

Complications After Mastectomy and Immediate Breast Reconstruction for Breast Cancer

A Claims-based Analysis

Reshma Jagsi, MD, DPhil,* Jing Jiang, MS,† Adeyiza O. Momoh, MD,‡ Amy Alderman, MD, MPH,§ Sharon H. Giordano, MD, MPH,¶ Thomas A. Buchholz, MD,|| Lori J. Pierce, MD,* Steven J. Kronowitz, MD,** and Benjamin D. Smith, MD||

Objective: To evaluate complications after postmastectomy breast reconstruction, particularly in the setting of adjuvant radiotherapy.

Background: Most studies of complications after breast reconstruction have been conducted at centers of excellence; relatively little is known about complication rates in irradiated patients treated in the broader community. This information is relevant for decision making in patients with breast cancer.

Methods: Using the claims-based MarketScan database, we described complications in 14,894 women undergoing mastectomy for breast cancer from 1998 to 2007 and who underwent immediate autologous reconstruction (n = 2637), immediate implant-based reconstruction (n = 3007), or no reconstruction within the first 2 postoperative years (n = 9250). We used a generalized estimating equation to evaluate associations between complications and radiotherapy over time.

Results: Wound complications were diagnosed within the first 2 postoperative years in 2.3% of patients without reconstruction, 4.4% patients with implants, and 9.5% patients with autologous reconstruction ($P < 0.001$). Infection was diagnosed within the first 2 postoperative years in 12.7% of patients without reconstruction, 20.5% with implants, and 20.7% with autologous reconstruction ($P < 0.001$). A total of 5219 (35%) women received radiation. Radiation was not associated with infection in any surgical group within the first 6 months but was associated with an increased risk of infection in months 7 to 24 in all 3 groups (each $P < 0.001$). In months 7 to 24, radiation was associated with higher odds of implant removal in patients with implant re-

construction (odds ratio = 1.48; $P < 0.001$) and fat necrosis in those with autologous reconstruction (odds ratio = 1.55; $P = 0.01$).

Conclusions: Complication risks after immediate breast reconstruction differ by approach. Radiation therapy seems to modestly increase certain risks, including infection and implant removal.

Keywords: breast cancer, breast reconstruction, complications, mastectomy, radiation therapy

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An increasing proportion of American patients with breast cancer undergo breast reconstruction after mastectomy.^{1–6} Reconstruction can be accomplished using a variety of techniques that can involve the use of autologous tissues, implants, or a combination of the two. Patient factors (such as body habitus, comorbidities, and prior surgical procedures) affect which techniques are actually offered in any particular case, but many patients have a choice with respect to approach. To make decisions in this context, patients and their physicians must consider evidence regarding pertinent outcomes such as cosmetic satisfaction and complications with each approach.

Existing evidence suggests that satisfaction may vary considerably depending on technique,⁷ and complication rates are substantial.⁸ Patients who require postmastectomy radiation therapy may be particularly vulnerable to postreconstruction complications.⁹ Previous studies have suggested that radiation increases the risk of complications, both in patients receiving breast implants^{10–15} and in those undergoing autologous reconstruction,^{16–18} although many patients seem to successfully undergo both radiation and breast reconstruction when treated with a systematic and carefully considered approach.^{19–23} Unfortunately, most of these studies have come from centers of excellence, such as academic institutions, high-volume centers, or specialty practices; relatively little is known about complication rates in irradiated patients treated in the broader community.

Therefore, additional research is necessary to investigate the rates of complications that occur in patients undergoing breast reconstruction with different approaches, both with and without radiotherapy, given growing evidence of the importance of radiation therapy in improving not only locoregional control but also overall survival of appropriately selected patients.^{24–27} Therefore, we sought to evaluate surgical complications occurring within the first 2 postoperative years in a working-age, commercially insured sample of patients with breast cancer who underwent mastectomy and immediate breast reconstruction. We specifically sought to document complication rates over time in patients who did and did not receive radiation treatment.

METHODS

Data Set

We utilized the proprietary MarketScan Commercial Claims & Encounters database, licensed by Truven Health Analytics. This large,

From the *Department of Radiation Oncology, University of Michigan, Ann Arbor, MI; †Division of Quantitative Sciences, The University of Texas MD Anderson Cancer Center, Houston, TX; ‡Section of Plastic Surgery, University of Michigan Health System, Ann Arbor, MI; §The Swan Center for Plastic Surgery, Alpharetta, GA; ¶Departments of Health Services Research and Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; ||Division of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; and **Department of Plastic Surgery, Baylor College of Medicine, Houston, TX. Dr Alderman is in private practice in Alpharetta, GA.

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Reprints: Reshma Jagsi, MD, DPhil, Department of Radiation Oncology, University of Michigan, NCR 2800 Plymouth Rd, Bldg 16/420W, Ann Arbor, MI 48109. E-mail: rjagsi@med.umich.edu.

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nationwide, employment-based database includes medical claims data of employees and dependents from approximately 45 large employers covered by more than 100 payers. Initially, the database included only clients whose coverage was provided through large, self-insured companies; in 2002, the data set was expanded to include health plan clients—employees and dependents receiving insurance coverage through small and medium-sized firms.

For the current analysis, we used claims collected from 1998 to 2009 derived from individuals identified as having a cancer diagnosis.

Cohort Selection and Definitions

As previously described¹ and detailed further in Supplemental Digital Content Table 1 (available at <http://links.lww.com/SLA/A763>), a validated, claims-based algorithm identified incident cases of female breast cancer treated with mastectomy between 1998 and 2007 (n = 44,735).²⁸ Given our intention to study complications within the first 2 years of mastectomy, we limited our cohort to individuals with continuous enrollment from 3 months before to 23 months after mastectomy (n = 24,141). To enhance specificity, the cohort was then limited to patients without distant metastasis (as reconstruction is rarely performed in patients with metastatic disease), without radiation within 3 months before mastectomy (as this is uncommon and indicates extremely advanced disease), and at least 2 or more diagnosis codes for invasive or in situ breast cancer (which limits the impact of miscoding), leaving a sample size of 20,560. Of note, only patients with breast cancer were included; those undergoing prophylactic mastectomy for genetic risk or other reasons were not included.

To allow for comparative analyses of complications within the first 2 postoperative years, we limited our analytic sample to patients undergoing mastectomy and falling into 1 of 3 groups: those without claims for reconstruction within 2 years of mastectomy; those with claims for implant-based reconstruction on the same date as mastectomy (including placement of either a permanent breast implant or a temporary tissue expander, followed later by placement of a permanent implant); and those with claims for autologous tissue-based reconstruction on the same date as mastectomy. Patients who fell outside these criteria—including those patients who had claims for reconstruction on a date subsequent to their mastectomy but not on the date of mastectomy and those who had claims for both autologous and implant-based procedures—were omitted to ensure adequate numbers and homogeneity within each group and the same duration of follow-up in each group to allow for meaningful comparisons. Receipt of breast reconstruction was determined using *Common Procedural Terminology (CPT)* and *International Classification of Diseases, Ninth Revision (ICD-9)*, procedure codes indicating breast reconstruction (see Supplemental Digital Content Table 2, available at <http://links.lww.com/SLA/A763>) performed on the same date as mastectomy. The final analytic cohort included 14,894 patients.

Outcomes

We evaluated 3 general outcomes of interest in all patients: (1) 30-day rehospitalization, (2) wound complications within the first 2 postoperative years, and (3) skin or soft-tissue infections within the first 2 postoperative years. In addition, among patients undergoing implant-based reconstruction, we considered the outcome of implant removal within the first 2 postoperative years; of note, this included removal of the implant for any reason, including exchange of the implant (not necessarily permanent loss). Among those undergoing autologous tissue-based reconstruction, we considered the outcome of fat necrosis. The claims codes used to define these outcomes were derived after consideration of previous algorithms used to measure these outcomes^{29–31} are listed in Supplemental Digital Content Table 3 (available at <http://links.lww.com/SLA/A763>). These out-

comes were selected because they are outcomes that can be measured using administrative claims and for which detailed risk information would be expected to be useful for surgical decision making and decision satisfaction. Length of hospitalization for the index mastectomy with or without reconstruction was also determined, calculated as the number of days from admission to discharge, counting the admission date as day 1. Some patients were admitted on the day after mastectomy. Because this could reflect patients initially held in 24-hour observation who were subsequently converted to inpatient hospitalization, these events were considered hospitalization for the index mastectomy and length of stay was calculated from the date of mastectomy to the date of discharge. To be consistent with this definition, the outcome rehospitalization within 30 days was defined as any hospitalization that occurred between the 2nd day and the 30th day after index mastectomy.

Covariates

The MarketScan enrollment file provided data on age, geographic region (Northeast, North Central, South, or West), relationship to employer (employee vs spouse), and insurance type (health maintenance organization or capitated preferred provider organization vs noncapitated plan types). Year of mastectomy, laterality of mastectomy (bilateral vs unilateral), lymph node surgery (yes/no), chemotherapy (no, before mastectomy, or after mastectomy), and radiation (yes/no) were determined from claims (see Supplemental Digital Content Table 2, available at <http://links.lww.com/SLA/A763>).

Statistical Analysis

For our initial analyses, all outcomes were classified as binary variables, with patients considered to have experienced the outcome of interest if any claims code indicating the outcome of interest was present within 2 years of index mastectomy. For these binary outcomes, unadjusted associations between covariates and outcomes were tested using the Pearson χ^2 test. Multivariable logistic models for each binary outcome were created, with type of reconstructive surgery (none, implant, autologous), receipt of radiation, receipt of chemotherapy, and age included a priori due to clinical relevance. Additional covariables were included if significant in unadjusted analysis at $P < 0.20$. Models were iteratively refined to minimize collinearity. Goodness of fit was evaluated using the test of Hosmer and Lemeshow. For each model, the interaction term for type of reconstructive surgery with radiation was tested to determine whether radiation exerted a differential effect limited to certain reconstructive strategies.

To account for the distribution of events over time, and their temporal relationship relative to initiation of radiation therapy, we further divided outcomes on a month-by-month basis, with the outcome for month j equal to 1 if any claim for the outcome was present in month j , otherwise the outcome for month j was set to zero. Furthermore, we a priori grouped outcomes into those that occurred in months 1 to 6 after mastectomy and those that occurred in months 7 to 24. These intervals were chosen on the basis of the median time from mastectomy to initiation of radiation such that outcomes in the early interval generally reflected events that occurred before the completion of radiation and outcomes in the late interval generally reflected events that occurred during and after radiation, if radiation was administered. For each outcome, we used generalized estimating equations, adjusted for age, receipt of chemotherapy, bilaterality, and year of diagnosis, to estimate the association between receipt of radiation and the outcome of interest for both the time intervals. In certain cases, models had to be iteratively refined to ensure convergence.

Patients with missing covariate values were excluded from all multivariable analyses. All analyses were conducted using SAS v9.2 (Cary, NC) using 2-sided statistical tests. This project was granted

exempt status by the University of Texas MD Anderson institutional review board.

RESULTS

Among the 14,894 patients in the analytic sample, median age was 52 years (interquartile range = 46–57 years). As described in Table 1, surgery type varied significantly by age. For example, 40.4% of women younger than 40 years underwent mastectomy without reconstruction, 36.1% mastectomy with immediate implant-based reconstruction, and 23.5% mastectomy with autologous reconstruction; in contrast, 78.9% of women 60 years and older underwent mastectomy without reconstruction, 11.8% mastectomy with immediate implant-based reconstruction, and 9.3% mastectomy with immediate

autologous reconstruction. In this sample, 19.0% (n = 2831) of patients were in health maintenance organizations or capitated preferred provider organizations and nearly half were from the South. Overall, 11.6% underwent bilateral mastectomy, 52.4% received chemotherapy, and 35.0% received radiation therapy (of whom 22.2% underwent immediate reconstruction, as compared with 46.3% of those who did not receive radiation therapy).

Overall, slightly more than half (52.2%) of women undergoing mastectomy without reconstruction were hospitalized for their index surgery; most (74.6%) of those undergoing immediate implant-based reconstruction and almost all (96.0%) of those undergoing immediate autologous reconstruction were hospitalized. Among those who were hospitalized, the median length of stay was 2 days for those

TABLE 1. Baseline Characteristics and Type of Surgery

	Entire Cohort (n = 14,894)		Mastectomy and No Reconstruction (n = 9250)		Mastectomy and Immediate Implant-based Reconstruction (n = 3007)		Mastectomy and Immediate Autologous Reconstruction (n = 2637)		P*
	n	Column %	n	Row %	n	Row %	n	Row %	
Age at diagnosis, yr									<0.001
<40	1122	7.5	453	40.4	405	36.1	264	23.5	
40–49	4378	29.4	2209	50.5	1203	27.5	966	22.1	
50–59	7378	49.5	4997	67.7	1162	15.8	1219	16.5	
60 and older	2016	13.5	1591	78.9	237	11.8	188	9.3	
Year of mastectomy									<0.001
1998	381	2.6	258	67.7	30	7.9	93	24.4	
1999	592	4.0	394	66.6	59	10.0	139	23.5	
2000	608	4.1	410	67.4	58	9.5	140	23.0	
2001	874	5.9	566	64.8	118	13.5	190	21.7	
2002	1362	9.1	935	68.7	190	14.0	237	17.4	
2003	1749	11.7	1166	66.7	328	18.8	255	14.6	
2004	1779	11.9	1088	61.2	321	18.0	370	20.8	
2005	1829	12.3	1109	60.6	385	21.1	335	18.3	
2006	2537	17.0	1547	61.0	592	23.3	398	15.7	
2007	3183	21.4	1777	55.8	926	29.1	480	15.1	
Relationship with employer									0.26
Employee	8698	58.4	5372	61.8	1765	20.3	1561	18.0	
Spouse	6177	41.5	3863	62.5	1238	20.0	1076	17.4	
Unknown	19	0.1	15	79.0	4	21.1	0	0.0	
HMO or PPO with capitation									<0.001
No	12063	81.0	7506	62.2	2366	19.6	2191	18.2	
Yes	2831	19.0	1744	61.6	641	22.6	446	15.8	
Region of country									<0.001
Northeast	1180	7.9	624	52.9	251	21.3	305	25.9	
North Central	3802	25.5	2360	62.1	863	22.7	579	15.2	
South	7234	48.6	4433	61.3	1321	18.3	1480	20.5	
West	2456	16.5	1683	68.5	544	22.2	229	9.3	
Bilateral mastectomy									<0.001
No	13160	88.4	8625	65.5	2229	16.9	2306	17.5	
Yes	1734	11.6	625	36.0	778	44.9	331	19.1	
Lymph node surgery									<0.001
No	2592	17.4	1277	49.3	721	27.8	594	22.9	
Yes	12302	82.6	7973	64.8	2286	18.6	2043	16.6	
Chemotherapy									<0.001
No	7084	47.6	3846	54.3	1754	24.8	1484	21.0	
Before surgery	1372	9.2	1026	74.8	164	12.0	182	13.3	
After surgery	6438	43.2	4378	68.0	1089	16.9	971	15.1	
Radiation									<0.001
No	9675	65.0	5191	53.7	2459	25.4	2025	20.9	
Yes	5219	35.0	4059	77.8	548	10.5	612	11.7	

* χ^2 test.

undergoing mastectomy without reconstruction and those undergoing immediate implant reconstruction, and it was 5 days for those undergoing immediate autologous tissue reconstruction. As shown in Figure 1, the 30-day rehospitalization rate was 2.7% among patients undergoing mastectomy without reconstruction, 2.8% among those undergoing immediate implant reconstruction, and 4.4% among those undergoing immediate autologous reconstruction ($P < 0.001$).

As also detailed in Figure 1, claims codes for wound complications within the first 2 postoperative years were observed in 2.3% of those not undergoing reconstruction, 4.4% of those undergoing implant reconstruction, and 9.5% of those undergoing autologous reconstruction ($P < 0.001$). Codes suggesting diagnoses of infections within the first 2 postoperative years were observed in 12.7% of those undergoing mastectomy without reconstruction, 20.5% of those undergoing immediate implant reconstruction, and 20.7% of those undergoing immediate autologous reconstruction ($P < 0.001$). Implant removal was performed in 24.7% of those who underwent immediate implant reconstruction. Fat necrosis was diagnosed in 15.7% of those who underwent immediate autologous reconstruction.

In multivariable models, as shown in Table 2, patients who underwent immediate autologous reconstruction had increased odds of 30-day rehospitalization [odds ratio (OR) = 1.75], wound complication diagnosis within 2 years (OR = 5.17), and infection diagnosis within 2 years (OR = 1.94), compared with patients not undergoing reconstruction. Patients who underwent immediate implant reconstruction had increased odds of diagnoses of wound complications (OR = 2.10) and infections (OR = 1.84) within 2 years, compared with those not undergoing reconstruction. Radiation therapy was not associated with the risk of 30-day rehospitalization or wound complications but was significantly associated with the risk of infection (OR = 1.29); there were no statistically significant interactions observed between radiation receipt and surgery type.

Figure 2 demonstrates the incidence of each adverse outcome over time in patients who did and did not receive radiotherapy, within subgroups by reconstruction type. The first 2 rows show similar outcomes in all groups with respect to hospitalization and wound complications, regardless of radiation receipt. Specifically, as shown in the

first row, hospitalization rates were not significantly increased in patients receiving radiation in conjunction with undergoing mastectomy alone or implant reconstruction in either the first 6 months or months 7 to 24; hospitalization rates were increased in patients receiving radiation in conjunction with undergoing autologous reconstruction both in the first 6 months ($P = 0.02$) and in months 7 to 24 ($P < 0.001$). As shown in the second row, radiation receipt was not associated with wound complications in either group of patients who underwent reconstruction within months 1 to 6 or months 7 to 24. In the group undergoing mastectomy alone, radiation receipt was associated with an increased risk in months 7 to 24 in patients who did not undergo reconstruction (OR = 1.84; $P = 0.04$), but the absolute magnitude was very small, as shown in Figure 2D.

In contrast, the third and fourth rows demonstrate significant differences in rates of infections and procedure-specific complications by radiation receipt, all occurring within the time period after the expected time of radiation receipt and not preceding it. Specifically, as shown in the third row, regardless of surgery type, infection was not associated with radiation receipt within months 1 to 6 but was associated with radiation receipt in months 7 to 24 ($P < 0.001$ for all comparisons). Specifically, during months 7 to 24, infection was observed in 5.0% of women who did not receive radiation versus 8.1% of women who received radiation in the mastectomy-alone group; 10.9% (no radiation) versus 15.0% (with radiation) in the immediate implant reconstruction group; and 7.7% (no radiation) versus 14.5% (with radiation) in the immediate autologous reconstruction group. Finally, as shown in the fourth row of the figure, procedure-specific complications were more likely in irradiated patients only in months 7 to 24. During months 7 to 24, 13.1% of women who underwent implant-based reconstruction and did not receive radiation had implant removal compared with 21.9% of women in that group who received radiation; in the same time period, 8.7% of women who underwent autologous reconstruction and did not receive radiation had fat necrosis compared with 14.7% of women in that group who received radiation.

DISCUSSION

In this large, claims-based analysis of women undergoing mastectomy for breast cancer in recent years, we observed complications of immediate breast reconstruction to differ somewhat by approach. Autologous reconstruction is a more intensive surgical procedure that requires longer initial hospitalization and more frequent rehospitalization. However, both patients receiving immediate implant and patients undergoing autologous tissue reconstructions seem to face increased risks of infections and wound complications compared with those undergoing mastectomy without reconstruction. In addition, we observed that radiation therapy seems to modestly increase certain risks that primarily develop over time after the initiation of radiation, such as infectious complications in all patients, implant removal in patients undergoing implant reconstruction, and fat necrosis in patients undergoing autologous reconstruction.

We believe these to be the first claims-based data on length of stay, rehospitalization, and incidence of various surgical complications in a cohort of women treated in diverse settings across the United States. Previous studies have shown that rates of postoperative complications after breast reconstruction are substantial. For example, in the Michigan Breast Reconstruction Outcomes Survey, investigators evaluated outcomes of 326 patients treated at 12 centers from 1994 to 1998, finding that 45% had experienced a complication within 2 years of surgery. Major complications—defined as those requiring reoperation, rehospitalization, or nonoperative intravenous antibiotics—occurred in 32% of the sample.⁸ Unfortunately, however, the study included too few irradiated patients to detect an impact of radiation on complication rates.

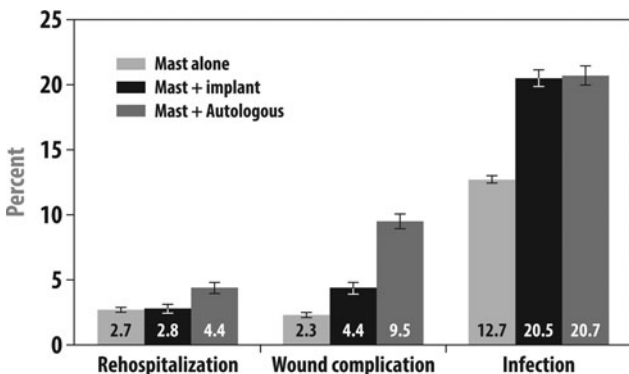


FIGURE 1. Adverse outcomes by surgery type. This figure presents the proportion of patients who developed the following complications by type of initial breast surgery: (1) rehospitalization within 30 days of initial mastectomy, (2) a diagnosis code indicating wound complications within 2 years of initial mastectomy, and (3) a diagnosis code indicating infection within 2 years of initial mastectomy. P values for all 3 outcomes by type of initial surgery were statistically significant at $P < 0.001$. Implant indicates implant-based reconstruction; Mast, mastectomy.

TABLE 2. Multivariable Models to Predict Risk of Adverse Outcomes by Type of Initial Surgery

	30-d Rehospitalization		Wound Complication Diagnosis Within 2 yr		Infection Diagnosis Within 2 yr	
	OR	95% CI	OR	95% CI	OR	95% CI
Type of surgery						
Mastectomy and no reconstruction	1		1		1	
Mastectomy + implant	1.116	0.86–1.45	2.10	1.67–2.66	1.84	1.64–2.07
Mastectomy + autologous	1.75	1.39–2.21	5.17	4.24–6.30	1.94	1.73–2.18
Radiation						
No	1		1		1	
Yes	1.038	0.83–1.30	1.154	0.94–1.42	1.29	1.15–1.44
Chemotherapy						
No	1		1		1	
Yes	1.186	0.96–1.47	1.16	0.96–1.40	1.082	0.98–1.20
Age						
<40	1		1		1	
40–49	0.949	0.65–1.38	1.07	0.76–1.51	1.063	0.89–1.27
50–59	1.016	0.71–1.46	1.34	0.97–1.86	1.158	0.97–1.38
60 and older	1.21	0.79–1.85	1.97	1.35–2.87	1.20	0.97–1.47
Year of mastectomy						
1998			1		1	
1999			0.722	0.33–1.59	1.00	0.68–1.49
2000			1.196	0.58–2.45	1.088	0.74–1.60
2001			0.884	0.44–1.79	1.145	0.80–1.64
2002			1.078	0.56–2.08	1.117	0.79–1.58
2003			1.097	0.58–2.09	1.045	0.75–1.47
2004			1.111	0.59–2.09	1.394	1.00–1.94
2005			1.691	0.91–3.14	1.365	0.98–1.90
2006			1.785	0.97–3.28	1.29	0.93–1.79
2007			1.639	0.89–3.00	1.449	1.05–2.00
Bilateral mastectomy						
No					1	
Yes					1.20	1.05–1.37
Region of country						
Northeast						
North Central						
South						
West						
HMO or PPO with capitation						
No						
Yes						
Goodness of fit (<i>P</i> value)	0.84		0.61		0.43	
Interaction of radiation by type of surgery (<i>P</i> value)	0.70		0.59		0.14	

CI indicates confidence interval; HMO, health maintenance organization; PPO, preferred provider organization.

The effects of radiation therapy on the irradiated chest wall and reconstructed breast are widely feared but poorly understood. Radiation effects include acute toxicities that are generally inflammatory in nature, including soft-tissue edema and skin erythema, sometimes accompanied by dry or moist desquamation of the treated skin. Late effects can include persistent skin changes, vascular compromise, and soft-tissue fibrosis. In the setting of breast reconstruction, these toxicities may lead to an increased incidence of complications of the sort evaluated in this study, which may require repeated surgical interventions for correction.

Existing evidence regarding complications of breast reconstruction in the setting of radiation therapy comes largely from retrospective, single-institution series. On the basis of unique differences between reconstructive techniques, the specific complications observed postoperatively can be expected to vary. This variation in the complication profile of procedures makes head-to-head comparison of specific complications after autologous or implant reconstruction difficult. Information gained from an understanding of expected com-

plications over time, however, can help guide decisions regarding reconstruction in the setting of radiation.

Autologous reconstruction techniques involve both a flap donor site and the reconstructed breast surgical site. Both sites are at risk for complications. As such, patients undergoing autologous breast reconstruction are theoretically at greater risk for wound complications and related readmissions than patients who undergo reconstruction with implants. This is consistent with our observation of the highest rates of wound complications in this subgroup as compared with patients undergoing reconstruction with implants or those not undergoing immediate reconstruction. However, we did not observe increased rates of wound complications in patients who received radiotherapy in the current study. Patients undergoing autologous reconstruction also face potentially increased risks of fat necrosis, fibrosis, atrophy, and flap contracture in the setting of radiotherapy.^{16–18} These flap-specific complications are difficult to quantify, and a lack of standardized reporting of these complications makes it difficult to assess their relative clinical significance. For instance, most flap

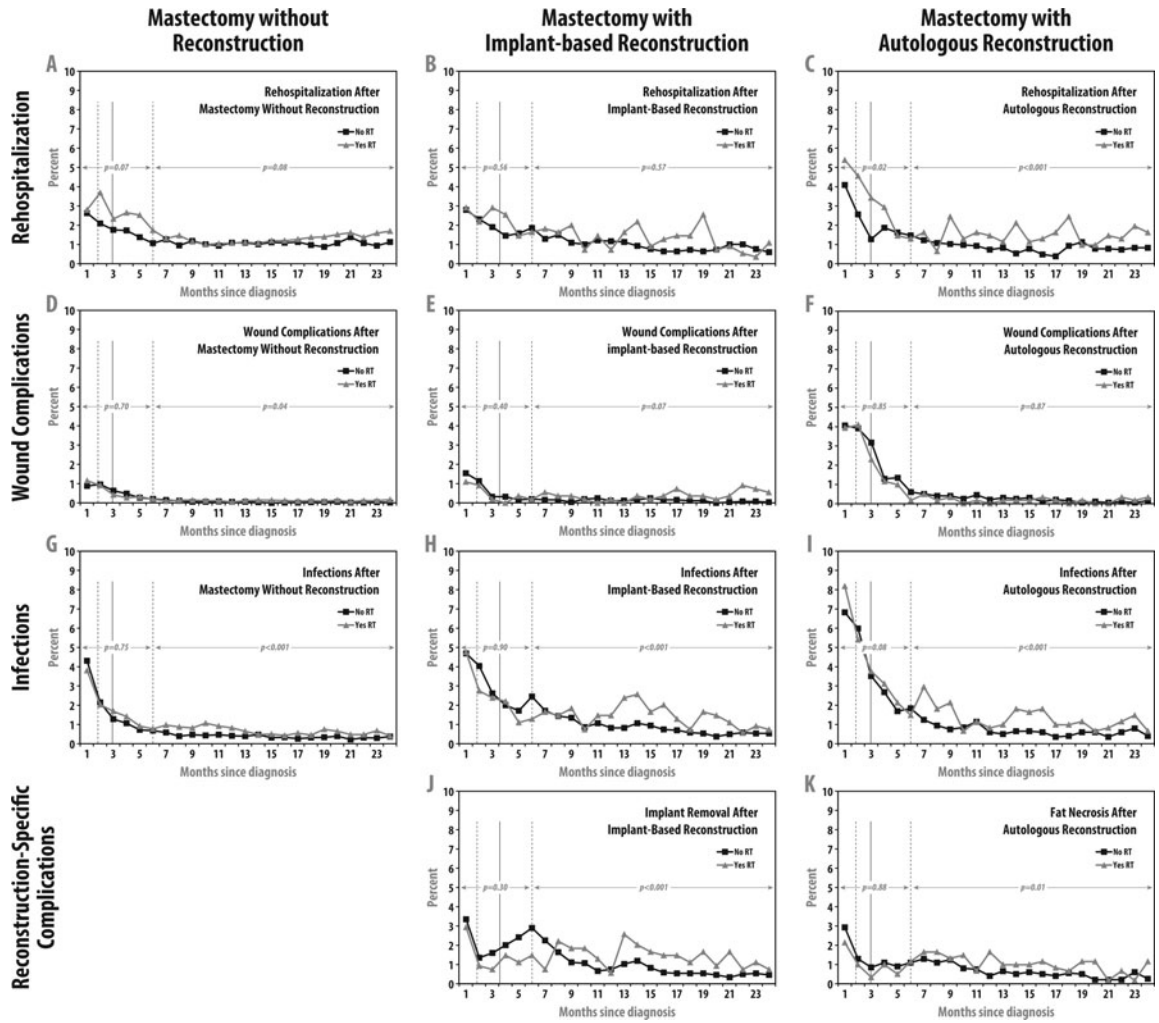


FIGURE 2. Adverse outcomes with and without radiotherapy among patients who underwent reconstruction over time. The top row of panels depicts rehospitalization rates; the second row wound complications; the third row infections; and the fourth row reconstruction-specific complications in the cohort of 14,894 women undergoing mastectomy for breast cancer from 1998 to 2007 and who underwent no reconstruction within the first 2 postoperative years ($n = 9250$), immediate implant-based reconstruction ($n = 3007$), or immediate autologous reconstruction ($n = 2637$), respectively. In each panel, the solid vertical line shows the median interval from mastectomy to start of radiotherapy and the 2 dotted vertical lines show the interquartile range. A, Radiation was not associated with rehospitalization in patients not undergoing reconstruction, either within the first 6 months ($P = 0.07$) or in months 7 to 24 ($P = 0.08$). B, Radiation was not associated with rehospitalization in patients undergoing implant-based reconstruction, either within the first 6 months ($P = 0.56$) or in months 7 to 24 ($P = 0.57$). C, Radiation was associated with increased risk of rehospitalization in patients undergoing autologous reconstruction, both within the first 6 months ($OR = 1.40$; $P = 0.02$) and in months 7 to 24 ($OR = 1.67$; $P < 0.001$). D, Within the first 6 months of mastectomy without reconstruction, wound complications were not associated with radiation ($P = 0.70$); in months 7 to 24, radiation was associated with a modest increase in wound complications ($OR = 1.84$; $P = 0.04$), but absolute risks were extremely low. E, Radiation was not associated with wound complication risk within the first 6 months ($P = 0.40$) or in months 7 to 24 ($P = 0.07$) after mastectomy with immediate implant-based reconstruction. F, Radiation was not associated with wound complications either within the first 6 months ($P = 0.85$) or in months 7 to 24 ($P = 0.87$) after mastectomy with immediate autologous reconstruction. G, Within the first 6 months of mastectomy without reconstruction, infection was not associated with radiation ($P = 0.75$), but in months 7 to 24, infection was more likely in irradiated patients ($OR = 1.79$; $P < 0.001$). H, Within the first 6 months of mastectomy with immediate implant-based reconstruction, infection was not associated with radiation ($P = 0.90$), but in months 7 to 24, infection was more likely in irradiated patients ($OR = 1.66$; $P < 0.001$). I, Within the first 6 months of mastectomy with autologous reconstruction, infection was not associated with radiation ($P = 0.08$), but in months 7 to 24, infection was more likely in irradiated patients ($OR = 2.07$; $P < 0.001$). J, After implant reconstruction, implant removal was not associated with radiation receipt ($P = 0.30$), but in months 7 to 24, implant removal was more likely in irradiated patients ($OR = 1.48$; $P < 0.001$). K, Radiation was not associated with an increased risk of fat necrosis among patients undergoing mastectomy with immediate autologous reconstruction within the first 6 months of surgery ($P = 0.88$) but was associated with high risk of fat necrosis in months 7 to 24 ($OR = 1.55$; $P = 0.01$).

contractures after radiation result in a firmer, less ptotic reconstructed breast, which in many cases can be addressed with a mastopexy or reduction of the contralateral breast.²³ Nevertheless, some flap contractures can be severe enough to warrant discarding the irradiated flap with a revision of the reconstruction with alternative techniques. Along similar lines, the presence of a small area of fat necrosis may not require intervention or might be resolved with simple liposuction, but fat necrosis can also sometimes lead to atrophy and contracture of the reconstructed breast.^{17,18,32–34} Although not all fat necrosis identified in this study may have been clinically consequential, we do believe that the increased rate of this complication in irradiated patients merits consideration, particularly because it can necessitate additional imaging, cause anxiety, and even require surgical intervention.

In contrast, patients with implants who receive radiation therapy may be at increased risk for capsular contracture, infection, pain, skin necrosis, fibrosis, and impaired wound healing.^{10–15,35} Specific complications related to radiation such as infection and impaired wound healing would also be expected to present within the 7- to 24-month observation period. As with autologous reconstructions, revision procedures including tissue expander exchanges are many times performed months after completion of chemotherapy and radiation. Therefore, we also find it noteworthy that an increased risk of infection was observed in irradiated patients with implant reconstruction only within months 7 to 24 and not within the first 6 months of surgery. These infections were likely related to revision procedures performed after the completion of radiation. Revision procedures in this setting would include procedures performed during the exchange of tissue expanders for implants or subsequent to an expander-implant exchange. As the irradiated breast soft tissue tends to be more resistant to the stretch required for breast ptosis, revision procedures are typically necessary to improve on the breast appearance and achieve symmetry with the non-irradiated contralateral breast. These procedures include capsulotomies, capsulectomies, and capsulorrhaphies, in addition to techniques utilized to lower the inframammary fold or reestablish the fold when needed. Most of these procedures require reentry into the implant pocket, potentially increasing the risk for postoperative infection. Radiation changes to the soft tissue are also a likely cause of the observed increased risk of infection as was shown in a recent study from Memorial Sloan-Kettering Cancer Center by Cordeiro et al.³⁶ Evaluating 319 implants exposed to radiation therapy after expander-implant exchange in comparison to 1814 non-irradiated implants, they found a significantly higher infection rate (10.3% vs 2.7%; $P < 0.01$) in irradiated patients; implant infections were the most common reason (41.4%) for implant removal in these irradiated patients.

Indeed, our findings strongly suggest that radiation is a risk factor for infection regardless of type of surgery or receipt of reconstruction, illustrating that the normal tissue effects of radiation, either through immune-mediated effects or damage to the skin and soft tissues or congestion of the lymphatic channels, result in a physiologic state characterized by an increased susceptibility to infection. Still, although a rise in infections was also noted in patients who underwent autologous reconstruction in the later time period, a critical difference exists in the ultimate clinical implication of this complication. Autologous reconstruction infections typically are managed and symptoms resolved by oral antibiotic therapy. Implant infections tend to require an extended course of intravenous antibiotics, with some of these infections ultimately resulting in removal of the infected implant. In this study population, 21.9% of the irradiated patients with implant reconstruction had their implants taken out during the 7- to 24-month observation period in comparison with 13.1% of non-irradiated patients; we believe that infections are a potential reason for a substantial number of the implant removals. Thus, the implications of infections

in the irradiated patient with implant reconstruction may be of greater clinical significance than they are in patients with flap reconstruction. We do find it reassuring that the rates of implant removal observed in this sample of patients treated in the community were generally similar to rates reported from centers of excellence.^{21,37}

The few multicenter studies investigating outcomes of the integration of radiation and reconstruction have had significant limitations, including failure to include patients treated with different techniques for comparison, failure to measure covariates, and/or limitation to centers of excellence or populations substantially different from those treated in the United States.^{38–40} Given the wide variation in complication rates reported in different institutional series, the general lack of comparison with patients not undergoing reconstruction, and the lack of inclusion of sufficient numbers of irradiated patients in studies such as the multicenter Michigan Breast Reconstruction Outcomes Survey discussed earlier, the evidence assembled in the current study fills a void in the existing literature.

This study has a number of strengths, including its access to information on a large sample of patients treated in diverse settings across the United States. It also has limitations. First, as in any observational study, associations may not reflect causation and may instead reflect imbalances in other features. We did adjust our models for those potentially confounding factors to which we had access, but this does not ensure the absence of confounding, particularly by factors that could not be measured from the claims data, including smoking history and body mass index. Second, the sample was restricted to patients with commercial insurance and mostly those of working age; if complications differ in settings in which patients with other insurance types are treated or, perhaps more plausibly, among older patients, our findings should not be generalized to those populations. The data set we used also includes a disproportionate share of patients from the Southern United States, so if outcomes differ by region, this may also affect generalizability.

Third, the measures were derived from claims, which can be vulnerable to underascertainment or misclassification. Certain outcomes are more likely to be accurately measured through claims (such as rehospitalizations and implant removal procedures) than others, including complications assessed on the basis of diagnosis codes (such as wound complications, infections, and fat necrosis). Moreover, our algorithms identified complications that would be expected to be heterogeneous in terms of severity. However, even for those complications assessed using diagnosis codes, one would not expect misclassification, underascertainment, or heterogeneity to vary systematically by surgery group for the complications we assessed across the different surgery types, so this is unlikely to undermine the validity of the differences observed between the surgery groups. Similarly, we do not expect systematic differences in the accuracy of claims-based measures of complications in irradiated versus non-irradiated patients, so this is unlikely to have biased our estimates of the impact of radiation therapy. Nevertheless, it should be noted that our results suggest that a small proportion (4%) of patients undergoing autologous reconstruction were not hospitalized at the time of their reconstructive surgery. To our knowledge, this is not a common practice. Although our finding may be reflective of actual practice, we cannot rule out the possibility of a low frequency of coding errors, for example, errors in the date of hospital admission, which could account for this finding.

Fourth, we were unable to differentiate what type of axillary surgery patients underwent in this cohort. There was not a specific *CPT* or *ICD-9* procedure code for sentinel lymph node biopsy with blue dye mapping during the span of years included in this study. Such patients may have been coded with more generic *CPT* or *ICD-9* procedure codes, such as axillary lymph node excision, not otherwise specified. In our prior work, approximately one third of patients

could not be accurately classified as undergoing either sentinel lymph node biopsy or axillary lymph node dissection when using only insurance billing claims.⁴¹ Studies seeking to differentiate outcomes in patients undergoing sentinel node biopsy versus axillary lymph node dissection must, therefore, await maturation and release of contemporary data sets, in which the recently introduced CPT code for sentinel lymph node biopsy with blue dye mapping will facilitate this distinction in the future.

Finally, this claims-based study was limited to the assessment of certain outcomes that were measurable through claims data and could not evaluate other meaningful endpoints such as pain and cosmetic satisfaction that cannot be measured using information present in claims data. Nevertheless, we believe that the outcomes we could measure, including wound complications, infections, rehospitalization, fat necrosis, and implant removals, are important to study because they are likely to have a meaningful impact on patients' quality of life, as they can compromise physical well-being, cause psychological distress, and impair social role functioning. To assess the absolute magnitude of all potentially relevant, patient-centered outcomes in this setting, future researchers should attempt to build plastic surgery registries with active, prospective data collection to this end.

CONCLUSIONS

Thousands of women with breast cancer each year must decide whether to pursue breast reconstruction, and if so, with what approach. Information on hospitalization experiences and complication rates is relevant for decision making in this context, especially if patients are also considering radiation therapy. The current study suggests that the complications of immediate breast reconstruction do differ depending on approach and that radiation therapy seems to modestly increase certain risks. Further research is necessary to determine whether the increasing use of acellular dermal matrices⁴² and autologous fat grafting⁴³ in implant-based reconstruction or the use of delayed reconstruction approaches (including a staged, "delayed-immediate" approach to autologous reconstruction with transfer of the flap after radiation) may alter these risks.^{9,44-46}

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Specifically:

1. Reshma Jagsi contributed substantially to conception and design of the study, analysis and interpretation of the data, wrote the manuscript, and gave final approval of the version to be published.
2. Jing Jiang contributed substantially to the analytic design and performed all analyses; she critically reviewed, edited, and approved the final manuscript.
3. Adeyiza O. Momoh contributed substantially to the design of the study, analysis and interpretation of data, and critically reviewed, edited, and approved the final manuscript.
4. Amy Alderman contributed substantially to the design of the study, analysis and interpretation of data, and critically reviewed, edited, and approved the final manuscript.
5. Sharon H. Giordano contributed substantially to data acquisition, the analysis and interpretation of data, and critically reviewed, edited, and approved the final manuscript.

6. Thomas A. Buchholz contributed substantially to the analysis and interpretation of data; he critically reviewed, edited, and approved the final manuscript.
7. Lori J. Pierce contributed substantially to the analysis and interpretation of data; she critically reviewed, edited, and approved the final manuscript.
8. Steven J. Kronowitz contributed substantially to the analysis and interpretation of data; he critically reviewed, edited, and approved the final manuscript.
9. Benjamin D. Smith contributed substantially to the conception and design of the study, analysis and interpretation of the data, and critically reviewed, edited, and approved the final manuscript.

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