Original Article

The risk factors and the relationship between radiation dose and complications and prosthetic reconstruction failure in patients with post-mastectomy breast implant reconstruction: a retrospective cohort study

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Background: The risk factors for breast implant reconstruction complications and prosthetic reconstruction failure are currently inconclusive. Besides, there is a lack of studies regarding the relationship between radiation dose distribution and complications. This study explored the risk factors for breast implant reconstruction complications and analyzed the influence of radiation dose distribution on complications.

Methods: Patients undergoing breast prosthesis reconstruction between January 2012 and June 2020 were retrospectively reviewed. Patient demographics, treatments, and perioperative factors were recorded, as well as complications and prosthetic reconstruction failures. Multivariable logistic regression models were used to explore the risk factors of reconstruction complications and prosthesis reconstruction failure. The radiation dose distribution was obtained by examining the dose-volume histogram and compared among patients with and without complications.

Results: Two hundred and sixteen patients (221 reconstructions) were not irradiated, whereas 59 (59 reconstructions) received radiotherapy (RT). The median follow-up period was 47.7 months. Multivariate regression analysis showed that RT [odds ratio (OR) =2.000; 95% confidence interval (CI): 1.065–3.754; P=0.031] and chemotherapy (OR =2.226; 95% CI: 1.032–4.799; P=0.041) were independent risk factors for overall reconstruction complications; and hypertension (HT) (OR =8.222; 95% CI: 1.056–64.034; P=0.044) or RT (OR =2.442; 95% CI: 1.009–5.908; P=0.048) were risk factors for prosthetic reconstruction failure. There was a statistically significant difference in the radiation dose distribution between patients with and those without complications. Patients with complications had a significantly higher mean dose of 5 or 10 cc around the maximum radiation dose in the planning target volume (PTV) (P=0.045 and P=0.034, respectively), irradiation volume with a dose of 107% of prescription dose (P=0.027), and proportion of irradiation volume with doses of 105% and 107% of prescription dose to the total PTV (P=0.019 and P=0.042, respectively).

Conclusions: RT can increase implant reconstruction complications and prosthetic reconstruction failure, but remains an acceptable option in a multidisciplinary setting. In addition to RT, chemotherapy is a risk factor for overall complications of breast implant reconstruction. HT is a risk factor for prosthetic reconstruction failure, so the patient's blood pressure should be actively monitored and controlled during the perioperative period. The radiation dose level and the volume with high-dose radiation should be limited to reduce complications.

Keywords: Breast cancer; breast implant reconstruction; risk factors; complications; radiation dose

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Submitted Oct 14, 2022. Accepted for publication Nov 08, 2022.
doi: 10.21037/gs-22-633
View this article at: https://dx.doi.org/10.21037/gs-22-633

Introduction

Breast cancer has become the most common malignant tumor in the world (1). Along with tumor control, radical mastectomy may negatively affect a woman's body image and sexual function, thus aggravating their psychological trauma and increasing social burden. However, this may be improved by breast implant reconstruction (2), which has risen in popularity globally (3). While the number of patients undergoing reconstruction in China is less than that in some Western countries, the numbers have gradually increased in recent years (4).

Physicians and patients have traditionally focused on complications, aesthetic outcomes of reconstructed breasts, and tumor control. Post-mastectomy radiotherapy (PMRT) can reduce the local recurrence rate and prolong disease-free survival and overall survival. In recent years, its indications have been gradually expanded with the publication of several large-scale clinical studies (5-8). However, the risk of complications after breast implant reconstruction, such as capsular contracture, infection, hematoma, seroma, bleeding, wound dehiscence, and breast implant reconstruction failure may increase with radiotherapy (RT) (9-11). Some studies have reported risk factors for reconstruction complications other than RT, but their results are currently inconclusive (12-14). Chemotherapy has been reported to be associated with a high rate of complications and reconstruction failure (10,15), but several studies showed the opposite result (14,16). Whether diabetes and hypertension (HT) are associated with postoperative complications is conflicting in implant-based breast reconstruction (12,17,18). It is well established that a high body mass index (BMI) increases the risk for surgical complications (12-14,19,20). Smoking is also considered as risk factor for complications, although some studies have failed to establish this relationship (13,14,16,20,21). Very little has been published on the association between complication and inflation volume (16,19). In the case of the implant-based reconstruction method, there is no agreement regarding its effect on complications (22,23). Besides, some research showed smoking, axillary lymph node dissection would increase the risk of prosthetic reconstruction failure (22,24,25).

The relationship between radiation dose distribution, radiation technology, clinical target volume (CTV), and reconstruction complications is currently unclear. Three studies reported that patients with reconstruction complications following PMRT have a higher degree of hot spots (radiation dose reaching 105–107% of the prescribed dose in the CTV) compared to those without complication, but their conclusions have not been consistent (26-28). In addition, Chinese women have relatively small breast volume compared to those in Western countries, which may influence the degree and location of hot spot doses. Therefore, this current investigation explored other risk factors for reconstruction complications and analyzed the relationship between dose distribution and reconstruction complications in Chinese women. We present the following article in accordance with the STARD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-633/rc).

Methods

Patients

Women with breast ductal carcinoma in situ (DCIS) or clinical stage I–III invasive breast cancer who underwent mastectomy and breast reconstruction with or without PMRT at the First Affiliated Hospital of Chongqing Medical University between January 2012 and June 2020, were retrospectively identified. Patients with the following conditions were excluded: (I) loss to follow-up or deceased; (II) incomplete expander-implant replacement; (III) implant removal for reasons unrelated to surgery; (IV) completed postoperative adjuvant RT in other medical institutions; and (V) presented with benign tumors. After excluding ineligible patients, a total of 275 patients were enrolled, including 59 patients who received PMRT (59 breast reconstructions) and 216 patients who did not receive PMRT (221 breast reconstructions). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the First Affiliated Hospital of Chongqing Medical University Ethics Committee (No. 2021-377) and individual consent for this retrospective analysis was waived.

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Demographic data

Their medical charts were reviewed, data on demographic parameters registered were age, BMI, smoking history, drinking history, breastfeeding history, menstrual history, concurrent morbidity (diabetes, hypertension), clinical data (including tumor type and stage, and adjuvant therapy), perioperative parameters (nipple and areola complex sparing, autologous fat filling, reconstruction stage, axillary lymph node dissection, implant volume) as well as follow-up-time.

Follow up

Complications were assessed by two surgeons through telephone interviews with patients, patient history database, physical examinations, and imaging examinations. Complications included postoperative bleeding, incision dehiscence, upper limb edema, nipple areolar complex (NAC) necrosis, flap necrosis, extrusion, hematoma, and seroma required unplanned surgery or medication. Breast implant reconstruction failure was defined as the removal of the prosthesis due to complications; 11 and 19 patients suffered from breast implant reconstruction failure among patients received with and without RT, respectively. The radioactive dermatitis was graded by physicians according to the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE 5.0). The follow-up time was defined from the date of completion of the mastectomy to the time of the last record.

Breast reconstruction

There were two types of prosthesis reconstructions, namely, immediate prosthesis reconstruction (immediate placement of a permanent implant after the subcutaneous breast resection) and immediate-delayed prosthesis reconstruction (expanders inserted immediately after the subcutaneous breast resection with an expander-implant exchange after adjuvant RT). During RT, the expander was partially inflated and the inflation was suspended to maintain dose homogeneity throughout the treatment. After completion of postoperative adjuvant chemoradiotherapy, expander-implant exchange was performed after more than 3 months of RT. All implants were placed between the pectoralis major and pectoralis minor/serratus anterior muscles without acellular dermal matrix (ADM) or other tissue patches. Antibiotics were used for three days to prevent infections.

Radiation therapy

RT was provided less than eight weeks after mastectomy or completion of the last cycle of adjuvant chemotherapy. The treatment plans were generated using the Varian Eclipse treatment planning system with simulation computed tomography (CT) scans. Patients were treated with 3-dimensional conformal radiation therapy (3DCRT) until 2017, after which they received 3DCRT or intensity-modulated radiation therapy (IMRT) according to the target area. The CTV includes the chest wall (including the marked mastectomy scar on the skin) and regional lymph nodes, including supraclavicular lymph nodes, with/without internal mammary lymph nodes. These were delineated according to the tumor characteristics and guidelines of the Radiation Therapy Oncology Group (RTOG). The European Society for Radiotherapy and Oncology-Advisory Committee in Radiation Oncology Practice (ESTRO-ACROP) published a consensus guideline in 2019 for target volume delineation in the setting of PMRT after implant-based immediate reconstruction for early-stage breast cancer. It suggested that in reconstructed breasts with expander/prosthesis placed below pectoralis major, the bottom of the implant should not be included in the CTV (29). Therefore, there is no uniform standard on whether to include the bottom of the expander/prosthesis in CTV. Most of the CTV delineated by physicians in this study included the bottom of the implant. The planning target volume (PTV) is the CTV plus a 5 mm expansion, except for the frontier edge of the chest wall. 6-MV X-rays were used for both IMRT and 3DCRT plans. The prescription dose was 50 Gy/25 F, except for 1 case of 50.4 Gy/28 F and 1 case of 46 Gy/23 F + 11 Gy/5 F. No bolus was used.

In general, 95% of the PTV should receive at least 95% of the prescription dose. Ipsilateral lung volumes at or exceeding 5 Gy (V5) and 20 Gy (V20) were mandated to ≤45% and ≤30%, respectively. For patients with left breast cancer, the mean cardiac doses with or without internal mammary lymph node radiotherapy (IMNI) were defined as <6 and <4 Gy, respectively. For patients with right breast cancer, the mean cardiac doses were defined as <2 and <0.5 Gy, depending on whether IMNI was performed.

Statistical analysis

Pearson's chi-square tests or Fisher's exact tests were used to compare the complication rates between the RT and non-

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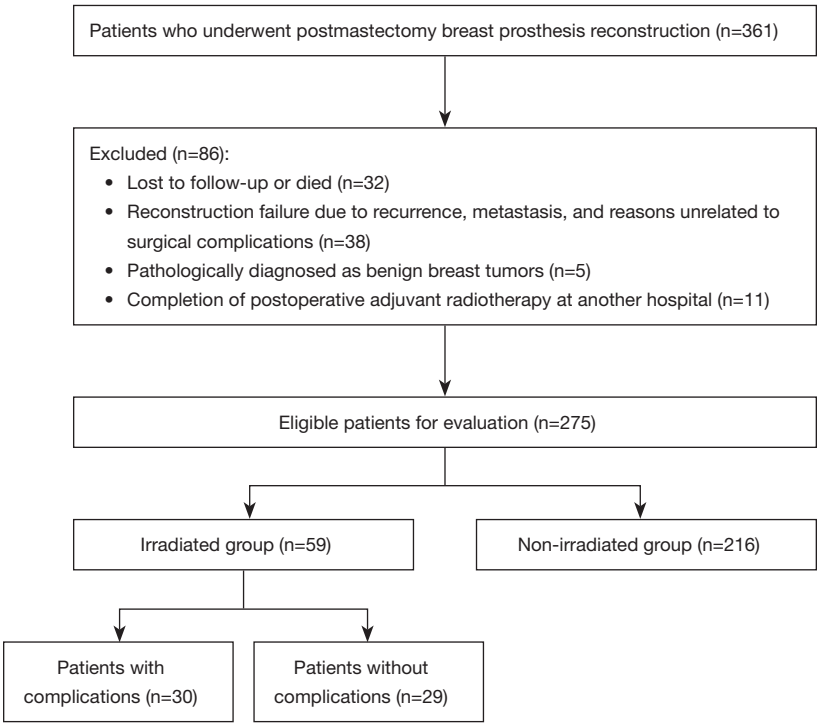

Figure 1 A flowchart showing the inclusion process of the breast cancer patients with implant-based reconstructions.

RT groups. Univariate and multivariate logistic regression analyses were performed to assess the correlation between complications and age, BMI, personal history, history, adjuvant therapy, reconstruction type, and implant volume, so as to determine the risk factors for complications and breast implant reconstruction failure.

Patients in the RT group were divided into two subgroups according to the presence or absence of complications. Independent samples *t*-tests, Mann-Whitney U tests, Pearson's chi-square tests, or Fisher's exact tests were selected according to the sample type to compare the characteristics of RT between the two groups, including RT techniques (IMRT/3DCRT), CTV (chest wall, supraclavicular lymph nodes, internal mammary lymph nodes), whether surgical scars were exposed to high-dose radiation, and radiation dose distribution.

The radiation dose distribution was collected by examining the dose-volume histogram and analyzed. The maximum point dose (Dmax), the mean dose to 0.03, 1, 2, 5, and 10 cc in the PTV (represented by D0.03cc, D1cc, D2cc, D5cc, and D10cc, respectively), the irradiation volume with the doses of 105% and 107% of prescription dose (represented by V105% and V107%, the unit is milliliters), and their ratio to the total PTV (represented by V%105% and V%107%) were selected to reflect radiation dose distribution and obtained from dose-volume histograms. The predictive values of each parameter for the development of complications were tested by the receiver operating characteristic (ROC) method. All significance tests were two-sided. A value of $P<0.05$ was considered statistically significant. Data analysis was performed using SPSS software (version 22.0, IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics

Figure 1 shows the selection process of the patients enrolled in this study. Patients who were excluded (and the associated reasons) or who withdrew from the study have been noted. A total of 275 patients undergoing 280 reconstructions were finally included. The baseline characteristics are shown in *Table 1*. The median follow-up time was 47.7 months (range, 11.7 to 108.8 months). Patients who were irradiated and those who were not irradiated differed significantly in pathological type, tumor

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Table 1 The baseline characteristics of the breast cancer patients

Characteristics	Irradiated group (%)	Non-irradiated group (%)	P
No. of patients	59 (21.5)	216 (78.5)	
No. of breasts reconstructed	59	221	
Age, mean ± SD, years	36.71±9.19	40.54±8.03	0.002
Median follow-up time, months	37.2	51.3	<0.001
BMI, mean ± SD, kg/m^2	21.53±2.45	21.51±2.38	0.950
DM			1
Yes	0 (0.0)	2 (0.9)	
No	59 (100.0)	214 (99.1)	
HT			1
Yes	1 (1.7)	5 (2.3)	
No	58 (98.3)	211 (97.7)	
Smoking history			0.689
Yes	1 (1.7)	8 (3.7)	
No	58 (98.3)	208 (96.3)	
Drinking history			1
Yes	2 (3.4)	9 (4.2)	
No	57 (96.6)	207 (95.8)	
Breastfeeding history			0.205
Yes	37 (62.7)	154 (71.3)	
No	22 (37.3)	62 (28.7)	
Menopause			0.499
Yes	5 (8.5)	25 (11.6)	
No	54 (91.5)	191 (88.4)	
NAC sparing			0.907
Yes	31 (52.5)	118 (53.4)	
No	28 (47.5)	103 (46.6)	
Autologous fat filling			1
Yes	2 (3.4)	11 (5.0)	
No	57 (96.6)	210 (95.0)	
Reconstruction stage			<0.001
1-stage	15 (25.4)	136 (61.5)	
2-stage	44 (74.6)	85 (38.5)	
Axillary lymph node dissection			<0.001
Yes	56 (94.9)	47 (21.3)	
No	3 (5.1)	174 (78.7)	

Table 1 (*continued*)

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Table 1 (*continued*)

Characteristics	Irradiated group (%)	Non-irradiated group (%)	P
Median implant volume, mL	240	245	0.900
Final stage*			<0.001
0	0 (0.0)	45 (20.8)	
IA	1 (1.7)	67 (31.0)	
IB	2 (3.4)	0 (0.0)	
IIA	10 (16.9)	80 (37.0)	
IIB	15 (25.4)	21 (9.7)	
IIIA	27 (45.8)	3 (1.4)	
IIIB	1 (1.7)	0 (0.0)	
IIIC	3 (5.1)	0 (0.0)	
Histology			<0.001
Invasive carcinoma	59 (100.0)	174 (78.7)	
DICS	0 (0.0)	47 (21.3)	
Grade			0.019
1	0 (0.0)	18 (8.3)	
2	49 (83.1)	176 (81.5)	
3	10 (16.9)	22 (10.2)	
Molecular subtype			0.593
Luminal A	12 (20.3)	53 (24.5)	
Luminal (HER2–)	23 (39.0)	69 (31.9)	
Luminal (HER2+)	11 (18.6)	30 (13.9)	
HER2+	6 (10.2)	33 (15.3)	
TN	7 (11.9)	31 (14.4)	
NACT			<0.001
Yes	23 (39.0)	27 (12.5)	
No	36 (61.0)	189 (87.5)	
Targeted therapy			0.544
Yes	13 (22.0)	176 (81.5)	
No	46 (78.0)	40 (18.5)	
ET			0.155
Yes	48 (81.4)	156 (72.2)	
No	11 (18.6)	60 (27.8)	
ACT			<0.001
Yes	59 (100.0)	166 (76.9)	
No	0 (0.0)	50 (23.1)	

*, higher of pathologic or pre-chemotherapy clinical stage. SD, standard deviation; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; NAC, nipple areola complex; DICS, ductal carcinoma in situ; HER2, human epidermal growth factor receptor 2; TN, triple negative; NACT, neoadjuvant chemotherapy; ET, endocrine therapy; ACT, adjuvant chemotherapy.

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Table 2 The rates of complications in the radiotherapy group and the non-radiotherapy group

Complications	Irradiated group (%)	Non-irradiated group (%)	P
No. of breasts reconstructed	59	221	
Reconstructive failure	11 (18.6)	19 (8.6)	0.027
Upper limb edema	6 (10.2)	5 (2.3)	0.013
NAC necrosis	2 (3.4)	3 (1.4)	0.284
Flap necrosis	0 (0.0)	0 (0.0)	NA
Bleed	4 (6.8)	9 (4.1)	0.483
Incision dehiscence	9 (15.3)	15 (6.8)	0.039
Threatened exposure	5 (8.5)	21 (9.5)	0.809
Seroma	2 (3.4)	5 (2.3)	0.641
Hematoma	0 (0.0)	1 (0.5)	1
Infection	13 (22.0)	21 (9.5)	0.009
Incision infection	14 (23.7)	35 (15.8)	0.156
Overall complication	30 (50.8)	73 (33.0)	0.012

NAC, nipple areola complex; NA, not applicable.

stage, and pathological grade. Patients with RT were less likely to have grade 1 tumors (8.3% *vs.* 0%, P=0.019) and carcinoma *in situ* (21.3% *vs.* 0%, P<0.001), but more likely to receive axillary lymph node dissection (ALND); 94.9% *vs.* 21.3%, P<0.001), neoadjuvant chemotherapy (39.0% *vs.* 12.5%, P<0.001), and adjuvant chemotherapy (100.0% *vs.* 76.9%, P<0.001). There were no significant differences in molecular subtypes, anti-human epidermal growth factor receptor 2 (anti-HER2) targeted therapy, and endocrine therapy. Immediate-delayed implant reconstruction may be recommended when there is a confirmed indication of PMRT, so as to reduce the adverse effects of RT on the permanent implant. Accordingly, the proportion of patients who received immediate-delayed implant reconstruction in the RT group was higher (74.6% *vs.* 38.5%, P<0.001). In addition, there were no significant differences in prosthesis volume nor NAC preservation between the two groups.

Reconstruction related complications

The incidence of complications is shown in *Table 2*. Complications occurred in 103 (36.7%) reconstructed breasts, including 30 (10.7%) prosthetic reconstruction failure. The overall complications in the irradiated and the non-irradiated groups were 50.8% and 33%, respectively (P=0.012). The incidences of upper limb edema, wound dehiscence, and infection in the irradiated group were significantly higher than those in the non-irradiated group (10.2% *vs.* 2.3%, P=0.013; 15.3% *vs.* 6.8%, P=0.039; and 22% *vs.* 9.5%, P=0.009, respectively). The rate of prosthesis reconstruction failure due to complications was 18.6% in the irradiated group and 8.6% in the non-irradiated group (P=0.027). After excluding patients without axillary dissection, the proportion of upper limb edema in the irradiated group was not significantly different from that in the non-irradiated group (10.7% *vs.* 4.3%, P=0.223).

The reasons for prosthetic reconstruction failure in patient with RT were infection (7/11), wound dehiscence (3/11), and prosthesis exposure (1/11), and in patients without RT, the causes of reconstruction failure were infection (9/19), wound dehiscence (5/19), prosthesis exposure (3/19), hematoma (1/19), and wound infection (1/19).

Risk factors for complications

In univariate analysis (*Table 3*), RT [odds ratio (OR) =2.197; 95% confidence interval (CI): 1.231–3.922; P=0.008] and adjuvant chemotherapy (OR =2.804; 95% CI: 1.338–5.875; P=0.006) were significant predictors of overall complications. Multivariate analysis (*Table 4*) also showed that RT (OR =2.000; 95% CI: 1.065–3.754; P=0.031) and

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Table 3 Univariate logistic regression analysis of risk factors for overall complications and prosthetic reconstruction failure

Characteristics	Subtypes	Overall complication			Reconstruction failure		
		OR	95% CI	P	OR	95% CI	P
Age, years	Continuous	1.013	0.984–1.043	0.383	1.015	0.970–1.062	0.521
BMI, kg/m^2	Continuous	1.078	0.973–1.194	0.150	1.047	0.895–1.225	0.565
DM	Yes/no	1.725	0.107–27.883	0.701	NA	NA	0.999
HT	Yes/no	0.856	0.154–4.759	0.859	4.393	0.770–25.073	0.096
Smoking history	Yes/no	0.634	0.164–2.444	0.508	1.043	0.126–8.640	0.969
Reconstruction stage	1-stage/2-stage	1.041	0.640–1.694	0.870	1.700	0.777–3.719	0.184
NAC sparing	Yes/no	1.380	0.845–2.252	0.198	1.169	0.545–2.509	0.689
Autologous fat filling	Yes/no	1.502	0.491–4.598	0.476	NA	NA	0.999
Implant volume, mL	Continuous	1.002	0.998–1.006	0.240	0.998	0.992–1.004	0.580
RT	Yes/no	2.197	1.231–3.922	0.008	2.375	1.061–5.315	0.035
CT	Yes/no	2.804	1.338–5.875	0.006	2.139	0.623–7.343	0.227
ET	Yes/no	0.988	0.569–1.718	0.967	0.674	0.299–1.516	0.340
Targeted therapy	Yes/no	1.077	0.586–1.978	0.811	0.423	0.124–1.449	0.171

OR, odds ratio; CI, confidence interval; BMI, body mass index; DM, diabetes mellitus; HT, hypertension; NAC, nipple areola complex; RT, radiation therapy; CT, chemotherapy; ET, endocrine therapy; NA, not applicable.

Table 4 Multivariate logistic regression analysis of risk factors for prosthetic reconstruction complications and prosthetic reconstruction failure

Characteristics	Subtypes	Overall complication			Reconstruction failure		
		OR	95% CI	P	OR	95% CI	P
Age, years	Continuous	1.020	0.987–1.054	0.247	1.018	0.968–1.070	0.486
BMI, kg/m^2	Yes/no	1.049	0.931–1.183	0.431	1.010	0.839–1.216	0.914
HT	Yes/no	0.617	0.098–3.880	0.607	8.222	1.056–64.034	0.044
NAC sparing	Yes/no	1.530	0.905–2.585	0.112	1.107	0.490–2.501	0.806
Autologous fat filling	Yes/no	1.615	0.496–5.252	0.426	NA	NA	0.998
Implant volume, mL	Continuous	1.002	0.998–1.006	0.340	0.997	0.990–1.004	0.421
RT	Yes/no	2.000	1.065–3.754	0.031	2.442	1.009–5.908	0.048
CT	Yes/no	2.226	1.032–4.799	0.041	1.905	0.506–7.174	0.341
ET	Yes/no	1.025	0.571–1.840	0.934	0.583	0.245–1.387	0.222

OR, odds ratio; CI, confidence interval; BMI, body mass index; HT, hypertension; NAC, nipple areola complex; RT, radiation therapy; CT, chemical therapy; ET, endocrine therapy; NA, not applicable.

chemotherapy (OR =2.226; 95% CI: 1.032–4.799; P=0.041) were associated with overall complications.

To avoid the ratio of RT as a confounding factor, the correlation between reconstruction type and complications in the irradiated and non-irradiated groups were analyzed. The results demonstrated that the reconstruction type was not associated with overall complications, regardless of RT (irradiated group: OR =3.346, 95% CI: 0.327–34.195, P=0.308; and non-irradiated groups: OR =0.665, 95% CI: 0.372–1.191, P=0.170).

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Prosthetic reconstruction failure was associated with RT in univariate analysis (OR =2.375; 95% CI: 1.061–5.315; P=0.035) (*Table 3*). Multivariate analysis showed RT (OR =2.442; 95% CI: 1.009–5.908; P=0.048) and HT (OR =8.222; 95% CI: 1.056–64.034; P=0.044) were independent risk factors associated with prosthetic reconstruction failure (*Table 4*).

Prosthetic reconstruction complications and radiation dose distribution

The differences between different RT techniques, CTV, whether the CTV included the posterior wall of implants, location of hot spots, and dose distribution between subgroups with and without complications were analyzed (*Table 5*). Patients with complications had significantly higher D5cc (108.26% *vs.* 107.12%, P=0.045), D10cc (108.04% *vs.* 106.61%, P=0.034), V%105% (30.95% *vs.* 19.29%, P=0.019), V107% (51.06 *vs.* 5.94 mL, P=0.027), and V%107% (8.90% *vs.* 1.12%, P=0.042) compared to patients without complications. Dmax and "near Dmax", such as doses to the hottest 0.03, 1, and 2 cc of PTV did not differ significantly between the two subgroups. In addition, there were no significant differences between the two subgroups in terms of RT techniques (IMRT *vs.* 3DCRT), whether the CTV included the bottom of the implant, the target volume (chest wall *vs.* chest wall + supraclavicular lymph nodes *vs.* chest wall + supraclavicular lymph nodes + internal mammary lymph nodes), location of the hot spot (proximal chest wall *vs.* proximal chest wall *vs.* proximal sternum *vs.* near mid-axillary side *vs.* implant surface *vs.* implant), nor whether surgical scars were irradiated with high-dose radiation. Therefore, the ROC curve was drawn to explore the relationship between radiation dosimetry and overall complications (*Figure 2*). Neither "hot spot" volumes nor their ratio to the CTV volume, such as D5cc [area under the curve (AUC) =0.631, P=0.094], D10cc [AUC =0.641, P=0.071], V107% [AUC =0.651, P=0.053], V%105% [AUC =0.659, P=0.042] and V%107% (AUC =0.659, P=0.042) was predictive of the development of complications (*Table 6*). No positive relationship between the severity of radiation dermatitis and complication rate was detected [dermatitis G0 7/11 (63.6%), G1 17/40 (42.5%), G2 1/2 (50%), and G3 5/6 (83.3%), P=0.200].

Discussion

With the development of the economy, the number of breast reconstructions after mastectomy for breast cancer has gradually increased in China in the past decade (30). Two studies published in 1997 identified the necessity of PMRT for patients with positive lymph nodes (5,6), and in 2013, this was further confirmed for patients with 1–3 positive lymph nodes (7,8). However, RT can increase the incidence of reconstruction complications, as well as prosthesis failure caused by severe complications, whether the implant is an expander or a permanent prosthesis (10,31). RT can also damage blood vessel cells, reduce blood supply, and cause tissue hypoxia. Additionally, it increases myofibroblast transformation and fibrosis, leading to capsular contracture (32).

The current study showed that the incidence of breast prosthesis reconstruction complications could be increased with RT, which is consistent with the conclusions of previous studies (10,31,33). The incidence of some specific complications were also increased in patient with RT, such as wound dehiscence (15.3 *vs.* 6.8%, P=0.039), infections (22.0% *vs.* 9.5%, P=0.009), and implant reconstruction failure (18.6% *vs.* 8.6%, P=0.027). Compared with the prosthesis loss rate reported in the study by Cordeiro *et al.* (9.1% *vs.* 0.5% in patients with and without RT) (9) and Nava *et al.* (7.1% *vs.* 2.3% in patients with and without RT) (11), the reconstruction failure rate was higher in patients without RT in our study, but RT increased the reconstruction failure rate by 1.16 folds. Therefore, the effect of RT on the failure rate of prosthesis reconstruction is acceptable.

The most common reason for implant reconstruction failure was infection (63.6% in irradiated implants and 47.4% in non-irradiated implants), consistent with previous studies (34,35). Thus, efforts to actively treat or prevent infections during the perioperative period should be made to reduce the risk of implant reconstruction failure.

In addition to infection, the sequence of RT and expander-implant replacement may be another reason for the higher failure rate. All patients in the study by Cordeiro *et al.* underwent expander-implant replacement before PMRT (9). This sequence was also used in two-thirds of RT patients in Nava *et al.*'s study. It reported that the incidence of reconstruction failure was 40% and 6.4% in patients treated with RT before and after expander-prosthesis replacement, respectively (P<0.0001) (11). Two meta-analyses also confirmed that expander-implant replacement before RT may be beneficial for reducing failure rates, but this sequence will inevitably delay the start of PMRT

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Table 5 Radiotherapy-related characteristics in the irradiation group

Variables	With complications (%)	Without complication (%)	P
No. of breasts reconstructed	30 (50.8)	29 (49.2)	
Irradiation technique			0.436
3DCRT	10 (33.3)	7 (24.1)	
IMRT	20 (66.7)	22 (75.9)	
Whether the posterior wall of the implant is included in the CTV			0.612
Yes	27 (90.0)	28 (96.6)	
No	3 (10.0)	1 (3.4)	
Radiation target			0.982
Chest wall/breast only	12 (40.0)	12 (41.4)	
Supraclavicular nodes	10 (33.3)	9 (31.0)	
IMNs	8 (26.7)	8 (27.6)	
Location of maximum dose			0.585
Cranial	8 (26.7)	8 (27.6)	
Caudal	4 (13.3)	4 (13.8)	
Medial	7 (23.3)	5 (17.2)	
Lateral	1 (3.3)	5 (17.2)	
Implant surface	7 (23.3)	6 (20.7)	
Within device	3 (10.0)	1 (3.4)	
Whether the hot spot is on the scar			0.054
Yes	12 (40.0)	5 (17.2)	
No	18 (60.0)	24 (82.8)	
Dmax (median, %)	109.08	108.56	0.396
D0.03cc (median, %)	108.40	108.04	0.288
D1cc (median, %)	108.71	107.91	0.111
D2cc (median, %)	108.52	107.70	0.069
D5cc (median, %)	108.26	107.12	0.045
D10cc (median, %)	108.04	106.61	0.034
V105% (mean, mL)	218.68	158.60	0.135
V%105% (mean, %)	30.95	19.29	0.019
V107% (mean, mL)	51.06	5.94	0.027
V%107% (mean, %)	8.90	1.12	0.042
Radiation dermatitis			0.200
0	7 (63.6)	4 (36.4)	
1	17 (42.5)	23 (57.5)	
2	1 (50.0)	1 (50.0)	
3	5 (83.3)	1 (16.7)	

3DCRT, three-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; CTV, clinical target volume; IMNs, internal mammary nodes; Dmax, maximum dose in the planning target volume; D0.03cc, mean dose to 0.03 cc in the planning target volume; D1cc, mean dose to 1 cc in the planning target volume; D2cc, mean dose to 2 cc in the planning target volume; D5cc, mean dose to 5 cc in the planning target volume; D10cc, mean dose to 10 cc in the planning target volume; V105%, the irradiation volume with a dose of 105% of prescribed dose; V%105%, the proportions of the irradiation volume with doses of 105% of prescribed dose to the total planning target volume; V107%, the irradiation volume with a dose of 107% of prescribed dose; V%107%, the proportions of the irradiation volume with doses of 107% of prescribed dose to the total planning target volume.

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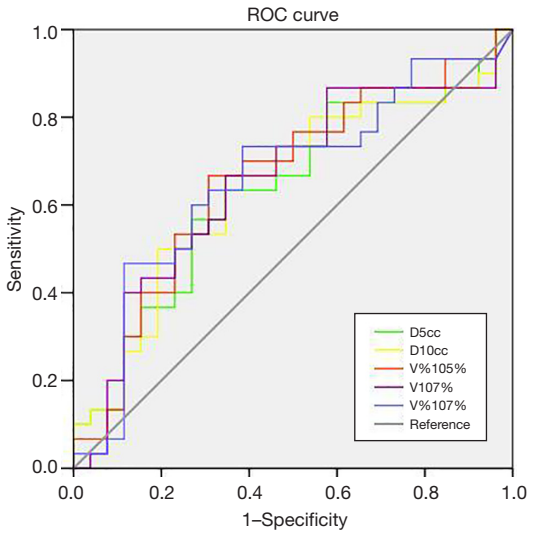

Figure 2 The ROC curve for the development of implant reconstruction complication. ROC, receiver operating characteristic.

Table 6 The area under the receiver operating characteristic curve for reconstruction complications

Variables	AUC	P
D5cc	0.631	0.094
D10cc	0.641	0.071
V%105%	0.659	0.042
V107%	0.651	0.053
V%107%	0.659	0.042

AUC, area under the curve; D5cc, mean dose to 5 cc in the planning target volume; D10cc, mean dose to 10 cc in the planning target volume; V%105%, the proportions of the irradiation volume with doses of 105% of prescribed dose to the total planning target volume; V107%, the irradiation volume with a dose of 107% of prescribed dose; V%107%, the proportions of the irradiation volume with doses of 107% of prescribed dose to the total planning target volume.

and may affect the anti-tumor efficacy (36,37). Therefore, delayed autologous reconstruction can be suggested for eligible patients when it is challenging to balance RT efficacy and the risk of complications (38).

Univariate and multivariate analyses suggested that RT and chemotherapy are independent risk factors for reconstruction complications. It is believed that chemotherapy inhibits cell proliferation by affecting DNA replication and mitosis, thereby affecting wound healing (39). Lam *et al.* demonstrated that postoperative prosthesis loss was 5.3% for patients undergoing adjuvant chemotherapy, and 11.3% for patients receiving chemoradiotherapy, suggesting that both RT and chemotherapy increased the risk of prosthesis loss (10). A previous study has also confirmed that RT and chemotherapy are related to reconstruction complications (15).

In our study, BMI, HT, diabetes mellitus (DM), and smoking history are not risk factors for overall complications, and this was inconsistent with the results of previous studies showing that age greater than 50 years, BMI higher than 25 kg/m^2, smoking history, and DM are risk factors (13,14,40). Chinese breast cancer patients are characterized by a younger age of onset and less willingness for breast reconstruction in older patients. Therefore, the average age is younger and the BMI is lower in this study, which suggests that the results of this study are mainly aimed at the relatively young patients with average weight. In addition, the small number of patients with a history of smoking and DM may affect the reliability of the univariate analyses, and a history of DM and smoking was not included in the multivariate analysis.

The meta-analysis concluded that immediate prosthesis reconstruction might be associated with a higher complication rate than immediate-delayed reconstruction, primarily increased flap necrosis, reoperation, and implant loss (41). Some scholars also believe that immediate prosthesis reconstruction is more likely to over expand the flap and increase its tension, leading to flap necrosis, infection, prosthesis exposure, and implant reconstruction failure (42,43). However, the results in this investigation showed that the reconstruction method was not associated with overall complications. The reason might be that surgeons tended to recommend 2-step breast implant reconstruction for patients with thinner subcutaneous fat layer, larger tumor size, and smaller breast that required PMRT, creating a selection bias.

Multivariate analysis also showed a higher risk of reconstruction failure in hypertensive patients, consistent with previous findings (17). HT can cause changes in microcirculatory function and structure, thereby affecting the perfusion of skin flaps (18). Therefore, a patient's blood pressure should be actively monitored and controlled during the perioperative period.

The association between RT and complications has been well-established, but the relationship between radiation dose distribution and complications remains to be fully elucidated. The results herein demonstrated that D5cc,

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D10cc, V%105%, V107%, and V%107% in patients with complications were significantly higher than that in patients without complications after treatment with PMRT (*Table 5*). However, there was no significant difference in Dmax, D0.03cc, D1cc, nor D2cc between the two subgroups. In contrast to our results, Muresan *et al.*'s study reported that reconstruction complications were associated with higher Dmax and D1cc (26), but there was no significant difference among patients with and without complications. Chang *et al.* and Chung *et al.* found that near Dmax parameters (D0.03cc, D2cc) were able to predict the risk of reconstruction complications (27,28). Muresan *et al.*'s study reported that patients with complications had higher mean Dmax and lower D10cc than those in our study (26). The other two studies reported by Korean scholars included hypofractionated RT, resulting in significantly higher D2cc (27,28). Thus, the radiation dose distributions were quite different and not comparable among previous and current studies. We therefore hypothesized that complications were not only related to excessive spot doses but also related to a larger volume with high radiation doses (specifically, V105% and V107% in this study).

ROC analysis involving 5 factors was conducted to determine the clinically relevant predictors of reconstruction complications in patients with PMRT in clinical practice (*Table 6*). Although the AUCs of V%105% and V%107% (AUC =0.659, P=0.042) for predicting the risk of complications was relatively low, it still indicated that the volume of the hot spot should be reduced while minimizing the maximum dose level.

The development of IMRT can deliver a more homogeneous dose of radiation throughout the breast and efficiently removes radiation hot spots. A previous study has demonstrated a higher rate of radiodermatitis with 3DCRT compared to treatment with IMRT in breast cancer patients, but no significant differences in terms of late toxicities, such as atrophy, telangiectasia, fibrosis, lymphoedema, or breast edema, were detected (44). We found no evidence that RT techniques (3DCRT *vs.* IMRT) were associated with complications, consistent with the findings before. Indeed, Muresan reported that different RT techniques (IMRT, 3DCRT, field-in-field irradiation, and hybrid RT techniques) do not affect the occurrence of complications. Chang *et al.*'s study showed that there was no difference in Dmax between patients undergoing different RT techniques (IMRT *vs.* 3DCRT) (27).

For the first time, the relationship between complication rates and surgical scars exposed to high-dose radiation was analyzed. The results demonstrated that complication rates were likely higher in patients with surgical scars exposed to high-dose radiation, even though there was no statistical significance (P=0.054), suggesting that we should take care to avoid high-dose radiation from surgical scars for patients in clinical practice. These results should be validated in future studies.

There were some limitations to this study. First, as this was a retrospective study, it has inherent biases in patient selection and treatment assignment. Second, this study excluded patients due to tumor recurrence, metastasis, death, and loss to follow-up. The lack of this data may affect the conclusions herein. Third, we only analyzed breast reconstruction complications from a physician's perspective and did not investigate the patients' perceptions.

Conclusions

RT is associated with overall implant reconstruction complications and can lead to an increased risk of implant reconstruction failure, but its effect on reconstruction outcomes is acceptable in a multidisciplinary setting. In addition to RT, chemotherapy is a risk factor for overall complications of breast reconstruction, and a history of HT increases the risk factor for reconstruction failure. For patients requiring PMRT, complication rates were likely higher in these patients with surgical scars received from high-dose radiation. The maximum dose in the PTV was not associated with the occurrence of reconstruction complications, while D5cc, D10cc, V105%, V%105%, V107%, and V%107% were significantly higher in patients with reconstruction complications. Controlling the hot spot volume, reducing the hot spot dose level, and keeping hot spots away from the scar may improve reconstruction outcomes.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-633/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-22-633/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-633/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the First Affiliated Hospital of Chongqing Medical University Ethics Committee (No. 2021-377) and individual consent for this retrospective analysis was waived.

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(English Language Editor: J. Teoh)

Cite this article as: Sun L, Zhu W, Zhang J, Zhong B, Li S, Li H, Gan L. The risk factors and the relationship between radiation dose and complications and prosthetic reconstruction failure in patients with post-mastectomy breast implant reconstruction: a retrospective cohort study. Gland Surg 2022;11(11):1817-1831. doi: 10.21037/gs-22-633

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