Integrating Postmastectomy Radiotherapy and Breast Reconstruction

By

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Thesis Defense in Partial Fulfillment of the Requirements for the Degree of Master of Medical Sciences in Clinical Investigation (MMSCI)

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Introduction:

For patients with breast cancer undergoing mastectomy, preserving the breast mound with immediate reconstruction represents a crucial step in preserving quality of life for these patients. In the United States, there has been significant increase in mastectomy rates, accompanied by a similar increase in breast reconstruction rates from 36.9% to 57.2% between 1998 and 2011(1). Another important goal for those patients, is maintaining local tumor control by delivering post mastectomy radiotherapy (PMRT) for certain patients according to national guidelines(2). Other national analyses showed the increased rates of PMRT from 19.1% to 30.3% between 2003 and 2012(3). Despite the increased rates, integrating PMRT in the settings of breast reconstruction is a challenging clinical situation. This challenge arises due to the underlying negative impact of PMRT on breast reconstruction, as it has been established that PMRT increases reconstruction complications(4).

The aim of this work is to mitigate the negative PMRT sequalae on breast reconstruction by reducing the complication rates while preserving local tumor control and PMRT benefits.
To achieve our goal we study different surgical approaches in the first project and different radiation techniques in the second project.

Regarding reconstruction options; the American Society of Plastic Surgeons recommends three different reconstruction types: Autologous, Two Stages Expander/Implant(TE/I) and single stage direct-to-implant (DTI)(5). The Autologous surgery implies reconstructing the breast using a part of another body muscle. Despite the stable cosmetic outcomes for this approach -as it uses native

body tissues- the donor site morbidity and longer operation times represent a burden on patients and caregiver. The second approach (TE/I), implies delivering an expander device during mastectomy to allow stretching the skin followed by exchange operation to permanent implant. While this approach avoids donor site morbidity and allows breast augmentation, the need for a second surgery, the challenges during PMRT planning imposed by the expander metal port and worse cosmetic outcomes, represent a major pitfall for this approach. On the other hand, single stage (DTI) an emerging reconstruction option, offers a middle ground between the previous two allowing completion of all operations in one setting with easier PMRT planning. There is still lack of evidence about comparing the three reconstruction types, therefore in the first project we compare the three types with and without PMRT.

For radiation techniques, the second project focuses on evaluating the impact of chest wall boost (CWB) on reconstruction complications and local tumor control.

CWB is an additional radiation dose delivered to the mastectomy scar using en-face electrons energy. The addition of CWB is thought to improve local control with many conflicting data regarding its benefit. Therefore, our goal in the second project to evaluate its impact on both reconstruction complications and local control.

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Clinical Investigation

Single Stage Direct-to-Implant Breast Reconstruction Has Lower Complication Rates Than Tissue Expander and Implant and Comparable Rates to Autologous Reconstruction in Patients Receiving Postmastectomy Radiation

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Summary

We compared 3 different breast reconstruction approaches (single stage, tissue expander and implant, and autologous) with and without postmastectomy radiation therapy (PMRT). PMRT increased complications across all reconstruction types. However, its impact on single-stage

Purpose: To compare single-stage direct-to-implant (DTI) immediate reconstruction to the commonly used 2-stages expander and implant (TE/I) or autologous reconstruction with focus on postmastectomy radiation therapy (PMRT) setting.

Methods and Materials: We reviewed the charts of 1,286 patients who underwent 1,814 breast reconstructions at our institution with and without PMRT from 1997 to 2017. Patients were divided into 6 groups according to type of reconstruction and PMRT status. Primary objective was reconstruction complications defined solely on surgical reintervention operative notes such as infection, skin necrosis, and fat necrosis across all groups. Implant-related complications such as capsular contracture, implant rupture or exposure, or implant failure were compared between TE/I and DTI. Kaplan−Meier estimates were used to calculate 5-year cumulative incidence of complications. The secondary objective was to compare the 3 reconstruction types in settings of immediate reconstruction followed by PMRT on multivariable analysis.

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reconstruction was 50% lower than on tissue expander and implant and was close to autologous reconstruction. Single-stage breast reconstruction is a promising strategy, particularly when PMRT is indicated.

Results: Median follow-up was 5.8 years. Among 1286 patients, 41.1% (N = 529/1286) received PMRT. Among 1814 reconstructed breasts, autologous, single-stage, and TE/I represented 18.7%, 34.8%, and 46.2%, respectively. With no PMRT, the 5-year cumulative incidence of any reconstruction complication was 11.1%, 12.6%, and 19.5% for autologous, DTI, and TE/I reconstructions, respectively. The addition of PMRT resulted in 5-year cumulative incidence of 15.1%, 18.2%, and 36.8%, respectively. The multivariable analysis showed that DTI was associated with lesser complications compared with TE/I, whereas no significant difference was noted between DTI and autologous.

Conclusions: Single-stage DTI reconstruction had significantly lower complication rates than TE/I with and without PMRT. Single-stage complication rates were not significantly different from autologous complication rates in PMRT settings. Single-stage reconstruction may offer a valuable option for patients receiving PMRT. © 2019 Elsevier Inc. All rights reserved.

Introduction

For patients with breast cancer undergoing mastectomy, preserving the breast mound with immediate reconstruction represents a crucial step in preserving quality of life for these patients.[1,2] In the United States, there has been a significant increase in mastectomy rates, accompanied by a similar increase in breast reconstruction rates from 36.9% to 57.2% between 1998 and 2011.[3]

The American Society of Plastic Surgeons considers several reconstruction techniques: 2-stage tissue expander and implants (TE/I), single-stage direct-to-implant reconstruction (DTI), and autologous tissue grafts (ATR). Choosing the optimum type of reconstruction represents a clinically challenging situation that depends on patient's preference, balancing the pros and cons of each technique, baseline risk factors for reconstruction failure such as high BMI or smoking, and the need for postmastectomy radiation therapy (PMRT).[4] PMRT has been shown to improve overall survival and local control for patients with disease-positive lymph nodes and large tumors.[5] Despite the oncological benefits, several studies have shown the negative impacts of PMRT on breast reconstruction.[6-11] National studies showed the decreased rates of reconstruction when PMRT is indicated.[12] Other reports showed increased national trends over time for TE/I with decreased trends for autologous reconstruction.[13] This variation is due to the focus of clinical studies on comparing TE/I to autologous outcomes with and without PMRT delivery, leading to a gap in knowledge regarding the comparison of all 3 types of reconstruction regardless of PMRT indication.

The goal of this study is to compare these 3 types of reconstruction techniques in both PMRT and non-PMRT settings and to evaluate the type of reconstruction associated with the lowest rate of complications in PMRT settings.

Materials and Methods

After institutional review board approval, we reviewed the charts of 1,860 patients who underwent breast reconstruction at our institution with and without PMRT from 1997 to 2017. Inclusion criteria included patients treated for breast cancer with mastectomy and reconstruction with and without PMRT delivery, and availability of surgical and PMRT notes. To obtain more homogeneity, exclusion criteria included receipt of neoadjuvant chemotherapy, patients treated with mastectomy and reconstruction for local recurrence, patients with bilateral cancer, and patients receiving 2 different types of reconstruction on each side. The rationale behind excluding neoadjuvant cases was to eliminate the hazardous effect of chemotherapy before surgery, which has been shown to affect postoperative tissue healing compared with those who did not receive such treatment.[14] Therefore, excluding those cases helped minimize confounding factors and achieve a more homogeneous analysis. Also, patients treated with mastectomy for local recurrence might have a different healing process owing to second reoperation in comparison to those treated with mastectomy for their primary tumor. After applying these criteria, 1,286 patients were available for the analysis. For patients receiving PMRT, dosimetric planning was based on computed tomography simulation, and radiation therapy (RT) was delivered with external beams using opposed-tangents technique. It is to be noted that all PMRT techniques used 3-dimensional conformal RT with a skin bolus 3 to 5 mm in thickness applied every other day. For patients receiving regional lymph nodes radiation, the supraclavicular and axillary lymph node areas were contoured according to the Radiation Therapy Oncology Group atlas, and the lateral border of this field was delineated per the discretion of the treating physician. Some patients received chest-wall boost (CWB) at the discretion of the treating physician. CWB was delivered with a median dose of 10 Gy in 5 fractions, using 6 to 9 Mev electrons. The boost targeted the full length of the mastectomy scar plus a circumferential 2 to 3 cm of surrounding chest wall or mostly chest wall.

Reconstruction techniques and complications

Reconstruction techniques included 2-stages TE/I, single-stage DTI, and autologous. Autologous flaps included the

transverse rectus abdominis muscle (TRAM), the latissimus dorsi muscle, the deep inferior epigastric perforators (DIEP) flaps, or a combination of flaps. DTI techniques have been described elsewhere.[15,16] Owing to the low numbers of DIEP flaps, latissimus dorsi flaps, and combined flaps among the reconstructed breasts, we analyzed all these together with TRAM flaps as the autologous approach. Taking into consideration the lack of a universal definition of minor and major surgical reconstruction complications and to avoid the interrater variability between assessing physicians leading to a wide subjective measurements, we chose to define our complications solely on surgical reintervention to achieve more objective measures. This also allowed us to equally unify the severity of complications across all groups. Complications were defined as infection, skin necrosis, fat necrosis requiring debridement for autologous or expander or implant removal or replacement, and washout. Implant-related complications between TE/I and DTI were defined as capsular contracture requiring capsulotomy, expander or implant rupture, expander or implant exposure requiring surgical reintervention, and reconstruction failure. To increase objectivity, no grading was provided for capsular contracture; only surgical reintervention to release the capsule was used as endpoint. Two different endpoints for reconstruction failure were considered: "absolute reconstruction failure" was defined as tissue expander or permanent implant removal with failure to replace and no salvage reconstruction, and "overall implant failure" was defined as implant removal regardless of the replacement outcome. All clinicopathologic data were stored in REDCap 7.0.14 (Vanderbilt University, Nashville, TN).

Statistical analysis

Patients were divided into 6 groups according to type of reconstruction and PMRT status. For patients who received contralateral prophylactic mastectomy with the same type of reconstruction, the prophylactic reconstruction was counted as an individual unit in the unadjusted crude and actuarial rates analysis. Multiple imputations were used to replace any BMI missing value based on age, smoking status, and diabetes. The crude rates of relevant endpoints were compared and analyzed using odds ratios and univariate logistic regression. The actuarial rates were estimated using Kaplan−Meier methodology. The multivariable adjusted analysis was based on logistic regression for patients who had immediate reconstruction and PMRT to explore what reconstruction type yields lesser complications in such settings. Delayed reconstructions, prophylactic mastectomies, and patients with no PMRT were excluded from the multivariate analysis. All multivariable models included reconstruction type as the primary independent variable and previously identified risk factors for reconstruction complications such as smoking history, BMI dichotomized at 25 kg/m^2, and CWB as covariates,[17-19] as well as any significant factor found to be associated with the outcome on univariate analysis. The P values less than .05 were considered statistically significant. All calculations were performed using Stata (StataCorp, College Station, TX).

Results

Patients characteristics

We studied 1,286 patients with 1,814 breast reconstructions. Patients receiving autologous reconstruction were 24.1% of the whole cohort (N = 311/1,286); 32.3% (N = 416/1,286) and 43.4% (N = 559/1,286) received DTI and TE/I, respectively (Table 1). Of the whole patient cohort, 41.1% (N = 529/1,286) received PMRT with a median dose of 50.4 Gy (range, 45-68 Gy). Overall median follow-up for all groups was 5.8 years. Overall median age was 49.3 years. Among the whole cohort, 4% were diabetic (N = 52/1,286) and 6.4% were smokers (N = 83/1,286). Patients with a more advanced pathologic stage received PMRT as well as adjuvant chemotherapy. Axillary dissection was more abundant in the groups that received PMRT, reflecting advanced local disease. Contralateral prophylactic mastectomy with the same type of breast reconstruction was more common in implant-based groups than in autologous groups.

Reconstructed breast characteristics

While studying each breast alone (Table 2), the prophylactic contralateral mastectomies of the patients with and without PMRT were added to the non-PMRT mastectomies as control. This concept has been used by Cordeiro et al.[20] We found that among 1,814 reconstructed breasts, DTI represented 34.8% (N = 633/1,814), TE/I represented 46.2% (N = 839/1,814), and autologous represented 18.7% of the reconstructed breasts (N = 342/1,814). Autologous reconstruction included TRAM (N = 282), the latissimus dorsi muscle (N = 7), DIEP flaps (N = 37), or a combination of flaps (N = 16). All types of different autologous flaps were studied together as the autologous approach. Among the 529 irradiated reconstructions, 23% (N = 122/529) were autologous, and 32.3% (N = 171/529) and 44.6% (n = 236/529) were DTI and TE/I, respectively. Delayed reconstruction was more common in autologous reconstruction, especially with PMRT. Around 98% of both types of implant-based reconstructions were offered immediately. Most of the implants (97%) in DTI settings were covered with acellular dermal matrix regardless of the PMRT indications. Muscle coverage was used more in the TE/I reconstruction group (Table 2). The median time of expander exchange to implant was 6.2 months, and median time to start PMRT was 5.8 months within TE/I group and 5.7 months for DTI. Out of the 236 reconstructed breasts with TE/I receiving PMRT, only 52 received PMRT after exchange of the expander to the implant. Implant-based

Table 1 Patient demographics

	Autologous		Single-stage		Expander and implant		
	PMRT	No PMRT	PMRT	No PMRT	PMRT	No PMRT	Total
Number of patients	122	189	171	245	236	323	1,286
BMI							
<25	42 (34.4%)	80 (42.3%)	74 (43.3%)	106 (43.3%)	134 (56.8%)	187 (57.9%)	623 (48.4%)
≥25	80 (65.6%)	109 (57.7%)	97 (56.7%)	39 (56.7%)	102 (43.2%)	136 (42.1%)	663 (51.6%)
Smoking							
Active smoker	11 (9%)	13 (6.9%)	4 (2.3%)	10 (4.1%)	16 (6.8%)	29 (9%)	83 (6.5%)
Ex-smoker	29 (23.8%)	42 (22.2%)	48 (28.1%)	72 (29.4%)	67 (28.4%)	90 (27.9%)	348 (27.1%)
Nonsmoker	60 (49.2%)	112 (59.3%)	115 (67.3%)	160 (65.3%)	139 (58.9%)	180 (55.7%)	766 (59.6%)
Diabetes							
No	121 (99.2%)	170 (90%)	167 (97.7%)	233 (95.1%)	231 (97.9%)	312 (96.6%)	1,234 (96%)
Yes	1 (.8%)	19 (10%)	4 (2.3%)	12 (4.9%)	5 (2.1%)	11 (3.4%)	52 (4%)
Median age, y	47.7	50.0	49.7	52.4	46.5	49.1	49.3
Median follow-up, y	9.41	9.66	4.33	4.16	6.25	6.08	5.8
Overall pathologic stage							
Stage 0	0 (0%)	27 (14.3%)	1 (.6%)	51 (20.8%)	0 (0%)	61 (18.9%)	140 (10.9%)
Stage I	9 (7.4%)	111 (58.7%)	15 (8.8%)	148 (60.4%)	17 (7.2%)	182 (56.3%)	482 (37.5%)
Stage II	75 (61.5%)	48 (25.4%)	92 (53.8%)	46 (18.8%)	139 (58.9%)	80 (24.8%)	480 (37.3%)
Stage III	38 (31.1%)	3 (1.6%)	63 (36.8%)	0 (0%)	80 (33.9%)	0 (0%)	184 (14.3%)
ALND*							
No	28 (23%)	120 (63.5%)	68 (39.8%)	234 (95.5%)	58 (24.6%)	275 (85.1%)	783 (60.9%)
Yes	94 (77%)	69 (36.5%)	103 (60.2%)	11 (4.5%)	178 (75.4%)	48 (14.9%)	503 (39.1%)
Contralateral prophylactic mastectomy with reconstruction	19 (15.6%)	12 (6.3%)	85 (49.7%)	132 (53.9%)	129 (54.7%)	151 (46.7%)	528 (40.1%)
Radiation boost		0 (0%)		0 (0%)		0 (0%)	
No	73 (59.8%)		90 (52.6%)		119 (50.4%)		282 (21.9%)
Yes	49 (40.2%)		81 (47.4%)		117 (49.6%)		247 (19.2%)
Regional lymph nodes radiation		0 (0%)		0 (0%)		0 (0%)	
Yes	73 (59.8%)		150 (87.8%)		181 (76.7%)		404 (31.4%)
No (Chest wall alone)	49 (40.16%)		21 (12.2%)		55 (23.3%)		125 (9.7%)
Chemotherapy							
Adjuvant CT	116 (95%)	79 (41.8%)	151 (88.3%)	7 (2.6%)	210 (89%)	126 (39%)	756 (58.8%)
No chemotherapy	6 (5%)	110 (58.2%)	20 (11.7%)	171 (69.8%)	26 (11%)	197 (61%)	530 (41.2%)

Abbreviations: ALND = axillary lymph node dissection; CT = chemotherapy; PMRT = postmastectomy radiation therapy.
* No ALND refers to sentinel node collection only without ALND or no axillary surgery at all.

reconstruction groups had more nipple-sparing mastectomies compared with autologous.

Complication rates without PMRT

Studying each reconstructed breast alone (Table 3) in absence of PMRT, 5.8% of TE/I reconstructions developed infection compared with 2.6% of DTI reconstructions (odds ratio [OR] = 2.3; 95% CI, 1.2-4.5; $P = .014$) and 1.8% of autologous reconstructions (OR = 3.3; 95% CI, 1.2-9.4; $P = .024$). There was no statistically significant difference between DTI and autologous in terms of infection rate (OR = 1.4; 95% CI, 0.4-4.5; $P = .53$). For skin necrosis and seroma or hematoma, there was no significant difference among the 3 groups. Fat necrosis was more prominent in autologous reconstruction. TE/I was associated with higher implant-related complications. Specifically, 4.5% of TE/I cases developed expander/or implant rupture versus 1.3% of DTI cases (OR = 5.1; 95% CI, 2.1-12.1; $P < .0005$), 4.6% versus 1.1% for capsular contracture (OR = 3.0; 95% CI, 1.7-5.2; $P < .0005$), and 21.2% versus 12.4% for overall implant failure (OR = 2.2; 95% CI, 1.7-2.9; $P < .0005$). There was no significant difference between TE/I and DTI in terms of both implant exposure and absolute implant failure (0.7% vs 1.3%; $P = .3$) and (3.0% vs 2.6%; $P = .7$), respectively. Within the autologous group, 1 of 17 patients (5.8%) with delayed reconstruction developed any complications compared with 24 of 203 (11.8%) with immediate autologous ($P = .4$). Within the TE/I group, the majority of complications occurred after the exchange of

Table 2 Reconstruction characteristics per breast

	Autologous		Single-stage		Expander and implant		
	PMRT (%)	No PMRT (%)	PMRT (%)	NO PMRT (%)	PMRT (%)	NO PMRT (%)	Total
Total no. breasts	122	220	171	462	236	603	1,814
Reconstruction time							
Immediate	90 (73.8%)	203 (92.3%)	170 (99.4%)	462 (100%)	231 (97.9%)	580 (96.2%)	1,754 (96.7%)
Delayed	32 (26.2%)	17 (7.7%)	1 (0.6%)	0 (0%)	5 (2.1%)	23 (3.8%)	60 (3.3%)
Coverage for implant based reconstruction							
Muscular	0 (0%)	0 (0%)	10 (5.8%)	15 (3.3%)	128 (54.2%)	368 (61.0%)	524 (28.9%)
ADM	0 (0%)	0 (0%)	161 (94.2%)	447 (96.7%)	108 (45.8%)	235 (39.0%)	1,290 (71.1%)
No nipple sparing	83 (68%)	93 (42.3%)	47 (27.5%)	71 (15.4%)	120 (50.8%)	152 (25.2%)	566 (31.2%)
Nipple sparing	39 (32%)	127 (57.7%)	124 (72.5%)	391 (84.6%)	116 (49.2%)	451 (74.8%)	1,248 (68.8%)

Abbreviations: ADM = acellular dermal matrix; PMRT = postmastectomy radiation therapy.
* The unit of analysis in this table is reconstructed breast, not patient. Patients with bilateral cancer were excluded from the study; therefore, the contralateral prophylactic mastectomies for all patients were analyzed among non-PMRT mastectomies as a control.

the expander to permanent implant (65.5%) versus (14.2%) before this exchange.

Complication rates with PMRT

Adding PMRT to the reconstructed breast increased rates of reconstruction complications in all 3 groups. Analyzing each irradiated reconstructed breast alone, TE/I was associated with higher complication rates (Table 3); 15.7% and 8.9% of TE/I reconstructions developed infection and skin necrosis, compared with 6.4% (OR = 2.7; 95% CI, 1.3-5.5; $P = .006$) and 4.1% (OR = 2.3; 95% CI, 0.9-5.5; $P = .06$) for DTI, respectively. Among autologous reconstructions, 4.1% developed infection and 4.1% developed skin necrosis. Those rates are lower compared with TE/I in terms of infection (OR = 4.4; 95% CI, 1.7-11.4; $P = .003$) and skin necrosis (OR = 2.3; 95% CI, 0.8-6.2; $P = .1$). The rates of infection and skin necrosis were not statistically significantly different between DTI and autologous cases (Table 3). The autologous reconstruction was associated with higher rates of fat necrosis (9.0%) compared with both DTI (0.6%; OR = 16.8; 95% CI, 2.1-132.3; $P = .007$) and TE/I (0.4%; OR = 23.3; 95% CI, 3.0-182.6; $P = .003$). There was no significant difference between the groups for seroma and hematoma. TE/I reconstruction was associated with significantly higher rates of implant-related complications compared with DTI, including implant rupture (5.1% vs 0.0%; OR = 12.7; 95% CI, 2.1-inf; $P = .003$), implant exposure (6.8% vs 2.3%; OR = 3.0; 95% CI, 1.0-9.2; $P = .05$), capsular contracture (15.3% vs 7.0%; OR = 2.4; 95% CI, 1.2-4.7; $P = .01$), absolute implant failure (9.1% vs 2.9%; OR = 3.3; 95% CI, 1.2-9.0; $P = .02$), and overall implant failure (38.7% vs 18.1%; OR = 2.8; 95% CI, 1.8-4.6; $P < .0005$). Within the autologous group with

Table 3 Complications rate per reconstructed breast

	Autologous		Single-stage		Expander and implant		
	PMRT (%)	No PMRT (%)	PMRT (%)	No PMRT (%)	PMRT (%)	No PMRT (%)	Total
Total no. breasts	122	220	171	462	236	603	1,814
Infection	5 (4.1%)	4 (1.8%)	11 (6.4%)	12 (2.6%)	37 (15.7%)	35 (5.8%)	104
Necrosis	5 (4.1%)	11 (5.0%)	7 (4.1%)	19 (4.1%)	21 (8.9%)	31 (5.1%)	94
Fat necrosis	11 (9.0%)	13 (5.9%)	1 (0.6%)	0 (0.0%)	1 (0.4%)	1 (0.2%)	27
Seroma hematoma	4 (3.3%)	3 (1.4%)	3 (1.8%)	10 (2.2%)	12 (5.1%)	13 (2.2%)	45
Implant complications							
	Single-stage		Expander and implant				
	PMRT (%)	No PMRT (%)	PMRT (%)	No PMRT (%)			
Capsular contracture	12 (7.0%)	5 (1.1%)	36 (15.3%)	28 (4.6%)			81
Implant rupture	0 (0.0%)	6 (1.3%)	12 (5.1%)	27 (4.5%)			45
Implant exposure	4 (2.3%)	6 (1.3%)	16 (6.8%)	4 (0.7%)			30
Absolute failure	5 (2.9%)	12 (2.6%)	21 (9.1%)	17 (3.0%)			55
Overall Failure	31 (18.1%)	57 (12.4%)	89 (38.7%)	121 (21.2%)			298

Abbreviation: PMRT = postmastectomy radiation therapy.

PMRT, 4 of 32 (12.5%) delayed reconstruction cases developed complications compared with 15 of 90 cases (16.6%) for immediate autologous ($P = .5$). Within TE/I group, the majority of complications occurred after the exchange (75%) versus (26.1%) before the exchange.

Timing of complications

The majority of complications (74%) happened within the first 3 years for all the groups. Taking into consideration the different follow-up time between the groups, we aimed to report the cumulative incidence rate for reconstruction complications. With no PMRT, the 5-year cumulative incidence of any reconstruction complication was 11.1% (95% CI, 7.6%-16.2%), 12.6% (95% CI, 9.6%-16.6%) and 19.5% (95% CI, 16.3%-23.1%) for autologous, DTI, and TE/I reconstructions, respectively (Fig. 1). The addition of PMRT resulted in a 5-year cumulative incidence of 15.1% (95% CI, 9.8%-22.9%), 18.2% (95% CI, 13.0%-25.3%), and 36.8% (95% CI, 30.8%-43.6%), for autologous, DTI, and TE/I, respectively (Fig. 1). These results indicate that PMRT risk of complications significantly increased with TE/I compared with DTI and autologous.

Furthermore, DTI and autologous results were similar with and without PMRT (Fig. 1). For implant-based

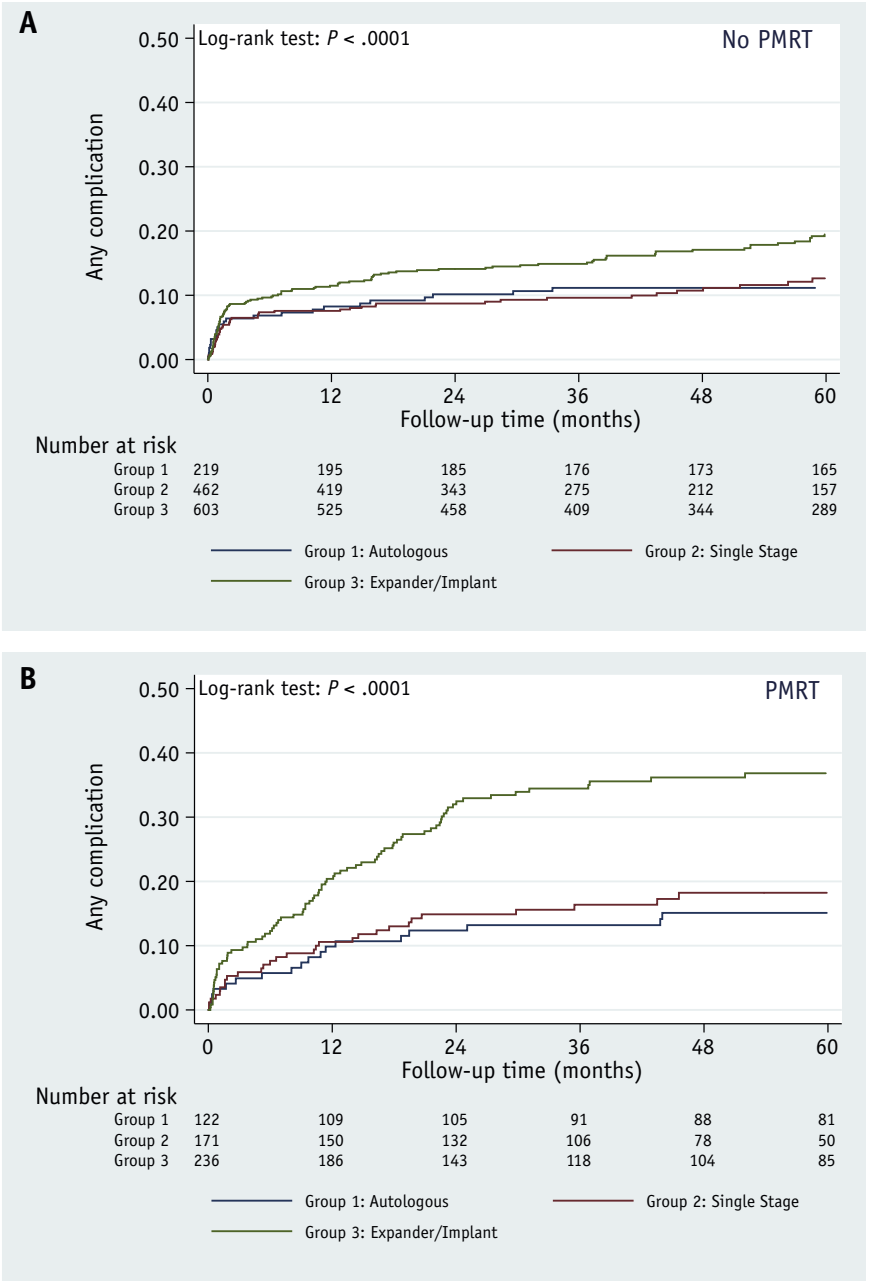

Fig. 1. (A) Cumulative incidence of any reconstruction complication per reconstructed breast in absence of PMRT. (B) Cumulative incidence of any reconstruction complication per reconstructed breast with PMRT.

reconstruction, the 5-year cumulative incidence of absolute failure in absence of PMRT were 2.9% (95% CI, 1.6%-5.3%) and 2.9% (95% CI, 1.8%-4.9%) for DTI and TE/I, respectively (Fig. 2A)). For overall failure, this was 8.6% (95% CI, 6.0%-12.2%) and 14.5% (95% CI, 11.7%-17.9%), respectively (Fig. 2B). The addition of PMRT increased the 5-year cumulative incidence rates of absolute and overall failure in both groups. The 5-year cumulative incidence rates of absolute failure were 3.4% (95% CI, 1.4%-8.0%) and 8.9% (95% CI, 5.6%-14.1%) for DTI and TE/I, respectively (Fig. 2A). The overall implant failure rates were 16.4% (95% CI, 11.1%-23.8%) and 29.7% (95% CI, 24.0%-36.4%) for DTI and TE/I, respectively (Fig. 2B). The significant increase in both endpoints of implant failure owing to PMRT was in the TE/I group.

Factors associated with complications in PMRT settings

We studied patients with immediate reconstruction receiving PMRT to explore the factors associated with reconstruction complications (patients with delayed reconstruction were excluded; Table 4). On univariate analysis, factors such as

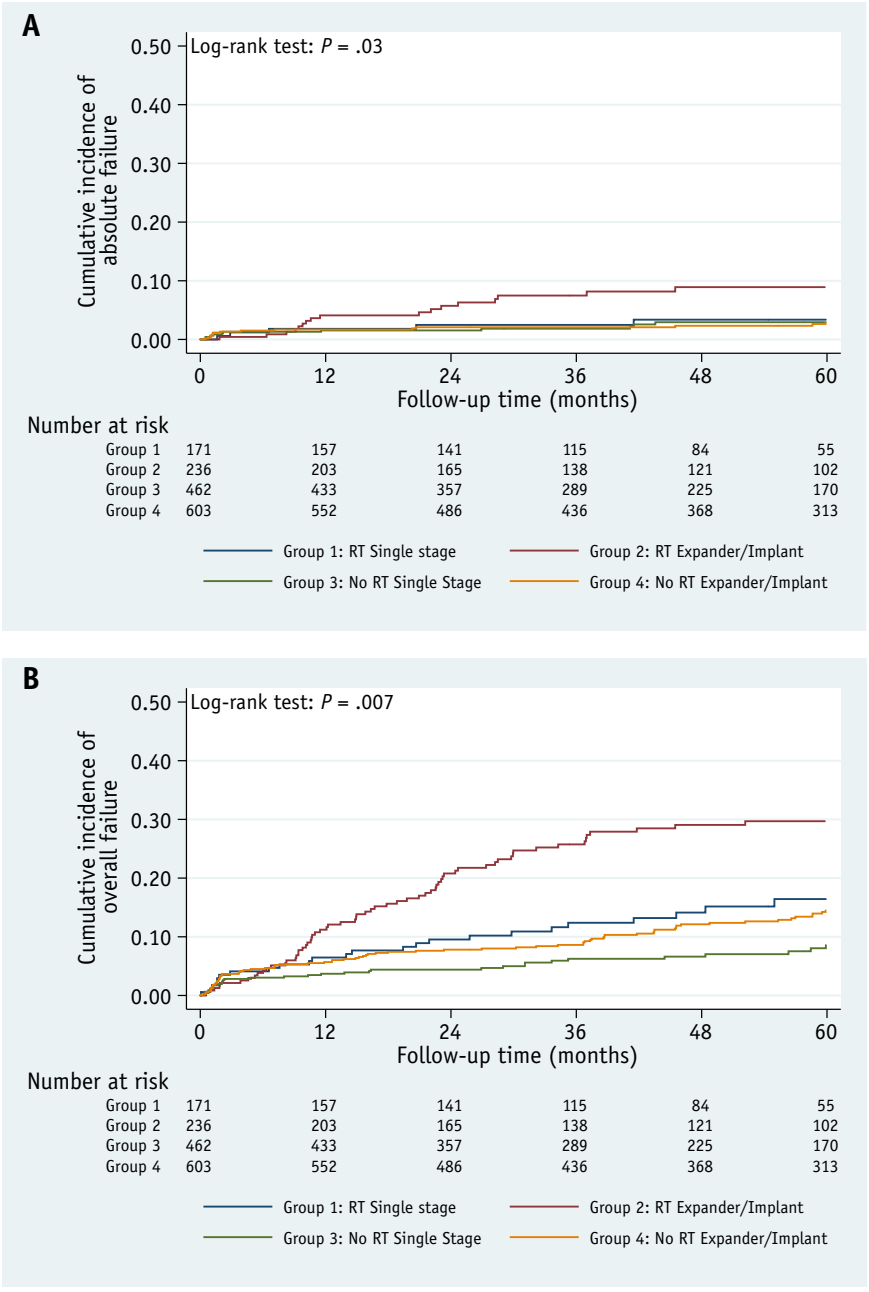

Fig. 2. (A) Cumulative incidence of absolute reconstruction failure per reconstructed breast with and without PMRT. (B) Cumulative incidence rate of overall implant failure per reconstructed breast with and without PMRT.

Table 4 Multivariable logistic models*

Variable/comparison	Odds ratio estimate (95% CI)	*P* value
Infection		
Two stages vs single-stage	2.9 (1.4-6.1)	.004
Autologous vs single-stage	0.77 (0.2-2.5)	.67
Current smoker vs nonsmoker	2.4 (0.8-6.9)	.08
Ex-smoker vs nonsmoker	1.1 (0.5-2.2)	.7
BMI at diagnosis ≥25 vs <25	1.9 (1.02-3.67)	.04
Boost vs no boost	2.2 (1.19-4.2)	.01
Skin necrosis		
Two stages vs single-stage	3.02 (1.21-7.54)	.018
Autologous vs single-stage	0.83 (0.19-3.5)	.8
Current smoker vs nonsmoker	3.06 (0.86-10.8)	.08
Ex-smoker vs nonsmoker	0.73 (0.3-1.77)	.49
BMI at diagnosis ≥25 vs <25	6.1 (2.32-16.31)	<.0001
Boost vs no boost	2.31 (1.03-5.17)	.041
Fat necrosis		
Two stages vs single-stage	0.83 (0.05-13.59)	.9
Autologous vs single-stage	21.2 (2.5-174.46)	.004
Current smoker vs nonsmoker	—	—
Ex-smoker vs nonsmoker	1.5 (0.39-6.03)	.53
BMI at diagnosis ≥25 vs <25	1.69 (0.4-7.09)	.47
Boost vs no boost	0.5 (0.12-2.26)	.39
Capsular contracture		
Two stages vs single-stage	2.63 (1.26-5.47)	.009
Current smoker vs nonsmoker	1.11 (0.29-4.18)	.87
Ex-smoker vs nonsmoker	0.97 (0.47-1.99)	.94
BMI at diagnosis ≥25 vs <25	1.44 (0.74-2.78)	.27
Boost vs no boost	2.06 (1.06-4.03)	.03
Implant exposure		
Two stages vs single-stage	3.16 (1.03-9.99)	.04
Current smoker vs nonsmoker	5.34 (1.38-20.55)	.01
Ex-smoker vs nonsmoker	1.22 (0.42-3.5)	.7
BMI at diagnosis ≥25 vs <25	2.2 (0.81-6.09)	.12
Boost vs no boost	2.9 (1.02-8.37)	.04
Absolute implant failure		
Two stages vs single-stage	2.7 (0.97-7.86)	.057
Current smoker vs nonsmoker	4.75 (1.42-15.9)	.011
Ex-smoker vs nonsmoker	0.56 (0.17-1.79)	.33
BMI at diagnosis ≥25 vs <25	1.6 (0.65-4.09)	.288
Boost vs no boost	2.1 (0.844-5.4)	.1
Overall implant failure		
Two stages vs single-stage	3.09 (1.8-5.13)	<.001
Current smoker vs nonsmoker	2.93 (1.1-7.77)	.03
Ex-smoker vs nonsmoker	1.02 (0.60-1.711)	.939
BMI at diagnosis ≥25 vs <25	2.15 (1.32-3.49)	.002
Boost vs no boost	1.86 (1.13-2.97)	.009

Abbreviation: CI = confidence interval.

* The unit of analysis in this model is the primary affected breast treated with immediate reconstruction followed by PMRT. Delayed reconstructions, prophylactic mastectomies with reconstruction are excluded from this model to achieve homogeneity.

diabetes, axillary lymph node dissection (ALND), age >50, nipple-sparing mastectomy, and adjuvant chemotherapy were not significantly associated with any complications. On multivariable analysis, TE/I compared with DTI was significantly associated with higher risks of infection and skin necrosis (OR = 2.9, P = .004 and OR = 3.0, P = .018, respectively). There was no significant difference between autologous reconstruction and DTI in terms of infection and skin necrosis. Autologous reconstruction was associated with more risks of fat necrosis compared with DTI and TE/I. For implant-related complications, we noted that TE/I compared with DTI was significantly associated with more risks of capsular contracture, implant exposure, and overall implant failure (OR = 2.6, P = .009; OR = 3.1, P = .04; and OR = 3, P < .0001, respectively). The absolute failure rate for TE/I (9.1%) compared with DTI (2.9%) was borderline significant (OR = 2.7; P = .057). It was not possible to analyze implant rupture on a multivariable level as 12 cases in the TE/I group suffered that outcome versus 0% in the DTI group.

Discussion

The rising trends in mastectomy, advancements in breast reconstruction techniques, along with increased indications for PMRT, have led to wide variability in surgical practice throughout the US.[21] The current National Comprehensive Cancer Network guidelines endorse either TE/I or autologous reconstruction with a lack of evidence comparing DTI to these 2 other reconstruction options.[22] Autologous reconstruction has been adopted by many institutions owing to an underlying belief in its safety, especially with PMRT.[23-25] Several studies comparing patient satisfaction with autologous versus TE/I reconstruction showed more satisfaction stability with autologous reconstruction over the time since surgery.[26-30] Despite all these advantages to an autologous approach, the longer operation times, longer recovery time, length of hospital stay, and donor-site morbidity do represent a burden for the patient and the caregiver.[4] A nationwide analysis of cost of autologous flaps showed wide variations in costs and complications across the United States with autologous reconstruction.[31]

Recently, TE/I reconstructions have become more common with the increased use of skin- and nipple-sparing mastectomies.[32] Yet the long-term complications reported with expanders in several studies, along with the need for several fillings, deflation, and another surgery for implant exchange, call into question the validity of this approach.[32] Also, the optimal timing for PMRT to the expander or implant after expander exchange remains debatable. This debate is extrapolated from the disruption of PMRT dosimetry in the presence of the expander either because of the presence of the metal port or the required coordinated filling and deflation with PMRT.[33-36] Furthermore, the exchange from the expander to permanent implant, regardless of radiation, might increase the risk of surgical complications. This was supported by our findings, in which a majority of complications within the TE/I group occurred after the exchange surgery with or without PMRT (75% and 65%, respectively).

Recently, more patients at our institution received DTI (Fig. E1, available online at https://doi.org/10.1016/j.ijrobp.2019.11.008), allowing completion of all surgeries in 1 setting and avoiding the above-mentioned disadvantages of both autologous and TE/I reconstruction.[15,37-41] Moreover, despite this rise in DTI rates, all 3 types of reconstructions remain offered at our institution depending on patient and physician preferences and discussion. Furthermore, a national cost-effectiveness analysis showed significant cost decrease and effectiveness of DTI compared with TE/I in postmastectomy settings.[42] It is to be noted that the Mastectomy Reconstruction Outcomes Consortium (MROC) study—the largest multicenter, observational, prospective study in breast reconstruction—included both TE/I and DTI. The final analysis of the irradiated breasts showed that implant reconstruction was significantly associated with higher complication rates compared with autologous. However, this analysis did not stratify by implant subtypes DTI or TE/I.[43] Unlike the MROC study, in our cohort, we couldn't compare the different types of autologous flaps to DTI or TE/I as the number of each type was relatively small.

Without PMRT, the 5-year cumulative incidence rates of any complication were similar in autologous and DTI (11.2% and 12.6%, respectively), and there was a higher incidence of complications in TE/I-reconstructed breasts (19.5%). The addition of PMRT resulted in increased 5-year cumulative risk for complications across the 3 reconstruction types, and the increase was more significant in TE/I (36.8%) compared with DTI and autologous (18.2% and 15.1%, respectively). The reported rates of complication within TE/I and autologous in PMRT settings were comparable with other studies.[20,44-49]

Because immediate reconstruction is being more commonly used, as it is associated with better psychological outcomes for the patients, and PMRT is known to be detrimental in such settings, we decided to restrict our multivariable analysis to immediately reconstructed breasts followed by PMRT. The goal of such restriction was to explore the reconstruction type associated with fewer complications in a setting with a more homogeneous patient population. This restriction also allowed us to evaluate the effect of PMRT on the reconstructed breasts as the delayed autologous cases received PMRT before reconstruction. However, our study was not designed to explore differences between immediate and delayed autologous reconstruction; also, relatively small numbers of delayed autologous reconstruction with PMRT (32 of 122, 26%) will underpower any analysis in this regard. Results from a recent meta-analysis demonstrated that immediate versus delayed autologous reconstruction had similar complication rates.[50] The multivariable model adjusted for other risk factors such as increased BMI, smoking, and use of a radiation boost showed that TE/I is significantly associated with higher odds of infection and skin necrosis compared with DTI (OR = 2.9, P = .004 and OR = 3.02, P = .018, respectively), whereas DTI and autologous were not significantly different from each other. Fat necrosis was higher in autologous reconstruction compared with DTI and TE/I, and these findings were comparable to other studies.[51]

For implant-related complications such as capsular contracture, implant exposure, and absolute and overall implant failure, the rates were higher in TE/I compared with DTI in settings of both PMRT and no PMRT. Again, the adjusted multivariable analysis showed significant increased risk of implant related complications with TE/I compared with DTI in settings of PMRT after immediate reconstruction.

The results of our study suggest the superiority of the DTI approach compared with TE/I and its comparable safety profile to autologous. Although patient eligibility for DTI depends on the skin flap condition, aggressive postoperative treatments, and extensive ALND versus sentinel node sampling, we haven't found that nipple-sparing mastectomy—known for preserving the skin flap close to normal[52]—or ALND or adjuvant chemotherapy affects the complications (Fig. E2, available online at https://doi.org/10.1016/j.ijrobp.2019.11.008). These findings are endorsed by other studies.[30,53] Of note, the choice of reconstruction is driven by many factors such as patient's preference, patient's anatomy, physician assessment, and patient tolerance to PMRT. Despite the advancements in radiation techniques and surgical techniques for use as spy angiography to intraoperatively assess flap vascularity and increased rates of acellular dermal matrix use in implant-based reconstruction, the pitfalls for TE/I in the form of second surgery and donor-site morbidity for autologous reconstruction could make those options potentially less desirable. Therefore, our results provide the data for appropriately selected patients -mostly desiring same breast size for whom immediate single-stage implant reconstruction could be beneficial-, that the side effects profile for DTI was found to be comparable to that of autologous reconstruction but with less surgical burden. Yet future dosimetry studies assessing the impact of DTI on PMRT delivery as well as different radiation techniques in the presence of permanent implants versus expanders are needed.[54]

Limitations of our study include its retrospective nature, which our multivariable analysis attempted to address by adjusting for several risk factors. Although randomization would overcome the pitfalls of observational studies, this remains challenging to achieve in breast reconstruction given the impact of strong preferences by patients, surgeon experience, and institutional practice patterns in driving the choice for reconstruction. Inclusion of the 3 types of reconstruction in our study from the same institution helped minimize institutional biases as well as surgical experiences biases.

The unadjusted cumulative incidence rates as well as crude odds ratios stratified by PMRT status included delayed reconstructed breasts and prophylactic reconstructed breasts. Despite this heterogeneity reflecting daily

clinical practice reconstruction options, DTI remained superior to TE/I and comparable to autologous with and without PMRT. To overcome such heterogeneity, we restricted our multivariable analysis to immediately reconstructed breasts followed by PMRT delivery. In our study, the great majority of the TE/I group received PMRT to the expander. Therefore, we couldn't evaluate whether it is better to irradiate before or after the expander exchange to implant in TE/I group. Consequently, introducing the single-stage approach instead of TE/I for patients requiring PMRT and desiring reconstruction will avoid the debate over whether to irradiate the expander or the implant. The nature of our study hindered the collection of patient-reported surveys, as well as evaluation of the cost-effectiveness between the 3 groups.

To this end, we conclude that single-stage direct-to-implant reconstruction had significantly lower complication rates than TE/I with and without PMRT. Single-stage complications were not significantly different from autologous with and without PMRT. Single-stage reconstruction may offer a valuable option for patients receiving PMRT.

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Clinical Investigation

The Impact of Chest Wall Boost on Reconstruction Complications and Local Control in Patients Treated for Breast Cancer

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Summary

Chest wall boost (CWB) is a common practice in post-mastectomy radiation therapy (PMRT) in the United States, where more than 65% of women receiving PMRT receive CWB. We studied 746 patients who received PMRT and reconstruction; 379 (51%) of them received

Purpose: Giving an additional radiation dose to the incision or chest wall has been a practice, but it has never been studied in a randomized setting, and it might lead to inferior cosmetic outcomes. This study aims to evaluate whether delivery of a chest wall boost (CWB) to the mastectomy scar or chest wall is independently associated with reconstruction complications and to assess its disease control efficacy in the setting of breast reconstruction.

Methods and Materials: We conducted a retrospective chart review of 746 patients with breast cancer who underwent mastectomy, breast reconstruction, and PMRT; all underwent treatment at our institution during 1997 to 2016. Various reconstruction techniques were used among this cohort including autologous reconstruction, single-stage direct-to-implant reconstruction, and 2-stage tissue expander implant. Cohorts were divided by administration of CWB. The primary objective was comparing the

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CWB, and the remaining 367 (49%) did not. On multivariate analysis, CWB was significantly associated with reconstruction complications and failure and was not associated with local tumor control benefits, even in high-risk subgroups.

rate of reconstruction complications including skin necrosis, fat necrosis and infection between groups. Subgroup analysis for patients with implant-based reconstruction was performed to evaluate the effect of CWB on implant-related complications such as capsular contracture, implant exposure, and implant failure. The secondary objective was comparison of the cumulative incidence of local failure between groups overall and within clinically high-risk subgroups.

Results: The median follow-up was 5.2 years. Most clinicopathologic features were well balanced between the 379 (51%) patients who received CWB and the 367 (49%) who did not. On multivariate analysis, CWB was significantly associated with infection, skin necrosis, and implant exposure. For implant reconstruction patients, CWB independently increased risks of implant failure. CWB administration was not associated with local tumor control benefits, even in high-risk subgroups.

Conclusions: Our findings suggest that omission of chest wall boost in postmastectomy radiation improves breast reconstruction outcomes without compromising local tumor control. © 2019 Elsevier Inc. All rights reserved.

Introduction

The challenge for patients with breast cancer who are undergoing mastectomy, reconstruction, and radiation therapy lies in preserving esthetic outcomes while maintaining tumor control.[1] Despite the therapeutic benefit of postmastectomy radiation (PMRT) in locally advanced breast cancer patients, the optimal integration of PMRT in the setting of breast reconstruction remains a challenge.[2] Several studies have demonstrated the negative effects of PMRT on breast reconstruction, including flap fibrosis, fat necrosis, and implant shrinkage that could lead to revision surgeries or complete reconstruction failure.[3-7] One study of 62,442 patients who underwent mastectomy in the United States indicates that reconstruction rates tend to be higher in the settings where PMRT is not indicated,[8] reflecting the bias of caregivers and patients to avoid reconstruction when the requirement for PMRT is known.

Recent research studies have focused on optimizing PMRT delivery by assessing the timing of reconstruction in relation to PMRT,[9-11] the best type of reconstruction,[12,13] and advances in planning and PMRT delivery.[2] However, aspects of PMRT techniques, such as using chest wall boost (CWB), which is delivered to the mastectomy chest wall or scar with the aim of improving local tumor control, have yet to be explored in the setting of breast reconstruction.

A pattern of care analysis using the National Cancer Database showed that among 51,660 patients who received PMRT in the United States, 65% received CWB.[14] Similarly, a survey filled by 271 radiation oncologists revealed that CWB was delivered in clinically high-risk patients or omitted to preserve reconstruction outcomes.[15] These studies indicate a wide variation in utilization of a CWB, with factors such perceived risk, conflicting evidence about CWB and tumor control,[16-19] and the relative benefits and hazards of PMRT in the setting of reconstruction making the decision more challenging.

The aim of this study was to evaluate the impact of CWB on the reconstruction outcome and local control in patients who underwent mastectomy, breast reconstruction, and PMRT.

Methods and Materials

After IRB approval was obtained, a chart review was conducted for all female patients with invasive breast cancer who had undergone any type of breast reconstruction and PMRT at our institution between 1997 and 2016 (N = 872). Inclusion criteria required all patients with primary tumor treated with mastectomy and reconstruction followed by PMRT. Patients treated with mastectomy and PMRT for local recurrence, patients with secondary contralateral breast cancer, inflammatory breast cancer, or stage IV cancer at diagnosis were excluded (as depicted in supplementary consort diagram). Only patients with accessible radiation records and reconstruction surgical notes were included. After applying these criteria, 746 patients were eligible for inclusion in the final study population. The clinicopathologic data including radiation plans and reconstruction notes were stored in our database using REDCap 7.0.14 (Vanderbilt University, Tennessee).

Radiation therapy and reconstruction surgery

All patients received chest wall radiation with a median dose of 50.4 Gy in 28 fractions. The study cohort was divided into 2 groups: CWB and no-boost. The CWB group

received an additional median dose of 10 Gy in 5 fractions. CWB was delivered at the discretion of the treating physician, based on risk factors without institutional guidelines. The CWB field target included the full length of the mastectomy scar plus a circumferential 2 to 3 cm of surrounding chest wall or most chest wall using 6 to 9 Mev electrons using a bolus. All radiation therapy was delivered with external beam, and the majority of plans were 3-dimensional conformal using a skin bolus of 3 to 5 mm thickness, applied every other day.

Both autologous and implant-based reconstruction were included. Reconstruction complications were captured from operative notes for patients who underwent revision surgeries after radiation therapy. The definitions of these complications were based on the physician intraoperative assessment as infection requiring surgical washout, skin necrosis requiring debridement, capsular contracture requiring release of the capsule, and symmetry procedure. Two different endpoints for reconstruction failure were considered: "Absolute reconstruction failure" defined as tissue expander (TE) or permanent implant (PI) removal with failure to replace and no salvage reconstruction. "Overall implant failure" was defined as PI removal regardless of the replacement outcome.

Statistical Analysis

Primary endpoints

Univariate and multivariate logistic regression models were used to evaluate the association between CWB and odds of reconstruction complications including infection, skin necrosis, fat necrosis, and seroma or hematoma. Subgroup analyses were performed among patients who had implant-based reconstruction to assess whether CWB was associated with risk of implant-related complications, including capsular contracture, implant rupture, implant exposure, absolute reconstruction failure, and overall implant failure. Patient and treatment-related characteristics evaluated in the reconstruction complication models include age at diagnosis, body mass index (BMI $\leq$ 25 vs $>$25 kg/m^2), smoking (active smoker vs former or never smoker), type of reconstruction (single-stage implant vs 2-stage implant with TE vs autologous reconstruction), timing of reconstruction (immediate vs delayed), type of chemotherapy (adjuvant only, neoadjuvant with or without adjuvant or none), and use of tangent bolus (yes or no).

Secondary endpoint

The Kaplan-Meier method was used to estimate the cumulative incidence of locoregional recurrence (LRR) rates at 5 and 10 years after diagnosis, overall and by CWB group. Univariate and multivariate Cox proportional hazards models were used to assess the association between CWB and LRR. CWB was defined as a time-dependent covariate in these models. Additional covariates included tumor stage, grade, nodal involvement, lymphovascular involvement, margin status, hormone receptors. Subgroup analyses based on clinical risk factors for LRR were performed to evaluate benefit of CWB.

Results

Patients characteristics

Among the 746 breast cancer patients in the study population, 379 (51%) received CWB and 367 (49%) did not. The median follow-up was 5.2 years (range, 0.4-20.5 years). Age, BMI, smoking status, tumor grade, overall stage, final margins, and hormonal status were balanced between both groups (Table 1). Patients with lymphovascular invasion (N = 386; 55%) were more likely to receive CWB (211 of 386; 55%) versus (175 of 386; 45%) in the no-boost group (P = .01). The majority (559 of 746; 75%) of the study cohort underwent implant-based reconstruction. The boost cohort was more likely to have autologous reconstruction (104 of 379; 27%) than the no-boost cohort (83 of 369; 22%), although this difference did not achieve statistical significance (P = .06). Overall, 94 of 746 patients (13%) received delayed reconstruction after PMRT and 71 of 94 patients (75.5%) in this group were in the CWB cohort, whereas 23 of 94 patients (24.5%) were not (P < .001). Furthermore, a majority of patients in the delayed reconstruction group (81 of 94; 86%) specifically had autologous reconstruction. Patients who received adjuvant chemotherapy were similar, whereas more CWB patients received neoadjuvant chemotherapy compared with the no-boost group (Table 1).

Reconstruction complications

Among patients who received CWB, 13% (48 of 379) developed reconstruction infection versus 6% (22 of 367) in the no-boost cohort (odds ratio [OR], 2.27; P < .01; Table 2). The rate of skin necrosis was 8% in the boost group (29 of 379) versus 3% (11 of 367) in the no-boost group (OR, 2.68; P < .01). There was no significant difference between cohorts in the terms of seroma or hematoma and fat necrosis (OR, 0.87 [P = .76] and OR, 1.8 [P = .17], respectively; Table 2).

Univariate logistic regression was used to determine other clinical factors related to infection and skin necrosis. Two-stage expander−implant reconstruction but not single-stage reconstruction was significantly associated with higher risks of complications compared with autologous reconstruction. Other clinical factors such as BMI > 25 kg/m^2 and smoking were associated with complications. Delayed reconstruction in comparison with immediate reconstruction was associated with lower rates of reconstruction infection, but not other complications, on univariate analysis. Other clinical factors,

Table 1 Distribution of clinicopathologic features among boost and no-boost groups

Demographics	No boost (n = 367)	Boost (n = 379)	Total (N = 746)	*P* value
Median age, years (range)	46.6 (24.8-79.7)	45.8 (20.3-76.2)	46.4 (20.3-79.7)	.3
Reconstruction type				.06
Autologous	83 (22%)	104 (27%)	187 (25%)	
Single stage	145 (40%)	120 (32%)	265 (36%)	
Two stage	139 (38%)	155 (41%)	294 (39%)	
Overall stage				.21
0*	24 (6.5%)	20 (5%)	44 (6%)	
1*	32 (9%)	38 (10%)	70 (9%)	
2	203 (55%)	186 (49%)	389 (52%)	
3	108 (29.5%)	135 (36%)	243 (33%)	
T stage				.12
T0†	34 (9.2%)	29 (7.6%)	63 (8.5%)	
T1	156 (42.51%)	131 (34.6%)	287 (38.5%)	
T2	129 (35.15%)	154 (40.6%)	283 (38%)	
T3	45 (12.26%)	61 (16%)	106 (1.5%)	
T4	3 (0.82%)	4 (1.0%)	7 (9.5%)	
N stage				.02
N0	93 (25%)	109 (29%)	202 (27%)	
N1	194 (53%)	168 (44%)	362 (48.5%)	
N2	57 (15.5%)	59 (16%)	116 (15.5%)	
N3	23 (6.5%)	43 (11%)	66 (9%)	
Hormonal status				.92
ER Positive	302 (82.3%)	317 (83%)	619 (83%)	
ER Negative	57 (15.5%)	62 (17%)	119 (16%)	
Unknown	8 (2.2%)	0	8 (1%)	
HER2 FISH				.4
Positive	49 (13.3%)	66 (17.4%)	115 (15.5%)	
Negative	209 (57%)	235 (62%)	444 (59.5%)	
Unknown	109 (29.7%)	78 (20.6%)	187 (25%)	
LVI				.01
Negative	174 (47.4%)	145 (38.3%)	319 (42.8%)	
Positive or suspicious	175 (47.6%)	211 (55.7%)	386 (51.7%)	
Unknown	18 (5%)	23 (6%)	41 (5.5%)	
Final margins				.78
Negative	279 (76%)	280 (73.9%)	559 (75%)	
Close <2 mm including <1 mm	70 (19%)	80 (21.1%)	150 (20%)	
Positive	18 (5%)	19 (5%)	37 (5%)	
Final tumor grade				.46
1	15 (4.1%)	18 (4.7%)	33 (4.4%)	
2	184 (50.1%)	174 (46%)	358 (48%)	
3	162 (44.1%)	182 (48%)	344 (46.1%)	
Not assessed	6 (1.6%)	5 (1.3%)	11 (1.5%)	
Body mass index at diagnosis				.09
<25 kg/m^2	169 (46%)	156 (41.2%)	325 (43.6%)	
≥25 kg/m^2	169 (46%)	205 (54%)	374 (50.1%)	
Unknown	29 (8%)	18 (4.8%)	47 (6.3%)	
Smoking status				.24
Active smoker	328 (89.3%)	342 (90.2%)	670 (89.8%)	
Non active smoker	20 (5.4%)	30 (8%)	50 (6.8%)	
Unknown	19 (5.1%)	7 (1.8%)	26 (3.4%)	
Chemotherapy				.01
Adjuvant only	226 (61.5%)	226 (59%)	452 (61%)	
Neoadjuvant with or without adjuvant	110 (30%)	138 (37%)	248 (33%)	
None	31 (8.5%)	15 (4%)	46 (6%)	

(*continued on next page*)

Table 1 (*continued*)

Demographics	No boost (n = 367)	Boost (n = 379)	Total (N = 746)	*P* value
Reconstruction time				<.001
Immediate	344 (94%)	308 (81%)	652 (87%)	
Delayed	23 (6%)	71 (19%)	94 (13%)	
Tangent bolus				<.001
Yes	206 (56.1%)	279 (73.7%)	485 (65%)	
No	109 (29.7%)	63 (16.6%)	172 (23%)	
Not reported	52 (14.2%)	37 (9.7%)	89 (12%)	

Abbreviations: ER = Estrogen Receptor; FISH = fluorescence in situ hybridization; HER2 = Human epidermal growth factor receptor 2; LVI = lymphovascular invasion.

To compare between continuous and dichotomous characteristics in both groups we used Man Whitney test and Fischer exact test, respectively.

* All stage 0 and stage 1 in both groups are neoadjuvant cases that showed complete or partial response during surgery.

† T0 cases include neoadjuvant cases whom surgical pathology did not show any tumor in breast.

including chemotherapy, bolus, and age, were not associated with complications.

The multivariate analysis (Table 3) revealed that CWB was significantly associated with reconstruction infection (OR, 2.43; $P < .01$) and skin necrosis (OR, 2.61; $P = .01$). It also demonstrated that 2-stage reconstruction with an expander compared with autologous was significantly associated with increased rates of both infection and necrosis (OR, 5.84 [$P < .01$] and OR, 3.25 [$P = .01$], respectively), whereas single-stage reconstruction compared with autologous was not associated with either complication (Table 3).

Subgroup analysis for implant related complications

In our study cohort, 559 of 746 patients (75%) received implant-based reconstruction with either 2-stage expander−implant reconstruction (39%) or single-stage permanent implant (35.5%). Among this subgroup, 49% (275 of 559) received CWB, and 51% (284 of 559) received no boost (Table 4). The difference in the frequency of the 2 reconstruction types among CWB and no-boost group was not significant ($P = .07$). Results showed that 7.6% of the CWB group (21 of 275) developed implant exposure versus 1.76% in the no-boost (5 of 284; OR, 4.6; $P = .0025$). There was borderline significance between both groups in terms of capsular contracture (8.4% in no-boost versus 13.4% in boost; OR, 1.6; $P = .059$). There was no significant difference between the CWB and no-boost group in terms of implant rupture (2.5% vs 1.4%; OR, 1.8; $P = .34$).

Administration of CWB was significantly associated with both types of failure; 10.18% (28 of 275) and 3.8% (11 of 284) developed absolute reconstruction failure in the boost and no-boost groups, respectively (OR, 2.8; $P < .01$). Furthermore, 34.5% (95 of 275) of the boost group developed overall implant failure with or without salvage reconstruction, compared with 19.3% (55 of 284) of the no-boost group (OR, 2.19; $P < .0001$). Other factors, such as active smoking, BMI > 25 kg/m^2 at diagnosis, and 2-stage reconstruction were associated with higher rates of reconstruction failure on univariate level, whereas chemotherapy, use of skin bolus, delayed reconstruction, and age were not associated with any implant-based complications.

The multivariate analysis (Table 5) showed that CWB remained significantly associated with higher rates of implant exposure, absolute reconstruction failure, and overall implant failure (OR, 4.02 [$P < .01$]; OR, 3.15 [$P < .01$]; OR, 2.04 [$P < .001$], respectively), adjusted for other significant risk factors. The association between increased risk of capsular contracture and CWB was not significant on multivariate analysis ($P = .09$).

Local tumor control outcomes

After median follow-up of 5.2 years since diagnosis, the overall 5-year cumulative incidence of LRR was 3.7% for

Table 2 Reconstruction complication rates in patients treated with and without chest wall boost

Complication	No boost (n = 367)	Boost (n = 379)	OR (95% CI)	*P* value
Infection	22 (6.00%)	48 (13.00%)	2.27 (1.34-3.85)	<.01
Skin necrosis	11 (3.00%)	29 (7.65%)	2.68 (1.32-5.45)	<.01
Fat necrosis	10 (2.72%)	9 (2.37%)	0.86 (0.35-2.16)	.76
Seroma or hematoma	8 (2.18%)	15 (3.96%)	1.85 (0.77-4.41)	.16

Abbreviations: CI = confidence interval; OR = odds ratio.

Table 3 Multivariate results for risk of infection and skin necrosis

Variable or comparison	OR estimate (95% CI)	*P* value
Infection		
Boost vs No boost	2.44 (1.38-4.30)	<.01
BMI at diagnosis ≥25 vs <25 kg/m^2	1.88 (1.08-3.27)	.025
Reconstruction type: 2 stages vs autologous	5.84 (2.38-14.32)	<.01
Reconstruction type: single stage vs autologous	2.32 (0.89-6.07)	.08
Skin necrosis		
Boost vs No boost	2.62 (1.23-5.54)	.01
BMI at diagnosis ≥25 vs <25 kg/m^2	4.46 (1.96-10.15)	<.01
Current smoker (yes vs no)	2.56 (0.97-6.75)	.05
Reconstruction type: 2 stages vs autologous	3.25 (1.3-8.07)	.01
Reconstruction type: single stage vs autologous	1.12 (0.40-3.16)	.82

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

the entire cohort (95% confidence interval [CI], 2.5%-5.5%). All patients were free of LRR events at the start of follow-up in this analysis. There was no significant difference between cohorts in LRR cumulative incidence (P = .81). Five-year cumulative incidence of LRR was 2.9% (95% CI, 1.5%-5.6%) in the no-boost group and 4.4% (95% CI, 2.7%-7.2%) in the CWB group, and the 10-year LRR incidence rates were 5.4% (95% CI, 3.3%-8.6%) in the no-boost and 4.3% (95% CI, 2.3%-7.9%) in CWB groups, respectively (Fig. 1A).

Unadjusted and adjusted Cox proportional hazards models were used to assess clinical factors associated with local failure supplementary table in supplementary materials. The multivariate analysis revealed that CWB treatment did not protect against local failure (hazard ratio [HR], 1.16; P = .72). Only lymphovascular invasion (LVI) was associated with higher risks of LRR on multivariate analysis. Subgroup analysis for those with LVI showed that CWB was not beneficial in this subgroup at high risk for local failure (HR, 1.05; P = .92; Fig. 1B). Furthermore, adding CWB did not improve local control for patients with close or positive margins (HR, 1.11; P = .89; Fig. 1C), partial response or tumor progression after neoadjuvant therapy (HR, 0.76; P = .60; Fig. 1D), or those younger than 40 years at diagnosis (HR, 0.64; P = .50).

Discussion

Patients with breast cancer who are undergoing PMRT typically receive radiation doses between 50 and 50.4 Gy in 1.8- to 2-Gy fractions daily, 5 days per week.[20] Adding CWB to the mastectomy scar or chest wall for at least a total dose of 60 to 60.4 Gy remains debatable among radiation oncologists.[15,16] The rationale for boost is extrapolated from clinical evidence of improved local tumor control with a boost to the lumpectomy cavity in a breast-conserving management setting.[21] The lack of structured guidelines along with limited data supporting CWB benefits in PMRT has led to wide variability of practices among institutions.[14,15] On the other hand, the challenge in combining reconstruction and PMRT requires the optimization of radiation techniques being used.[2] Our study evaluates the effects of adding CWB on reconstructed breast and tumor control outcome to assess the risk-and-benefit dilemma faced by the treating physician. Our study demonstrated on multivariate analysis that CWB administration significantly increased reconstruction complications (infection [OR, 2.43; P < .01] and skin necrosis [OR, 2.61; P = .01]), regardless of the type of reconstruction; for implant-based groups, it was significantly associated with reconstruction failure. Reconstruction failure was defined as either absolute or overall because of the

Table 4 Rates of implant-related complications among implant-based reconstruction patients treated with and without chest wall boost

Complication	No boost (n = 284)	Boost (n = 275)	OR (95% CI)	*P* value
Implant exposure	5 (1.76%)	21 (7.64%)	4.61 (1.71-12.41)	<.01
Absolute reconstruction failure*	11 (3.87%)	28 (10.18%)	2.81 (1.37-5.77)	<.01
Overall implant failure†	55 (19%)	95 (35%)	2.19 (1.49-3.23)	<.0001
Capsular contracture	24 (8.45%)	37 (13%)	1.68 (0.97-2.89)	.059
Implant rupture	4 (1.41%)	7 (2.55%)	1.82 (0.52-6.31)	.34

Abbreviations: CI = confidence interval; OR = odds ratio.

* Absolute reconstruction failure defined as tissue expander or permanent implant removal with failure to replace and no salvage reconstruction.

† Overall implant failure defined permanent implant removal with or without salvage reconstruction and ii).

Table 5 Multivariate results for risk of implant- related complications

Variable or comparison	OR estimate (95% CI)	*P* value
Implant exposure		
Boost vs No boost	4.01 (1.47-10.91)	<.01
Current smoker vs No smoker	3.38 (1.14-9.99)	.027
Two stages vs Single stage	2.85 (1.11-7.30)	.028
Absolute reconstruction failure		
Boost vs No boost	3.15 (1.45-6.86)	<.01
Current smoker vs No smoker	2.43 (0.86-6.85)	.091
Overall implant failure		
Boost vs No boost	2.03 (1.34-3.09)	<.001
BMI at diagnosis $\geq$ 25 vs <25 kg/m^2	2.06 (1.36-3.15)	<.001
Current smoker vs No smoker	3.72 (1.72-8.02)	<.001
Two stages vs Single stage	2.81 (1.82-4.33)	<.0001
Capsular contracture		
Boost vs No boost	1.60 (0.93-2.77)	.08
Two stages vs Single stage	2.09 (1.18-3.70)	.01

Abbreviations: BMI = body mass index; CI = confidence interval; OR = odds ratio.

lack of universal definition. Some studies defined it as removal of the implant−expander without salvage reconstruction,[22,23] whereas others defined it as TE implant or PI removal regardless of implant replacement outcome (i.e., need for correction surgery after PMRT).[24-26] Regardless of how it is defined, CWB was significantly and independently associated with both reconstruction failure classifications. This finding is supported by the knowledge that radiation induces complex tissue changes as scar formation, capsular contracture, impaired skin healing and flap fibrosis, and atrophy of autologous tissues.[1]

Furthermore, our study did not demonstrate that CWB improves local control outcomes, suggesting that the hazards of reconstruction from the CWB outweighs any potential benefit in local control. In our study, we found that tumor characteristics such as stage, hormonal receptors, and grade were well balanced between both groups, except for LVI, which was more prevalent in the boost cohort. It should be noted that CWB was given at the discretion of the treating physician, which explains the imbalance of LVI between cohorts. Therefore, we performed a Cox multivariate analysis for local failure adjusting for all different types of clinical risk factors, and CWB did not show any significant benefit.

Considering the low number of local recurrence events in our study, it could be inferred that CWB was beneficial only for patients with high-risk factors. With that assumption in mind, we conducted several subgroup analyses of high-risk patients with features such as positive LVI, young age at diagnosis (<40 years), incomplete response to neoadjuvant chemotherapy, and close or positive margins. In each of these subgroups, there was no significant difference in the cumulative incidence of local failure between those who received CWB and those who did not, suggesting that 50 to 50.4 Gy to the chest wall is sufficient to achieve a high local control rate. Nevertheless, given the low incidence of locoregional failure in our study population, we cannot rule out that the possibility of inadequate power to detect a subtle effect of CWB.Few retrospective studies have evaluated the effect of CWB on local control in PMRT settings. A prior investigation of 256 patients with inflammatory breast cancer suggested a benefit to the use of CWB to a total dose of 66 Gy in high-risk patients with progression after neoadjuvant chemotherapy.[19] In our study, we excluded all inflammatory breast cancer patients because they are typically treated with CWB. Another study by Panoff et al[17] included 582 patients and defined CWB as dose greater than 50.4 Gy. The study reported the 5-year cumulative incidence rate of local recurrence in patients receiving a total dose of <50.4 Gy and >50.4 Gy as 12.7% and 5.7%, respectively[17]; however, only 7.3% (43 of 582) of cohort received no boost, and the study included inflammatory breast cancer patients (73 of 582).

A large analysis of 4747 women in California cancer registry (including 195 women with stage IV cancer) concluded from multivariate analysis that CWB was not associated with any improvement of breast cancer and overall survival. The subgroup analysis from their study showed that omitting CWB is hazardous only in patients who did not receive chemotherapy which was 14.7% (701 of 4747) of the whole cohort (6.6% with no boost and 8.1% with boost; HR, 1.77; $P = .016$).[16] In contrast, 6.2% (46 of 746) of patients in our study did not receive chemotherapy, and none of them developed local failure; therefore, the role of CWB in this subgroup of our cohort could not be validated. A study of 339 patients by Shah et al,[18] including those with stage IV disease, found no significant difference in cumulative incidence of local recurrence between the group who received CWB and those who did not. In a more recent detailed report, Albert et al[27] analyzed 140

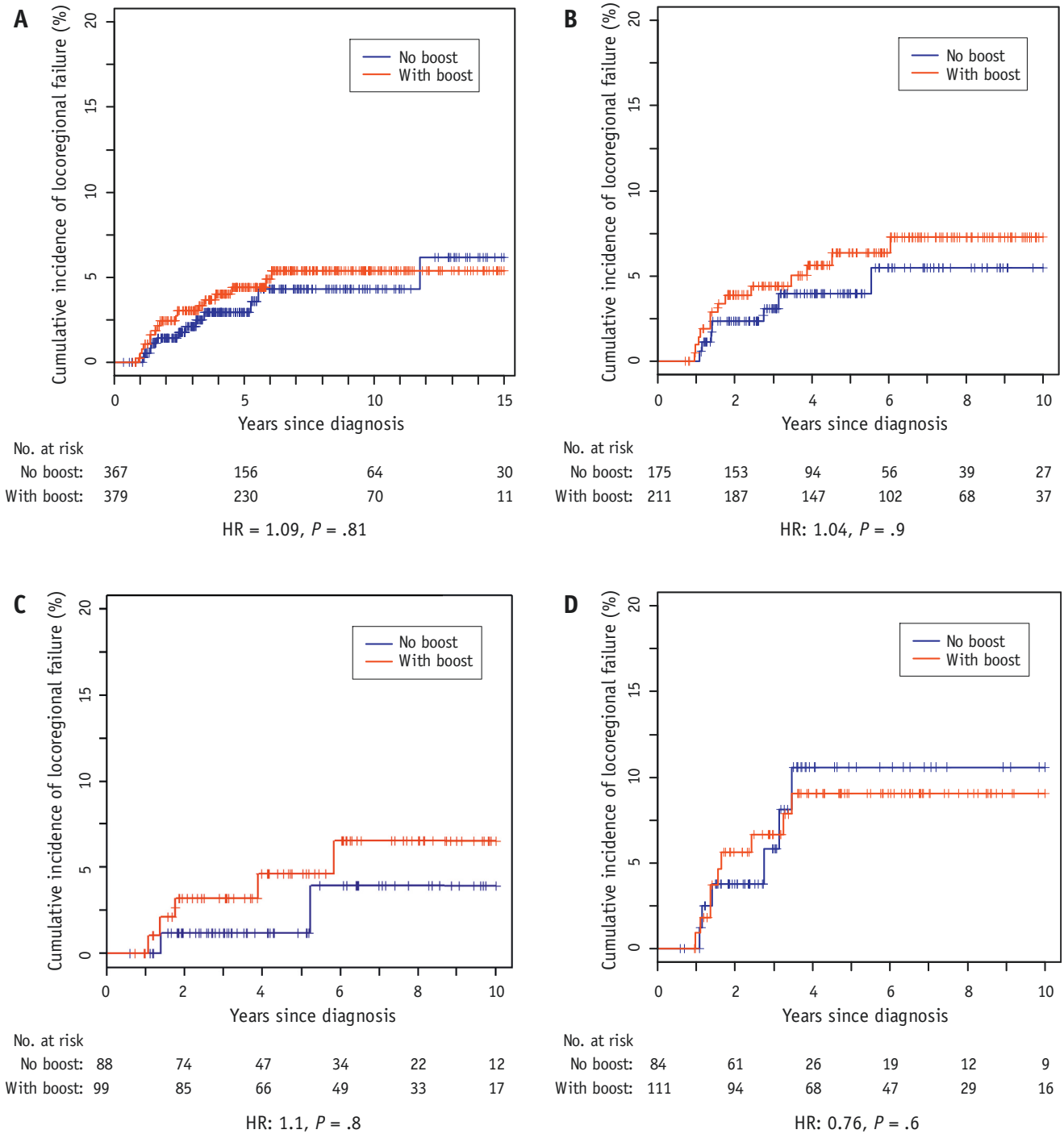

Fig. 1. (A) Cumulative incidence of locoregional failure by treatment with chest wall boost (N = 746). (B) Cumulative incidence of locoregional failure by treatment with chest wall boost among patients with lymphovascular invasion (N = 386). (C) Cumulative incidence of locoregional failure by treatment with chest wall boost among patients with positive or close margins (N = 187). (D) Cumulative incidence of locoregional failure by treatment with chest wall boost among patients who did not respond to neoadjuvant therapy (N = 195).

patients—46 patients (33%) of whom did not receive CWB. There was no significant difference in local control between the 2 groups. Subgroup analysis from their study showed that boost was not significantly associated with any improvement of 5-year local control for patients with lymphovascular invasion, close margins, or high-risk T4 tumors. Collectively, these results support our findings of the lack of benefit from CWB, even in high-risk groups.

Unique strengths of our study include the large population of patients with PMRT and reconstruction, and

inclusion of various types of reconstruction—with their inherently different complication profiles—which allowed us to demonstrate the hazardous effect of CWB irrespective of reconstruction types. Considering the heterogenicity of reconstruction, we conducted subgroup analysis for those with implant-based reconstruction to assess implant failure, capsular contracture, and implant exposure. Furthermore, including a large cohort with either 2-stage expander−implant reconstruction or single-stage direct implant in PMRT settings enabled us to study the single-stage implant as a factor affecting reconstruction complications in PMRT settings. Given the retrospective nature of the study, we were unable to capture whether receipt of CWB prevented delayed reconstruction. In addition, the influence of reconstruction complications on quality of life using validated patient-reported outcomes was not included. For capsular contracture definition, we could not assess its severity using a grading scale such as the Baker scale. Rather, we used the surgical operational note for releasing the capsule (capsulotomy) as our guide to identify capsular contracture in an objective manner. Finally, we acknowledge that complications such as infection, skin necrosis, and reconstruction failure can be multifactorial, which we addressed by controlling for established risk factors as high BMI at diagnosis,[28] smoking,[29,30] and type and timing of reconstruction either delayed or immediate in the analysis of reconstruction outcomes.

Conclusion

Our study results suggest that in patients with breast cancer treated with mastectomy followed by reconstruction and PMRT, the addition of a scar or CWB does not improve local control rate. In lieu of a clinical benefit, it significantly increases the rate of reconstruction complications and failure. Thus, CWB should not be used routinely for patients receiving postmastectomy radiation.

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Summary and conclusions:

First Project: We compared the 3 different breast reconstruction approaches with and without PMRT. PMRT increased complications across all reconstruction types. However, its impact on single-stage reconstruction was 50% lower than on tissue expander and implant and was close to autologous reconstruction. Single-stage breast reconstruction is a promising strategy, particularly when PMRT is indicated.

Second Project: We studied 746 patients who received PMRT and reconstruction; 379 (51%) of them received CWB, and the remaining 367 (49%) did not. On multivariate analysis, CWB was significantly associated with reconstruction complications and failure and was not associated with local tumor control benefits, even in high-risk subgroups.

Strengths and Weaknesses:

In both studies, inclusion of all patients from a single institution limited surgical biases. Also, analyzing different reconstruction types in both papers allowed generalization of the results. Different analyses: Regression and Time to event analyses both showed similar results in terms of complications and reiterating the increased complication rates either with expanders or with chest wall boost. Despite this might seem intuitive that second surgery as well as an extra radiation dose might lead to increased complications, these studies represent to our knowledge the first piece of evidence proving that. Most surgeons avoid single stage DTI to allow the correction of any damage caused by PMRT or the first surgery. Here, we disputed this prejudice that led to increased national trends of tissue expanders reconstructions. Additionally, the

discretion of the treating physician in delivering CWB depending on aggressive risk factors as lympho-vascular invasion or poor response after neoadjuvant chemotherapy, was addressed by different subgroup analyses revealing no benefit of CWB. The fact that both groups were well balanced in terms of tumor biology in the second project (table 1 in boost paper), helped minimizing major confounding issues between both groups. The fact that data collectors were not blinded to the collection of complication rates from surgical notes might introduced a reporter bias which is commonly associated with retrospective studies. Furthermore, this retrospective nature hindered us from assessing any skin flap thickness. However, we aimed to mitigate that by using Nipple Sparing as surrogate endpoint for thick flaps in the analysis. The results provided in supplementary analysis of the first project showed that nipple sparing mastectomy was not associated with any increased odds of complications. We could not report any patient satisfaction using (Breast Q surveys) between the three reconstruction types and no cost effectiveness analysis was conducted.

Future Directions:

A future step in reconstruction field will aim to assess patient satisfaction and reported outcomes across the different reconstruction types. Also, assessing the difference between Pre-pectoral and Sub-pectoral implants in PMRT settings will add more evidence about mitigating PMRT side effects on direct to implant reconstructions. For patients requiring breast augmentation or have thin skin flap, TE/I will still be recommended by the plastic surgeons. Therefore, assessing the timing of PMRT in TE/I in relation to the exchange operation is still recommended taking into consideration the heated debate in literature regarding when to irradiate in TE/I settings. Several reports suggested a link of association between reconstruction and breast cancer related lymphedema BCRL, therefore future studies assessing the “CAUSAL” association between

reconstruction and BCRL using Inverse probability weighting analysis and Propensity Scores remains necessary. Finally, with the lack of a randomized controlled trial comparing the three reconstruction types, a machine learning nomogram using many enriched datapoints can help predicting the anticipated personalized complication rate depending on the clinical scenario. Such tool can help guide the physicians and patients in making informed decisions.

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