Radiotherapy After Skin-Sparing Mastectomy and Implant-Based Breast Reconstruction

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Abstract

We aimed to evaluate the cosmetic results of radiotherapy in 170 breast cancer patients after implant-based reconstruction. Cosmetic results were excellent or fair in most patients after radiotherapy. However, bolus use, lymphatic irradiation, and the volume receiving at least 110% of the prescribed dose being >1% significantly deteriorated the outcomes.

Introduction: We evaluated the cosmetic results of radiotherapy (RT) after implant-based reconstruction (IBR). **Patients and Methods:** We retrospectively evaluated 170 patients with 171 breast cancers treated between December 2004 and January 2016 in 2 university hospitals. RT fields were reconstructed breast (RB) only in 24 (14%), and RB and regional lymphatics in 147 (86%) breasts, respectively. All but 1 patient received a total 50 Gy with conventional fractionation. All patients received systemic chemotherapy. One hundred thirty-eight (81%) patients received hormonal therapy; 118 tamoxifen and 20 aromatase inhibitor. **Results:** Median follow-up time was 46.8 months (range, 1-163 months). The 5-year disease-free and overall survival rate was 83% and 93%, respectively. Cosmetic results were considered excellent in 111 (65%), fair in 46 (27%), and bad in 14 (8%) RB by patients. Thirty-four (20%) RB had restorative surgery; because of surgeons' preference because of implant natural life time span in 5, and contracture, fibrosis, deformation, or dislocation of the implant, or cellulitis in the remaining. Statistically significant adverse factors in univariate analysis for impaired cosmetic outcome were bolus use on the RB, lymphatic irradiation, and volume that received at least 110% of the prescribed dose being $>$ 1%. The use of bolus material was the only prognostic factor for deterioration of the cosmetic result in multivariate analysis. **Conclusion:** RT after IBR yields acceptable cosmetic results. Although only 111 (65%) of RBs were considered to have excellent cosmetic results, only a small percentage of patients needed reoperation because of bad cosmetic outcome.

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Introduction

Breast cancer is the most frequent cancer among women.[1] Mastectomy is still performed in nearly one-third of patients.[2] After mastectomy, patients might complain about changes in body image, impairment of posture, decrease in self-confidence, and concept of femininity leading to anxiety and depression.[3,4] Breast reconstruction plays an important role in conserving these functional and emotional features.

Forming a breast bulge resembling the previous breast shape after mastectomy is simply called a "breast reconstruction." The implementation of this procedure has increased in the past decade.[5,6] The indications for radiotherapy (RT) in patients with breast reconstruction, however, have not changed. Implant-based reconstruction (IBR) is a technique that is performed either concurrently with skin-sparing mastectomy (SSM) or as a 2-step process; first placing a tissue expander, then a permanent implant as a delayed procedure after removing the expander. Nevertheless, there are not sufficient data in the literature about the optimal RT technique, dosimetric analysis, or long-term cosmetic results in patients with IBR. To address this issue, we retrospectively evaluated the cosmetic outcomes of breast cancer patients who underwent IBR after SSM before RT.

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Patients and Methods

A total of 183 female patients with a diagnosis of breast cancer were treated with RT in 2 university hospitals (Hacettepe University, Ankara, Turkey and Baskent University, Adana, Turkey) between December 2004 and January 2016 after IBR concurrently with SSM. To learn about the last cosmetic status, all patients and/or next of kin were called by phone and asked to rate their cosmetic status and satisfaction. Thirteen patients could not be reached, and they were excluded from the study. Therefore, the data of 170 patients with 171 breast cancers were analyzed.

All patients had undergone SSM with neoadjuvant or adjuvant chemotherapy before RT. Planning computed tomography was performed with a slice thickness of 2.5 to 5 mm in supine position with a breast board, starting from the cranial base to the level of the first lumbar vertebrae. RT was performed via 2-dimensional (2D) conventional RT before 2009, and forward-planned (FP) intensity-modulated RT (IMRT) or inverse-planned (IP)-IMRT after 2009. The reconstructed breast (RB) and lymph nodes (LNs) at risk were delineated according to the Radiation Therapy Oncology Group guidelines.[7] Clinical target volume (CTV) was the whole chest wall and RB in all patients. When the axillary LNs were positive, level 3, or full axilla, depending on the adequacy of the excision and extracapsular extension, supraclavicular fossa (SCF) with or without mammaria interna (MI) LNs were also contoured. Planning target volume (PTV) was defined as CTV plus a margin of 2 cm for 2D-conventional RT. For the IMRT plans, PTV was formed by adding 7 mm to the chest wall CTV, and 5 mm to the axilla, SCF, and MI CTVs. Organs at risk were also contoured at each slice. In one of the centers, bolus is routinely applied in patients with breast reconstruction to increase the skin dose. In that center, a 1-cm bolus is used for 11 days (between days 8 and 18) for FP-IMRT, on the basis of dosimetric studies performed on patients to keep the minimum skin dose of 45 Gy. In IP-IMRT plans, a 0.5-cm bolus is used during the whole treatment, and the PTV is formed so as to include the bolus. Treatment plans were optimized according to the requirement that $\geq$95% of the PTV and $\geq$99% of the CTV received 95% of the prescribed dose. RT was administered via Philips SL25 (Philips Healthcare, Andover, MA), Elekta Synergy Platform (Elekta AB, Stockholm, Sweden), or Varian Clinac DHX High Performance (Varian Medical Systems, Inc, Palo Alto) linear accelerators.

After RT was completed, all patients were followed-up and examined every 3 months during the first 2 years, every 6 months during the next 3 years, and annually thereafter. Follow-up information for survival rates was obtained from the department charts, hospital notes, referring doctors, and from patients and/or next of kin. Cosmetic results were assessed subjectively and solely by patients either face to face during their routine follow-up visit or by calling them on phone. No physician assessment was included. Cosmetic results were grouped as excellent, fair, or bad. When the patient did not complain about the cosmesis at all, it was accepted as "excellent." When she described a little or mild disturbance such as mild deformation, dislocation, contracture, fibrosis, or infection, the cosmetic result was evaluated as "fair." When the patient described serious complaints, the cosmetic result was evaluated as "bad." Patients were also asked whether they underwent another reconstructive surgery after RT because of impaired cosmetic results.

All statistical analyses were performed using Statistical Package for the Social Sciences version 18.0 (SPSS Inc, Chicago, IL). The primary end points were cosmetic results of RT. Secondary end points included overall survival (OS), disease-free survival (DFS), and treatment toxicity. Univariate analyses to identify variables associated with cosmetic outcome was investigated using the χ^2 test. For the multivariate analysis, possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine predictors of cosmetic outcome. Survival analyses were carried out using the Kaplan–Meier method and compared using the log rank test. All time-related events (failure or death) were calculated from the first day of RT to the last follow-up or death. A P value $< .05$ was considered significant.

The incidence of acute and late toxicity was defined as the total number of patients reaching that grade at any time on the basis of Common Terminology Criteria for Adverse Events version 4.0.[8] Late toxicity was reported when it appeared more than 3 months after the end of the treatment.

Results

Patient, Tumor, and Treatment Characteristics

A total of 170 female patients with 171 breast cancers were retrospectively analyzed. Median age was 40 years (range, 28-73 years). Twenty-one (12%) patients had a history of cigarette smoking, and 37 (22%) patients had comorbidities. All patients had undergone SSM and concurrent IBR. Right-sided SSM, left-sided SSM, and bilateral SSM was applied to 72 (42%), 88 (52%), and 10 (6%) patients, respectively. One patient with bilateral SSM had bilateral breast cancer. Other patients received surgery on the contralateral breast by their own wish for prophylaxis. The type of reconstruction was a permanent implant in 154 (90%) breasts and a tissue expander in 17 (10%) breasts.

All patients received adjuvant or neoadjuvant chemotherapy. Hormonal therapy (HT) was applied in 138 (81%) patients; tamoxifen in 118, and aromatase inhibitor in 20 patients. Total RT dose was median of 50 Gy (range, 50-60 Gy) in a median of 2-Gy (range, 1.8-2 Gy) fractions. The only patient who received 60 Gy as a total dose was first administered 50 Gy to the RB and chest wall and then a boost dose of 10 Gy to the nipple bed where Paget disease was present very close to the anterior resection margin. The maximum dose to the RB was a median of 55.4 Gy (range, 52.25-64.19 Gy). The volume that received at least 105% of the prescribed dose (V105) was a median of 7% (range, 0-92%), and the volume that received at least 110% of the prescribed dose (V110) was median of 0% (range, 0-33%). According to each center's own policy, a bolus was used on 121 (71%) RBs and not used on 50 (29%). Other patient and treatment characteristics are shown in Table 1.

Follow-up and Survival

Median follow-up was 46.8 months (range, 1-163 months) in all patients. The 2-, 5-, and 10-year OS rate was 98%, 93%, and 91%, respectively. At the last contact, 146 (86%) patients were alive with no evidence of disease, 16 (9%) were alive with disease, and 8 (5%) were dead; 7 because of disease, and 1 for an unknown reason. The 2-, 5-, and 10-year DFS rate was 91%, 83%, and 83%, respectively.

Table 1 Patients and Treatment Characteristics

Characteristic	Number of Patients/Breasts (%)
Menopause Status	
Premenopausal	134 (79)
Perimenopausal	29 (17)
Postmenopausal	7 (4)
Disease Site	
Right breast	76 (45)
Left breast	93 (54)
Bilateral breast	1 (1)
Stage of the Disease	
I	6 (3)
II	82 (50)
III	68 (39)
IV	9 (5)
Unknown	6 (3)
Axillary Surgery	
SLNS	38 (22)
SLNS and ALND	41 (24)
ALND	87 (51)
No axillary surgery	5 (3)
Chemotherapy	
Neoadjuvant	25 (15)
Adjuvant	145 (85)
Chemotherapy Type	
Taxane-containing	139 (81)
Adriamycin-containing	122 (71)
RT Technique	
2D conventional	5 (3)
FP-IMRT	69 (40)
IP-IMRT	97 (57)
RT Field	
RB only	24 (14)
RB and SCF and level III axilla	16 (9)
RB and SCF and full axilla	44 (26)
RB and SCF and level III axilla and MI	50 (29)
RB and SCF and full axilla and MI	37 (22)

Abbreviations: ALND = axillary lymph node dissection; 2D = 2-dimensional; FP-IMRT = forward planning intensity-modulated radiotherapy; IP-IMRT = inverse planning intensity-modulated radiotherapy; MI = mammaria interna; RB = reconstructed breast; RT = radiotherapy; SCF = supraclavicular fossa; SLNS = sentinel lymph node sampling.

One patient developed local recurrence (LR) in the subcutaneous tissue of the RB, and 22 developed distant metastasis (DM) during the follow-up. The patient with LR underwent several surgeries, and is still alive with local disease at 52 months of follow-up. Among the 22 patients who developed DM, 12 were in remission after systemic therapy and 3 were alive with disease at the last follow-up, but 7 were succumbed to disease.

Cosmetic Results

Among 171 breasts treated with RT, cosmetic result was excellent in 111 (65%), fair in 46 (27%), and bad in 14 (8%) RBs. In total, 34 (20%) breasts underwent resurgery; 5 (5%) in the excellent, 24 (52%) in the fair, and 5 (36%) in the bad cosmetic result group. In the 5 patients with an excellent cosmetic result after RT, the reason for resurgery was surgeon's choice because of the implant's natural lifespan. In the 24 patients with a fair cosmetic result, the reason for resurgery was contracture and fibrosis in 13, deformation in the implant in 7, dislocation of the implant in 2, implant exposure out of skin in 1, and cellulitis in 1 patient. In addition, resurgery is planned for 5 other patients with a fair cosmetic result, but it has not yet been performed. In the 5 patients with a bad cosmetic result, the reason for resurgery was deformation of the implant, contracture, infection, dislocation of the implant, and opened stitches in each, respectively. Furthermore, resurgery was also planned for 5 other patients with a bad cosmetic result, but has not yet been performed. Patients who underwent resurgery reported that their cosmetic result improved and they were satisfied with the results of the restorative surgery. When the rate of reconstructive failure was defined as impaired cosmesis that necessitated resurgery, this was a total of 39 breasts of 171, which makes the rate 22.8%. The rate was higher with permanent implants (23%) compared with tissue expanders (18%) although not statistically significant ($P = .6$).

Cosmetic results (excellent vs. impaired [fair or bad]) were analyzed whether they were related to patient or treatment characteristics. In univariate analysis, age ($\leq$ 40 years vs. $>$ 40 years), history of cigarette smoking, presence of comorbidities (ie, hypertension, diabetes, thyroid dysfunction, hyperlipidemia, congestive heart failure, and chronic obstructive lung disease), reconstruction substance (permanent implant vs. tissue expander), presence of HT, type of HT (tamoxifen vs. aromatase inhibitor), RT technique (2D conventional vs. FP-IMRT vs. IP-IMRT), maximum dose to the RB ($\leq$ 55.4 Gy vs. $>$ 55.4 Gy), and V105 ($\leq$ 7% vs. $>$ 7%) did not affect the cosmetic outcome ($P = .9, .4, .4, .11, .8, .7, .9, .9$, and .12, respectively). However, lymphatic irradiation, a V110 value of $>$ 1% and bolus use significantly worsened cosmetic results (Table 2). In multivariate analysis, bolus use was the only significant prognostic factor that worsened the cosmetic outcome (relative risk = 6; 95% confidence interval = 2.2-16.6; $P < .001$).

Acute and Late Toxicity

Grade 4/5 acute toxicity was not observed in any patients; however, 2 patients experienced Grade 4-5 dermatitis during RT. The final cosmetic result was fair in these 2 patients, and resurgery is planned for 1 of them. As a late complication other than implant problems, lung fibrosis was observed in 1 patient who received RT to the RB only with a maximum dose of 57 Gy, rib fracture was observed in 1 patient who received RT to the RB and SCF and full axilla with a maximum dose of 57 Gy, and lymphedema (Grade 1-3) was observed in 7 patients.

Discussion

The current study focused on cosmetic outcomes related to RT in patients who underwent IBR. Most of the patients were satisfied with the results; however, 60 (35%) complained about impaired cosmetic. The risk factors for impaired cosmetic were lymphatic irradiation, a V110 value $>$ 1%, and bolus use. Cosmetic outcome of breast RT has been studied in several trials; however, to the best

Table 2 Univariate Analysis of Factors Effective on Cosmetic Outcome

Factor	Cosmetic Outcome		*P*
	Good	Impaired[a]	
Age			
≤40 years	56 (64)	31 (36)	.9
>40 years	55 (66)	29 (34)	
History of Cigarette Smoking			
Present	12 (57)	9 (43)	.4
Absent	99 (66)	51 (34)	
Comorbidity			
Present	26 (70)	11 (30)	.4
Absent	85 (63)	49 (37)	
Reconstruction Substance			
Permanent implant	97 (63)	57 (37)	.1
Tissue expander	14 (82)	3 (18)	
Hormonotherapy			
Present	91 (66)	48 (34)	.8
Absent	20 (63)	12 (37)	
Type of Hormonotherapy			
Tamoxifen	78 (66)	41 (34)	.7
Aromatase inhibitor	11 (61)	7 (39)	
RT Field			
RB only	21 (88)	3 (12)	<.001
RB and lymphatics	90 (61)	57 (39)	
RT Technique			
2D conventional	3 (60)	2 (40)	.9
FP-IMRT	45 (65)	24 (35)	
IP-IMRT	63 (65)	34 (35)	
Maximum Dose to the RB			
≤55.4 Gy	53 (65)	29 (35)	.9
>55.4 Gy	53 (65)	28 (35)	
V105			
≤7%	59 (71)	24 (29)	.1
>7%	47 (60)	32 (40)	
V110			
≤1%	96 (68)	45 (32)	.04
>1%	9 (45)	11 (55)	
Bolus			
Present	67 (55)	54 (45)	<.001
Absent	44 (88)	6 (12)	

Data are presented as n (%) except where otherwise noted.
Abbreviations: 2D = 2-dimensional; FP-IMRT = forward-planned intensity-modulated radiotherapy; IP-IMRT = inverse-planned intensity-modulated radiotherapy; RB = reconstructed breast; RT = radiotherapy; V105 = the volume that received at least 105% of the prescribed dose; V110 = the volume that received at least 110% of the prescribed dose.
[a]Fair or bad.

of our knowledge, this is the first study to evaluate the effect of V105 and V110 values and bolus use on cosmetic outcomes.

Breast reconstruction has gained popularity among oncologic surgeons in recent years. IBR is the most preferred technique.[9] It is always performed together with SSM, and cosmetic results are very good in patients who do not need adjuvant RT. The main purpose of reconstruction after mastectomy is to obtain good cosmesis and increase the quality of life without compromising oncological safety. The LR risk does not increase after SSM and concurrent reconstruction, but reconstruction complicates the patient follow-up.[10-13] In a study at M.D. Anderson Cancer Center (MDACC), the LR rate was 2.3% in 1694 patients after concurrent SSM and reconstruction after 10 years of follow-up.[14] Kneubil et al[15] reported a 5.5% LR rate in 1742 cases in a similar study. In our study, LR occurred in only 1 patient, and the OS rate was excellent.

Adjuvant RT increases locoregional control and OS rate in patients with LN metastasis or tumors > 5 cm or invasion of skin/fascia.[16-21] RT indications in patients who underwent SSM and breast reconstruction were similar to patients without reconstruction. In the supervision report of English National Mastectomy and Reconstruction, every 40 patients of 100 with reconstruction were reported to need adjuvant RT.[22] Several trials, mainly retrospective, reported their results on the relation between IBR and RT.[23-30] In the largest prospective study from Memorial Sloan Kettering Cancer Center, no relation was observed between RT and perioperative complications in 1100 patients with IBR.[23] However, when the 104 patients who received RT were evaluated, the rate of need for resurgery was reported as 29% after 7 years of follow-up.[24] In another prospective study by Krueger et al,[26] however, RT was reported to increase the rates of perioperative complications and reconstruction failure (from 8% to 37%; $P = .005$). In a meta-analysis in which 12 studies were evaluated, the rate of failure of reconstruction was 18.6% in 715 patients who underwent RT after IBR. This rate was 30% with a tissue expander and 7.7% with a permanent implant.[31] In a 2017 meta-analysis of 20 studies with 2348 patients, the rate of reconstructive failure was reported as 17.6%, and it was significantly higher with tissue expanders compared with permanent implants (20% vs. 13.4%).[32] In the literature, the reconstructive failure rate was reported as 0-29% for permanent implants, and 4.8-40% for tissue expanders.[33-35] This wide range might be because of the inhomogeneity of patient characteristics (eg, age, comorbidity, smoking status), level of surgeon's expertise on breast reconstruction, type of surgeon (plastic surgeon, breast surgeon, or oncologic surgeon), certain materials used during surgery, RT characteristics (eg, total dose, fraction dose, contouring, bolus use), radiation oncologist's expertise, and definition of the complication among the studies. The rate of reconstructive failure was 22.8% in our study, in accordance with the literature, and it was higher for permanent implants (23%) compared with tissue expanders (18%), although not statistically significant.

Cosmetic results can be evaluated either by subjective opinions of patients and clinicians, or more objective methods such as questionnaires. In a study that compared the 1-year outcome of irradiated versus nonirradiated patients with breast reconstruction, patients who underwent RT had worse results in the BREAST-Q questionnaires in sections of "Satisfaction with Breasts," "Psychosocial Well-being," "Sexual Well-being," "Physical Well-being of Chest," and "Satisfaction with Outcome."[36] In the review by El-Sabawi et al,[37] 29 trials on cosmetic outcomes, patient satisfaction, and the results of BREAST-Q questionnaire were evaluated. In patients with IBR followed by RT, the rate of good cosmetic outcome ranged between 36% and 100%, and patient satisfaction between 41% and 90%. In addition, the BREAST-Q scores of satisfaction with breasts, satisfaction with outcome, psychosocial well-being, sexual well-being, and physical well-being were worse in patients who received RT compared with patients who did not.

Treatment fields in patients who are planned to undergo RT after IBR can change. Exaggerated erectness of the breast can increase hot and cold dose points in the target volume in 2D treatment plans, and this can negatively affect the local control (LC) rate and cosmesis. In the MDACC series by Langstein et al,[14] 82% of locoregional recurrences were seen in the skin and subcutaneous tissue, and 28% in the chest wall after an 81-month follow-up. For this reason, doses to the skin and subcutaneous tissue are important and the same treatment planning rules as in the cases of mastectomy without reconstruction are valid. A bolus material can be used to increase the dose to the skin because it acts like an additional tissue and carries the dose closer to the skin level. Approximately 60% of radiation oncologists in Europe do not use bolus for patients with breast reconstruction unless there is skin involvement.[38] When used, generally a 0.5-cm bolus is reported to be placed on the RB during the entire treatment. Similarly, Thomas et al[39] reported the rate of using bolus in patients with breast reconstruction as approximately 50% in the United States with different schemes such as 0.5 cm every other day, 0.5 cm every day as tolerated, 1 cm every other day, and 1 cm every day as tolerated. It is a fact that bolus use increases the rate of acute skin complications and in patients with IBR it can also impair cosmetic outcomes. However, it is not logical to omit the use of bolus because it would increase the risk of LR. Therefore, although our study showed that bolus use significantly impaired the cosmetic outcome, we recommend using a bolus if it brings an advantage in terms of LC.

In the study by Muresan et al,[40] maximum doses to the whole skin (61.7 Gy vs. 58.5 Gy; $P = .05$) and 1 cc of the skin (57.4 Gy vs. 54.4 Gy; $P = .01$) were associated with increased complication rates. We could not find any relation between the maximum dose to the skin and cosmetic outcome; however, a V110 value of > 1% led to impaired cosmetic results. When they compared 3-D conformal RT, FP-IMRT, IP-IMRT, and hybrid techniques, Muresan et al did not find any difference among the rate of complications, which is similar to our findings. They also reported similar complication rates with tissue expanders and permanent implants, which is also the finding in our study. However, although the additional use of lymphatic irradiation did not affect complication rates in the study by Muresan et al, we found that lymphatic irradiation can impair cosmetic results.

Our study has some limitations as well. It is retrospective in nature, and based on subjective opinions of the patients. This study was carried in patients with IBR concurrent with SSM, and therefore might not be applicable to patients who underwent delayed reconstruction. Besides, cosmesis can change over time. Therefore, these results might not be the final results, and they might improve or, mostly expected, worsen with a longer follow-up.

Conclusion

Radiotherapy after IBR appears to be safe in terms of cosmetic results. Although it is retrospective and only presents the subjective opinions of patients, this study is important for its findings that lymphatic irradiation, a V110 value of > 1%, and bolus use significantly impair the cosmetic outcomes. Prospective trials using widely accepted questionnaires and objective opinions of clinicians can be more informative about cosmetic outcome.

Clinical Practice Points

- Breast reconstruction is frequently performed in patients with breast cancer.
- Indications for RT in these patients are the same as in patients without reconstruction.
- The additional use of these 2 modalities might impair the cosmetic outcomes.

- It is already known that irradiation of the lymphatic areas can deteriorate the results.
- We also showed that using a bolus material and the V110 value > 1% are also negative factors for cosmesis.
- It is important to inform the patients with breast reconstruction that these factors might impair their cosmetic results.
- Therefore, one should try to keep the V110 < 1%. However, bolus use and lymphatic irradiation should not be omitted only not to negatively affect the cosmetic outcome.

Disclosure

The authors have stated that they have no conflicts of interest.

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