.5)	186 (16.8)	

*Median household income and percentage of patients with at least high-school education in zipcode.
†Data missing for patients < 40 years old.

Reconstruction and OS

The survival cohort (those followed at least 1 year with complete timing information on chemotherapy, radiotherapy, and hormone therapy) included 9738 patients with 4781 deaths. The unadjusted median OS was 70.2 months (95% CI 67.0–73.8) for the survival cohort. OS differed by reconstruction ($P < 0.001$), with median OS of 93.7 months (95% CI 72.2–117.5) for the reconstruction

Table 3. Tumor Characteristics

Variable	Overall, N = 12,544 (%)	No Reconstruction, n = 11,237 (%)	Reconstruction, N = 1307 (%)	*P*
Grade				0.25
1	317 (2.5)	293 (2.6)	24 (1.8)	
2	3266 (26)	2902 (25.8)	364 (27.9)	
3	7279 (58)	6533 (58.1)	746 (57.1)	
4	131 (1)	120 (1.1)	11 (0.8)	
Unknown	1551 (12.4)	1389 (12.4)	162 (12.4)	
The American Joint Committee on Cancer stage				<0.001
1	832 (6.6)	704 (6.3)	128 (9.8)	
2	1381 (11.0)	1206 (10.7)	175 (13.4)	
3	10,331 (82.4)	9327 (83)	1004 (76.8)	
IBC diagnosis				<0.001
Clinical	8408 (67.0)	7471 (66.5)	937 (71.7)	
Pathology	1688 (13.5)	1533 (13.6)	155 (11.9)	
Both	2448 (19.5)	2233 (19.9)	215 (16.4)	
Tumor size				0.23
≤20 mm	1522 (12.1)	1372 (12.2)	150 (11.5)	
21–50 mm	3173 (25.3)	2857 (25.4)	316 (24.2)	
>50 mm	3831 (30.5)	3400 (30.3)	431 (33.0)	
Unknown	4018 (32)	3608 (32.1)	410 (31.4)	
Pathologic N stage				<0.001
N0 (0 nodes)	2622 (20.9)	2291 (20.4)	331 (25.3)	
N1 (1–3)	3166 (25.2)	2823 (25.1)	343 (26.2)	
N2 (4–9)	1300 (10.4)	1166 (10.4)	134 (10.3)	
N3 (≥10)	4095 (32.6)	3727 (33.2)	368 (28.2)	
None examined	819 (6.5)	748 (6.7)	71 (5.4)	
Unknown	541 (4.3)	481 (4.3)	60 (4.6)	
Estrogen receptor status				0.63
Negative/borderline	5662 (45.1)	5088 (45.3)	574 (43.9)	
Positive	6541 (52.1)	5843 (52.0)	698 (53.4)	
Missing	341 (2.7)	306 (2.7)	35 (2.7)	
Progesterone receptor status				0.36
Negative/borderline	7102 (56.6)	6343 (56.4)	711 (54.4)	
Positive	5097 (40.6)	4542 (40.4)	555 (42.5)	
Missing	345 (2.8)	352 (3.1)	41 (3.1)	
HER2 receptor status*				0.58
Negative or borderline	4476 (65.1)	3936 (65.3)	540 (63.8)	
Positive	2219 (32.3)	1933 (32.1)	286 (33.8)	
Missing	177 (2.6)	157 (2.6)	20 (2.4)	
Overall ER/PR status				0.71
ER–, PR– incl borderline	5374 (42.8)	4827 (43.0)	547 (41.9)	
ER+ and/or PR+	6824 (54.4)	6099 (54.3)	725 (55.5)	
Missing	346 (2.8)	311 (2.8)	35 (2.7)	

*HER2 receptor status collected by NCDB starting in 2010.
ER, estrogen receptor; PR, progesterone receptor.

group versus 68.1 months (95% CI 65.5–71.7) for the nonreconstructive group. Unadjusted OS and survival estimates are represented in Figure 4.

The unadjusted overall mortality hazard ratio (HR) for reconstruction versus no reconstruction was 0.79 (95% CI 0.72–0.88, $P < 0.001$). After adjustment for age, race, and Charlson score, the HR was 0.91 (95% CI 0.82–1.02, $P = 0.08$). After further adjustments for insurance, stage, and year of diagnosis with stratification by cancer history and treatment pattern, the HR was 0.95 (95% CI 0.85–1.06, $P = 0.35$) (Table 5). A landmark analysis for patients who were alive for at least 6 and 12 months was also performed. The HR in the landmark analysis was 0.94 (95% CI 0.844–1.043, $P = 0.24$) and 0.97 (05% CI 0.87–1.09, $P = 0.62$) at 6 and 12 months, respectively.

DISCUSSION

Before the introduction of systemic chemotherapy, surgery with or without radiation resulted in median survival of less than 15 months in IBC. The 5-year survival rates were reported to be 5%–24% for patients treated with surgery and radiation without neoadjuvant chemotherapy.[12,13] With the introduction of multimodal therapy incorporating neoadjuvant chemotherapy, the 5-year survival rates increased to 40%–70%, whereas the 10- and 15-year survival rates are up to 35% and 20%–30%, respectively.[2,3,12–16] There is increasing evidence that both clinical and pathologic responses to neoadjuvant chemotherapy in IBC are reliable prognostic indicators and are correlated with survival.[13,14,17] Objective response rates of up to 80% have been reported after neoadjuvant chemotherapy and many patients can be disease free with the addition of surgery and radiation. The rate of pathologic complete response is between 15% and 40% for anthracycline-based chemotherapy and about 28% for methotrexate- or doxorubicin-based chemotherapy.[13,15] Multiple studies have demonstrated significantly better outcomes in patients who achieve a pathologic complete response, with OS ranging from 82.5% to 89% at 5 years and 45% at 10 years in patients with complete response to multimodal therapy compared to 37.1%–64% at 5 years and 31% at 10 years in patients with residual disease.[13,18,19] It is evident that neoadjuvant systemic therapy defines

Table 4. Treatment Characteristics

Variable	Overall, N = 12,544 (%)	No Reconstruction, N = 11,237 (%)	Reconstruction, N = 1307 (%)	*P*
Surgery at reporting facility				0.024
No	2192 (17.5)	1993 (17.7)	199 (15.2)	
Yes	10,352 (82.5)	9244 (82.3)	1108 (84.8)	
Contralateral prophylactic mastectomy				<0.001
Yes	2965 (23.6)	2419 (21.5)	546 (41.8)	
No	9579 (76.4)	8818 (78.5)	761 (58.2)	
Type of mastectomy				<0.001
Simple mastectomy	2767 (22.1)	2385 (21.2)	382 (29.2)	
Modified radical mastectomy	9470 (75.5)	8590 (76.4)	880 (67.3)	
Radical mastectomy	307 (2.4)	262 (2.3)	45 (3.4)	
Regional lymph node surgery				0.32
Yes	11,929 (95.1)	10,675 (95.0)	1254 (95.9)	
No or unknown	615 (4.9)	562 (5.0)	53 (4.1)	
Treatment pattern*				<0.001
Chemotherapy + radiation + hormonal	4708 (37.5)	4159 (37.0)	549 (42.0)	
Chemotherapy + radiation	4641 (37.0)	4171 (37.1)	470 (36.0)	
Chemotherapy + hormonal	675 (5.4)	609 (5.4)	66 (5.0)	
Chemotherapy only	1818 (14.5)	1633 (14.5)	185 (14.2)	
Radiation and/or hormonal	410 (3.3)	389 (3.4)	21 (1.6)	
None	292 (2.3)	276 (2.5)	16 (1.2)	
Readmission within 30 d				0.45
None	11,614 (92.6)	10,405 (92.6)	1209 (92.5)	
Planned readmission, any	260 (2.1)	233 (2.0)	27 (2.1)	
Unplanned readmission only	235 (1.9)	206 (1.8)	29 (2.2)	
Unknown	435 (3.5)	393 (3.5)	42 (3.2)	

*In addition to surgery with or without immunotherapy.

long-term outcomes for patients with IBC and determines feasibility for undergoing mastectomy. Patients who have a good response to neoadjuvant chemotherapy are deemed appropriate candidates for mastectomy and lymph node dissection. Multiple studies have shown that surgery with adjuvant radiation improves local control and disease-free survival for patients who respond well to primary chemotherapy, whereas patients whose disease does not respond to chemotherapy do not derive such benefits.[4,12,20] As such, patients who achieve a good response to neoadjuvant chemotherapy and proceed to mastectomy and adjuvant radiation have potential for long-term survival.

Overall, postmastectomy breast reconstruction nearly doubled between 1998 and 2007.[21] In IBC, breast reconstruction is becoming more prevalent as well. This is demonstrated by our analysis, which shows the proportion of patients who underwent postmastectomy breast reconstruction for IBC increased by 5% from 2004 to 2016. The odds of undergoing breast reconstruction were increased by 6% each year during that period. It is likely that advances in multimodal therapy and operative techniques have

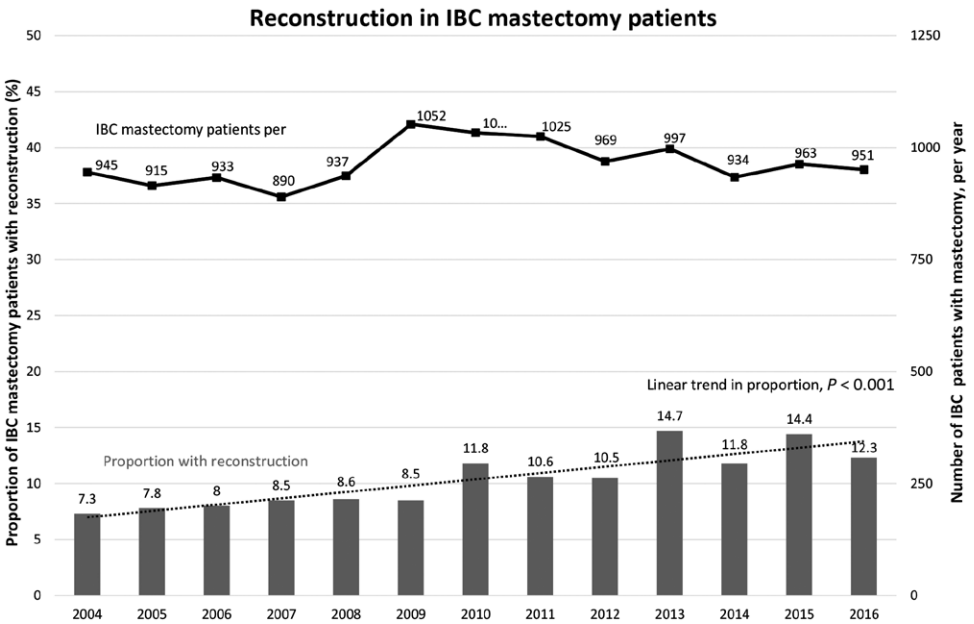

Fig. 1. Proportion of patients with IBC who underwent reconstruction over time.

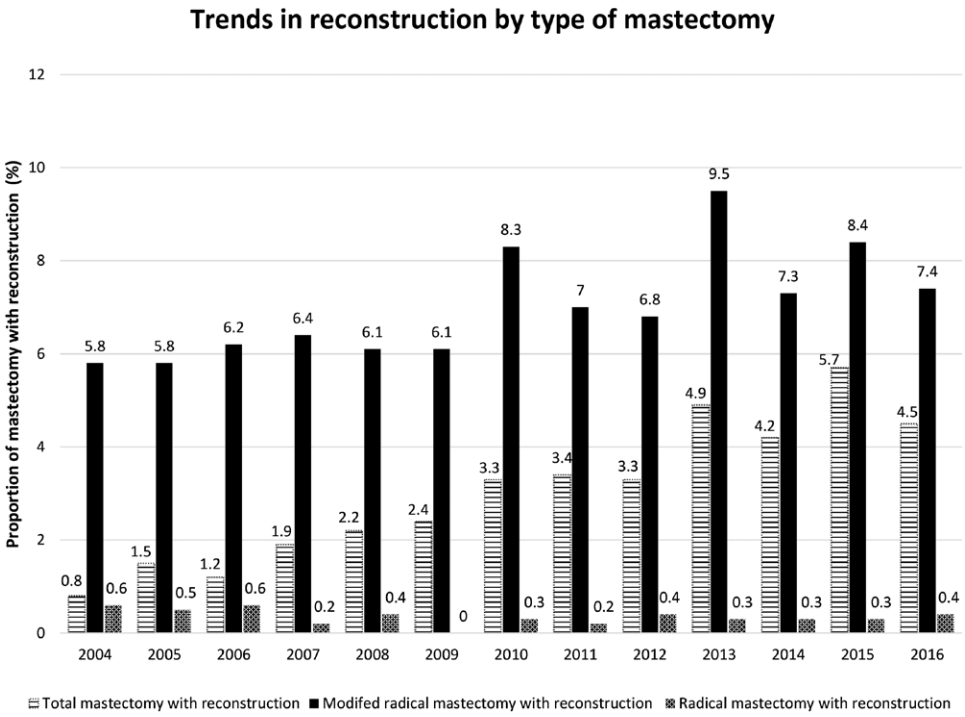

Fig. 2. Proportion of patients with IBC who underwent reconstruction based on type of mastectomy.

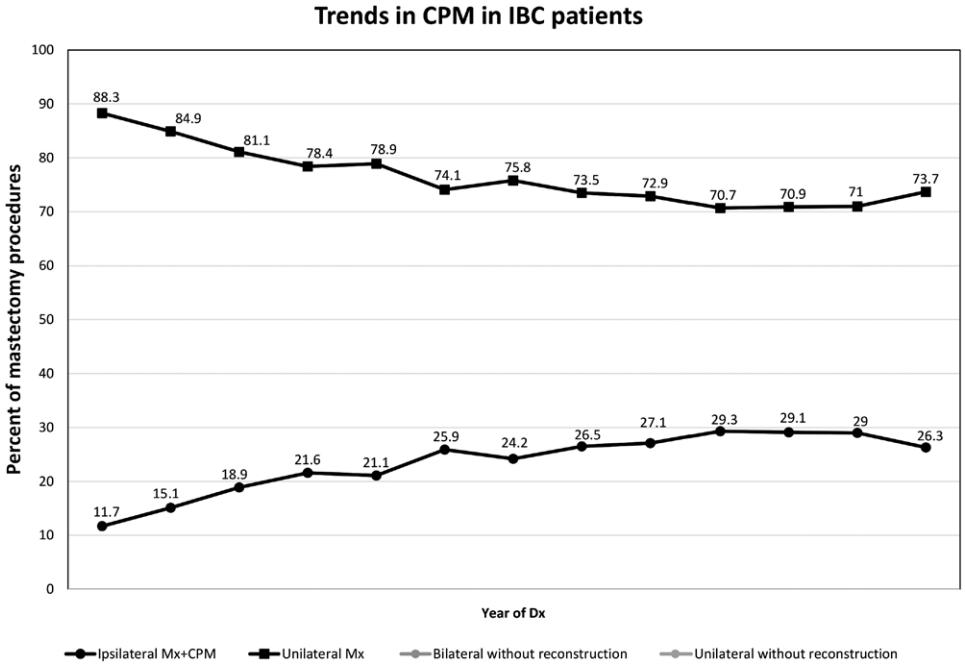

Fig. 3. Proportion of IBC patients who underwent mastectomy and those who underwent mastectomy with CPM.

resulted in improved survival rates and contributed to this trend. In a SEER population study from the years 1998 to 2000, Hance et al[2] reported a median survival of 2.9 years for women with IBC compared to >10 and 6.4 years for women with non-T4 breast cancer and locally advanced breast cancer, respectively. Our study demonstrated an OS of approximately 5.9 years, suggesting an improvement in IBC survival over time. Patients who did not undergo eventual reconstruction had a lower OS at 5.7 years, whereas reconstructed patients had an OS of 7.8 years. It is likely that patients who have a better prognosis based on cancer stage, age at diagnosis, response to neoadjuvant therapy,

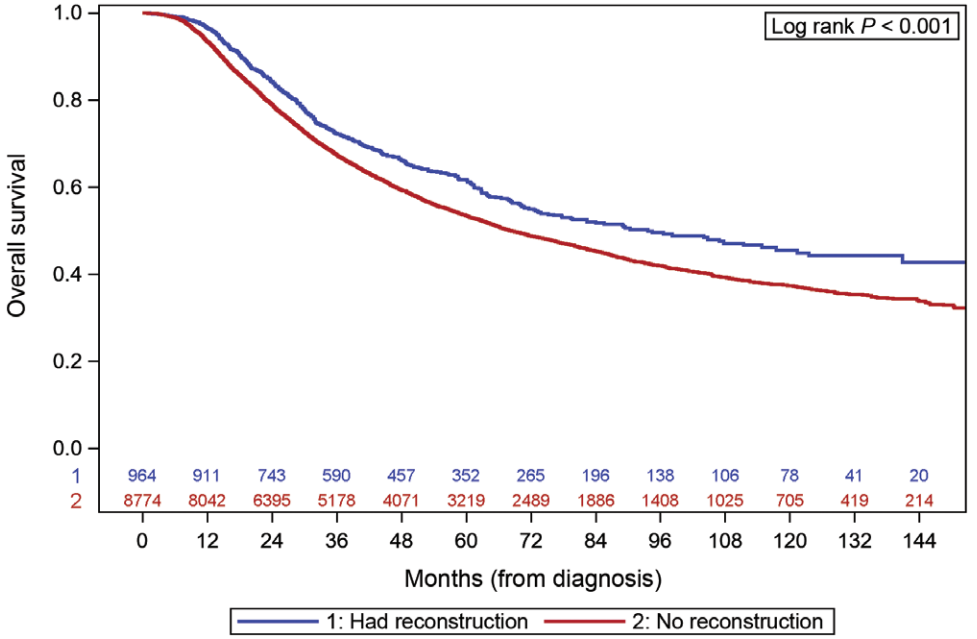

Fig. 4. Survival probability for IBC patients with and without breast reconstruction over time since diagnosis.

Table 5. Association of Reconstruction with Overall Mortality

	N Patients by Reconstruction			HR for Reconstruction vs No Reconstruction		
	N Patients	No	Yes	HR Estimate	95% CI	*P*
Unadjusted: reconstruction status only (ie, with no covariates)	9738	8774	964	0.79	0.72–0.88	<0.001
Partial adjustment: adjusts for age, race, and Charlson score	9738	8774	964	0.91	0.82–1.01	0.081
Full adjustment: in addition, adjusts for cancer history, treatment, insurance, stage, and diagnosis year	9738	8774	964	0.95	0.86–1.06	0.35
Subset analysis: only those with chemotherapy as part of treatment, with full adjustment covariates	9202	8263	939	0.95	0.85–1.06	0.37
Landmark analysis (6 mo): excludes those with <6 mo follow-up, with full adjustment covariates	9620	8667	953	0.94	0.84–1.04	0.24
Landmark analysis (12 mo): excludes those with <12 mo follow-up, with full adjustment covariates	8953	8042	911	0.97	0.87–1.09	0.62

Results of separate Cox models for covariate adjustment.

and comorbidities are more likely to undergo reconstruction and have higher observed survival. As the NCDB does not differentiate between immediate and delayed reconstruction, no recommendations can be made as to which patients may be good candidates for immediate reconstruction. Additionally, we observed an increase in the rate of CPM from 2004 to 2016 by 14.6%, concordant with prior studies, and this may further have contributed to the greater proportion of women undergoing breast reconstruction for IBC over time. This is further supported by our finding that CPM was a positive predictor of breast reconstruction.

Younger patients' age was also shown to be a strong predictor of postmastectomy breast reconstruction in several studies.[21–25] This study demonstrates a similar finding in IBC. Women with IBC who underwent reconstruction were on average 6.5 years younger than patients who did not undergo reconstruction. Women younger than 50 years were more than twice as likely to undergo reconstruction, whereas women older than 70 years were about 6 times less likely to undergo reconstruction. Breast reconstruction in the elderly has been reported to be safe, with acceptable outcomes and well-established psychosocial benefits comparable to younger patients.[26–30] There is a debate surrounding why older patients are less likely to undergo breast reconstruction. It is possible that the psychosocial benefits of breast reconstruction may be more valued in younger patients. Elderly patients may be less likely to elect for reconstructive surgery given misconceptions about complications, and they are less frequently offered postmastectomy reconstruction by their providers according to prior reports.[25,28,29] However, there is paucity of such data for patients specifically with IBC. It is possible that a lower proportion of elderly patients with IBC are offered reconstruction given its higher overall mortality compared with other types of breast cancer. In this study, older women with IBC were found to have a slightly increased risk of mortality. For example, when evaluating

5-year age differences, the HR for patients 75-years-old was 1.11 versus patients who are 70-years-old. This increased risk of mortality may be related to increased comorbidities in the elderly population.[25]

Additionally, there are disparities in the receipt of postmastectomy reconstruction by socioeconomic factors such as race, income, education, and insurance.[21,22,31] Prior studies demonstrated that being non-white, not having private insurance, and living in an area with lower median income and lower rates of high-school education were associated with a lower likelihood of undergoing breast reconstruction.[22,31] Our study reported similar results in the setting of IBC as patients who were uninsured or with government-based insurance (Medicaid, Medicare), resided in urban or rural areas, and earned a lower income were less likely to undergo breast reconstruction. This may be related to barriers to healthcare access faced by lower-income patients. Additionally, providers may be less likely to offer reconstruction for patients who are unemployed or uninsured. This represents a widening of the economic healthcare gap as prior studies have demonstrated a lack of equivalent gain in breast cancer survival in low-income groups.[32–36]

Debate exists regarding immediate breast reconstruction (IBR) in the setting of IBC given concerns over poor OS, recurrence, need for postmastectomy radiation, and delays in treatment. However, the benefits of IBR are well-established. The psychosocial, emotional, and functional benefits of breast reconstruction are clear.[37] Additionally, the OS for IBC has improved with multimodality therapy as previously mentioned, especially for those with a good response to chemotherapy. Although IBR has been historically discouraged in the setting of IBC on the basis of expert opinion rather than randomized trials, more recent reports suggest acceptable outcomes without decreased survival or increased recurrence rates.[1,5,16,38,39] The benefits of skin-sparing mastectomy and IBR are lost when wider skin resections are necessary, as is often the case with IBC. In patients with good response to neoadjuvant chemotherapy, a more limited skin resection may be possible, thereby facilitating improved aesthetic outcomes with IBR. However, although patients may have a good response to neoadjuvant chemotherapy clinically, they may not have complete pathologic response and require wider resection margins. Patients who are likely to benefit from IBR are those who are more likely to have a complete pathologic response to neoadjuvant chemotherapy. Therefore, determining which patients are more likely to have a pathologic response to neoadjuvant chemotherapy is important when deciding whether or not to perform IBR in the setting of IBC. Our data did not discriminate between immediate and delayed reconstruction due to limitations of the NCDB. This distinction is important as there has been a historical concern that IBR may delay necessary adjuvant therapy and therefore influence breast cancer–specific mortality. Although IBR may be associated with higher perioperative complications compared to delayed reconstruction in the IBC population, previous studies have suggested IBR to be oncologically safe compared to no reconstruction.[1,5] Prior studies have suggested that patients experiencing delays of more than 90 days in delivery of chemotherapy had worse OS and cancer-specific survival, and those who experienced a delay in radiotherapy more than 8 weeks had increased locoregional recurrence.[40,41] However, there is inconsistent data regarding the impact of IBR on the delivery of adjuvant therapy. Although postoperative complications are associated with treatment delays, a recent prospective study by O'Connell et al[42] demonstrated that IBR did not result in clinically significant delays to adjuvant therapy. Similar to our results, patients who underwent IBR were significantly younger and had fewer risk factors, suggesting that surgeons are cautious in offering IBR to patients who will require adjuvant therapy. However, it is likely that IBR does not lead to clinically significant delays in low-risk patients. Regardless of the procedure type, it is likely that postoperative complications are the main predictors of adjuvant treatment delays.[42] This highlights the importance of reducing complications through careful patient selection to improve outcomes of breast reconstruction.

Another concern for IBR in the IBC setting is the need for postmastectomy radiation. For patients requiring postmastectomy radiotherapy, irradiating an immediate deep inferior epigastric perforator (DIEP) flap may have negative effects on an aesthetic outcome. However, a retrospective study demonstrated no significant difference in the aesthetic outcome between immediate DIEP flap reconstruction with radiotherapy versus delayed DIEP flap with radiotherapy with or without a temporizing implant, although women undergoing delayed reconstruction were more satisfied overall.[43]

There is often discrepancy in variables in large datasets between clinical and pathologic data and staging. In this study, patients with T4d (whether diagnosed clinically or pathologic) are determined to have IBC. However, although nonmetastatic IBC is a stage IIIB or IIIC cancer, our cohort had 832 patients designated as stage I and 1381 designated as stage II. The American Joint Committee on Cancer relies on clinical features of IBC and considers pathologic features supportive, but not necessary for diagnosis.[2] It is likely that some patients were diagnosed with IBC clinically (cT4d) and later downstaged on pathology. In this study, more reconstructive patients were diagnosed with clinically defined IBC than nonreconstructive patients (72% versus 67%), and less reconstructive patients were diagnosed with pathologically defined IBC than nonreconstructive patients (14% versus 12%). This may represent further selection bias as patients with pathologically defined IBC have slightly shorter median survival times than patients with IBC defined clinically only (2.3 versus 3 years).[2] Additionally, patients with stage I breast cancer were more likely to undergo reconstruction in this study (OR 1.31, 95% CI 1.06–1.62, $P = 0.013$), indicating further selection bias.

CONCLUSIONS

Despite historic reluctance to perform breast reconstruction in the setting of IBC, advances in multimodal treatment have led to an increasing number of patients

undergoing eventual reconstruction in recent years with demonstrably good outcomes in carefully selected patients. Women who undergo reconstruction tend to be younger, have higher socioeconomic status, are more likely to have had CPM, and have a lower burden of disease based on staging. However, the number of patients who undergo reconstruction in the setting of IBC remains low. In this study, survival in women with IBC who undergo eventual reconstruction is similar to patients who undergo mastectomy without reconstruction after adjusting for age, comorbidities, and other patient or treatment-specific factors. Future evaluation of the safety of immediate reconstruction in select patients with IBC may further impact treatment guidelines.

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