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Review

Effect of Radiotherapy on the Type and Timing of Breast Reconstruction After Mastectomy in Breast Cancer Patients

Bulent Citgez,[1] Banu Yigit,[2] Buse Capkinoglu,[3] Altug Altinkaya[4]

[1]Department of General Surgery, Uskudar University Faculty of Medicine, Memorial Hospital, Istanbul, Türkiye
[2]Department of General Surgery, Bagcilar Training and Research Hospital, Istanbul, Türkiye
[3]Plastic and Reconstructive Surgeon, Private Practice, Istanbul, Türkiye
[4]Department of Plastic and Reconstructive Surgery, Memorial Hospital, Istanbul, Türkiye

Abstract

Breast cancer is the most common cancer type among women according to the World Health Organization data. While breast-conserving surgery has been increasingly performed in patients with early-stage breast cancer, unilateral or bilateral mastectomy is still performed in many patients. With the changes in mastectomy techniques and the development of breast reconstruction techniques over the years, today the aim of breast reconstruction is to create breast tissue in a shape and symmetry that will correct the anatomical defect that occurs after mastectomy, without affecting the patient's oncological treatment. Radiotherapy is applied to patients after breast-conserving surgery as well as selected patient groups after mastectomy. In addition, reconstruction methods can be recommended after mastectomy in a patient who has previously received radiotherapy treatment to the breast. The aim of radiotherapy is to improve local and regional control and increase survival rates. Radiotherapy will affect the expected cosmetic outcomes. Poor cosmetic results can be prevented by determination of correct surgical technique, reconstruction strategy, and new developing technologies.

Keywords: Breast cancer, flap, implant, mastectomy, radiotherapy, reconstruction

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While breast cancer was considered a local disease and radical mastectomy was performed in the last century, today the shape of the breast is recreated by reconstruction even if mastectomy is performed. The surgical approach to the breast has become increasingly conservative and preserving the skin during mastectomy has made simultaneous reconstruction possible. Furthermore, implant-based breast reconstructions can be successfully performed under healthy skin flaps by preserving the subcutaneous vascular plexus in mastectomies performed by paying attention to the different thickness of the tissue plane between the mammary gland and the skin in each patient. For these reasons, implant-based breast reconstructions have come to the fore in the last 20 years, and thus more patients have the opportunity for immediate reconstruction. Autologous breast reconstructions performed with the patient's own tissues also come to the fore in institutions that have microsurgery capacity and perform high-volume breast reconstruction surgery.[1]

Address for correspondence: Bulent Citgez, MD. Department of General Surgery, Uskudar University Faculty of Medicine, Memorial Hospital, Istanbul, Türkiye
Phone: +90 505 237 68 47 **E-mail:** bcitgez@yahoo.com

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There are two main ways to perform breast reconstruction after mastectomy: implant-based reconstruction, which involves one-stage implant placement or two-stage tissue expander placement followed several months later by its replacement with a permanent implant, and autologous reconstruction, which consists of moving a tissue or flap from another part of your body to rebuild the shape of the breasts. In parallel with the developing trends in mastectomy techniques, different approaches have also taken shape in breast reconstruction. Nowadays, instead of two-stage reconstructions, one-stage direct-to-implant (DTI) reconstructions are increasingly being performed, and total submuscular approaches have been replaced by muscle-sparing methods when creating the pocket under the muscle for the permanent implant.[2] When choosing one-stage/two-stage or subpectoral/prepectoral techniques, it is important to make the choice according to the characteristics of the patient in order to minimize the risks of possible complications in line with multidisciplinary treatment planning.

The aim of radiotherapy (RT) in breast cancer treatment is to improve locoregional control and increase survival rates in selected patient groups. There is a general consensus that RT should be considered for locally advanced disease including the patients with four or more positive axillary lymph nodes, tumor size greater than 5 cm, positive or close (<1 mm) surgical margins or selected group of patients with 1-3 positive axillary lymph nodes.[3] RT is applied to the chest wall, axillary fossa, supraclavicular fossa, and internal mammary chain. Although RT has beneficial effects on oncological treatment outcomes, patients experience some early and late side effects due to collateral damage to the chest wall or breast tissue. Early side effects of RT include erythema, edema, and dry or moist desquamation, while late side effects include fibrosis, telangiectasia, thinning of the skin (atrophy), pigmentation, ulceration, and secondary malignancy (Figs. 1, 2). These side effects also negatively affect breast reconstruction.[4] Despite the fact that breast or chest wall RT is associated with greater morbidity in breast reconstruction after mastectomy, there is no definitive consensus regarding the choice of breast reconstruction in patients requiring RT. Also, patient preference should be taken into account when deciding on breast reconstruction options. The decision to be made for reconstruction should not conflict with oncological principles, and the possibility of delay in initiating adjuvant treatments due to complications and the possible consequences of adjuvant treatments on reconstruction should be taken into account.

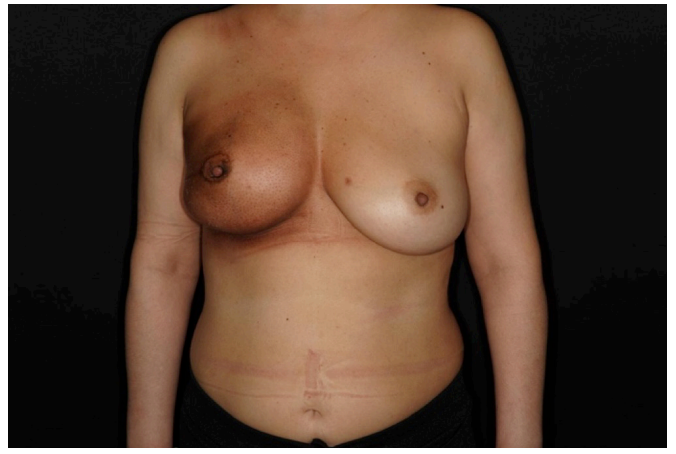

Figure 1. A 57-year-old female showed moderate radiation dermatitis with nipple-sparing mastectomy and radiation for right breast cancer (Front).

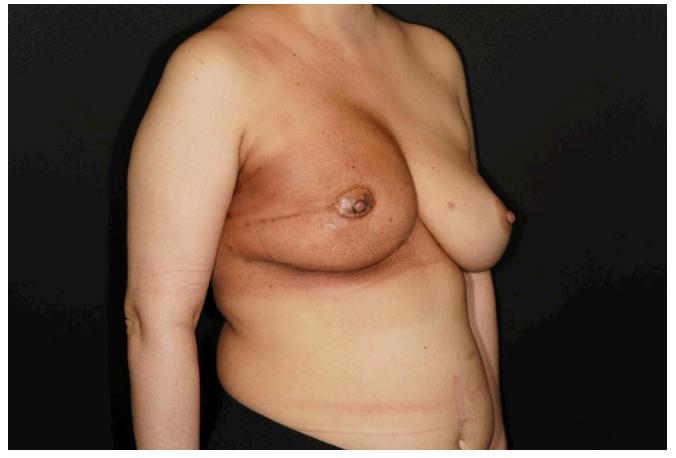

Figure 2. A 57-year-old female showed moderate radiation dermatitis with nipple-sparing mastectomy and radiation for right breast cancer (Oblique).

Radiotherapy After Breast Reconstruction with an Implant or Tissue Expander

Two-stage implant-based reconstruction after mastectomy, which includes initial placement of a tissue expander followed by its exchange for a permanent implant, reduces pressure on the mastectomy flaps, provides opportunity for recovery of any excess that may occur in the skin, gives the patient a choice regarding the final breast size, and gives the surgeon the opportunity for revision in the second session.[5] In the light of new developments in recent years, single-stage implant reconstruction has become possible with fewer complications and higher success rates.[6-8] These developments include advances in skin-sparing/nipple-sparing mastectomy (SSM/NSM) techniques (sufficient subcutaneous tissue thickness, hidden incisions), new generation of implants (anatomical-shaped breast implants

filled with high cohesive silicone gel), biological (acellular dermal matrix) or synthetic (mesh) materials for soft tissue support, indocyanine green perfusion scintigraphy technology to assess mastectomy skin flap and autologous flap perfusion, and fat grafting.

There are many studies investigating advantages and disadvantages of both one-stage and two-stage breast reconstruction techniques. Most of the studies have reported that one-stage DTI breast reconstruction has lower complication rates than two-stage tissue expander/implant breast reconstruction and comparable rates to autologous reconstruction in patients receiving RT.[6-8] In a prospective series of 257 patients, Nava et al.[9] showed that the failure and complication rates with tissue expanders were higher in patients receiving RT than with permanent implants. The failure rates of breast reconstruction observed in the control group without RT, in group 1 where RT was applied to permanent implants, and in group 2 where RT was applied to tissue expanders were 2.3%, 6.4% and 40%, respectively.

Cordeiro et al.[10] reported that the reconstructive failure during the 6-year follow-up period was significantly higher for the group receiving RT to the tissue expander compared with the group receiving RT to the permanent implant, at 32% versus 16.4%, respectively. Therefore, the data obtained in this study support the conclusion that the permanent implant should be irradiated instead of tissue expander if reconstructive failure is to be minimized. On the other hand, patients who received RT to the permanent implant had higher rates of severe capsular contracture (grade III and IV) than patients who received RT to the tissue expander (15.9% and 1.22% versus 44.6% and 6.3%, respectively), and the patients who received RT to the tissue expander were more likely to achieve very good to excellent aesthetic results (75% and 67.6%, respectively). The lower rates of severe capsular contracture and thus better aesthetic outcomes in the group received RT to the tissue expander were probably due to the aggressive capsulotomy performed during the exchange procedure. These results are consistent with previous meta-analyses.[11]

Predicting which patients will actually receive RT after surgery, informing the patient, mastectomy skin flap viability, location of implant pocket (pre/retropectoral), acellular dermal matrix (ADM) use, optimal incision, implant and skin reduction types play an important role in preventing RT-related complications. Although the 2021 oncoplastic breast consortium expert panel suggested that planned or anticipated RT should generally have no impact on selection of skin incision, the panel also acknowledged consistent observations in the literature that location of incision is a risk factor for severe mastectomy flap necrosis.[12] The routinely used incisions after SSM/NSM include inframammary fold, lateral, and mastopexy incisions.[13,14]

- Inframammary fold incision: Although this type of incision has a more aesthetic and proportional appearance, it is difficult to access the upper pole through the incision and complications such as compression and necrosis may occur in the incision line due to traction. Since additional incisions are often required for sentinel lymph node biopsy and axillary dissection, it is preferred in small-volume breasts.
- Lateral incision: It is widely accepted as an incision of first choice for many patients because it provides easy access to all quadrants of breast tissue, does not require an additional incision in the axilla, and is designed to cause minimal damage to the dermal plexus (Figs. 3, 4).
- Mastopexy incisions: These are incisions made in large breasts to reduce the skin envelope and the volume of breast tissue and to reshape the nipple position.

The condition of the recipient site can be evaluated after mastectomy according to the implant pocket selection algorithm suggested by Nahabedian et al.[15] If flap perfusion is good and flap thickness is adequate after mastectomy, a

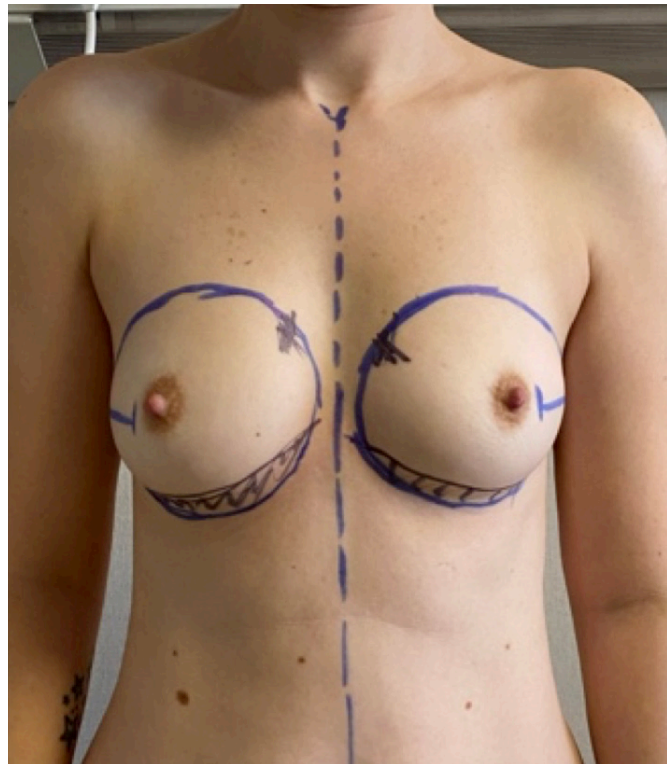

Figure 3. Bilateral lateral incisions. Preoperative appearance of a 42-year-old woman with BRCA mutation and a strong family history of breast cancer who underwent bilateral one stage implant-based breast reconstruction following nipple-sparing mastectomy using lateral incisions.

Figure 4. Bilateral lateral incisions. One-year postoperative appearance of a 42-year-old woman with BRCA mutation and a strong family history of breast cancer who underwent bilateral one stage implant-based breast reconstruction following nipple-sparing mastectomy using lateral incisions.

prepectoral implant should be preferred. If flap perfusion is good but there is inadequate flap thickness, a subpectoral implant should be preferred. If flap perfusion is poor after mastectomy, the risk of necrosis is high and the reconstruction should be postponed. If necessary, delayed reconstruction can be performed with fat grafting in the second session. The dual-plane approach (partial retropectoral pocket) allows RT treatment and imaging follow-up in deep-seated tumors close to the pectoralis major muscle to be more effective, does not prevent the detection of breast cancer recurrence, and provides better perfusion of the implant pocket, especially in patients who are current smokers and have previously received RT. In addition, several studies have shown that irradiation of prepectoral implants is safe and has similar complication rates as the subpectoral approach.[16,17]

Synthetic meshes are cost-effective as soft tissue support, but biological materials that provide better implant capsule modification and have a lower complication rate are preferred. Biological soft tissues are of human or animal origin, and pericardial tissue-derived grafts are most frequently used. They act as a barrier between the implant surface and the overlying skin envelope of the lower pole. They facilitate the creation of lower and lateral breast folds during mastectomy. They reduce pain and regional morbidity by eliminating the need for dissection of the serratus and rectus fascia. Since they can expand the implant pocket by lengthening the muscles, it makes reconstruction possible with larger-volume implants. Although ADM has risk factors including seroma, numerous studies support that the breast is less affected by RT and capsular contracture is less common with the use of ADM.[11,18] Prepectoral breast reconstruction techniques with the use of a mesh pocket or ADM support include breast implant packaging in which the implant is completely wrapped, tent technique in which only the front face of the implant is covered, or combined techniques with a dermal flap in the lower pole and synthetic mesh or ADM in the upper pole are used in skin-reducing mastectomies.[19] Techniques in which the implant is completely wrapped with ADM may not be preferred due to their high cost. Also, the risk of seroma and implant loss is stated to be higher in techniques that cover the entire surface of the implant, compared to only front face-covered methods.[20] On the other hand, Sinnott et al.[21] showed a higher rate of capsular contracture in subpectoral implant-based breast reconstructions than in prepectoral implant-based breast reconstructions. It may have been related to the increased implant surface area covered by ADM with the prepectoral implant-based breast reconstruction.

One of the technological advancements aimed at eliminating long-term complications due to implant weight is lightweight breast implants. These implants are produced with a filler material that consists of the integration of cross-linked silicone gel into borosilicate microcrystals and is one-third lighter than conventional silicone gel.[22] Lightweight breast implants, which do not interfere with radiological imaging and RT treatment, are preferred especially in prepectoral breast reconstruction where implant weight is of great importance. Although there have been few studies investigating this subject, the use of lightweight implants has also been found beneficial in postoperative pain control and recovery time. The risks of capsular contracture, rupture, and rippling deformity with this product are stated to be similar or less than those with conventional silicone gel.[23] However, long-term results and prospective study data, especially for its use in the field of reconstructive surgery, need to be evaluated.

The most common complication in implant-based reconstruction is early implant loss due to mastectomy flap necrosis. Seroma formation and infection are complications

that develop due to perfusion problems in the early period, and therefore it should be known that the most important factor in reducing the risk of reconstruction failure is a good mastectomy technique. In partial skin flap necrosis, repair can be performed in two steps with conservative follow-up, debridement after the 3rd week, and primary closure or switching to expander depending on the size of the defect (Figs. 5, 6). Early detection of seroma and aspiration under sterile conditions guided by ultrasonography reduces the risks of infection and implant loss. Since the risk of local recurrence increases in patients whose postoperative initiation of RT is delayed, complications should be managed as quickly as possible in patients who are likely to receive RT after surgery.[24]

Radiotherapy After Autologous Breast Reconstruction

Autologous breast reconstruction has greatly increased its reliability and options, especially after the developments in the field of microsurgery. Additionally, when implant-related problems are observed or anticipated, autologous reconstruction appears to be the most appropriate option. Some of the complications and adverse outcomes of breast implants and tissue expanders include severe contracture, fibrosis, implant exposure, infection, and failed reconstruction. RT has been shown to be associated with complications after implant-based breast reconstruction, particularly capsular contracture, reconstructive failure, higher rates of revision surgery, worse cosmetic outcomes, and lower patient satisfaction (Figs. 7, 8). In the study by Reinders et al.[25], among 109 patients who underwent SSM with immediate breast reconstruction (IBR) followed by RT, immediate autologous reconstruction was applied to 29 (27%) patients and immediate implant-based reconstruction was applied to 80 (73%) patients. Reconstruction failure was detected in 17 patients (21%) with implant-based reconstruction, and none with autologous reconstruction. Furthermore, patient-reported satisfaction outcomes measured by BREAST-Q were significantly less in patients treated with immediate implant-based reconstruction.

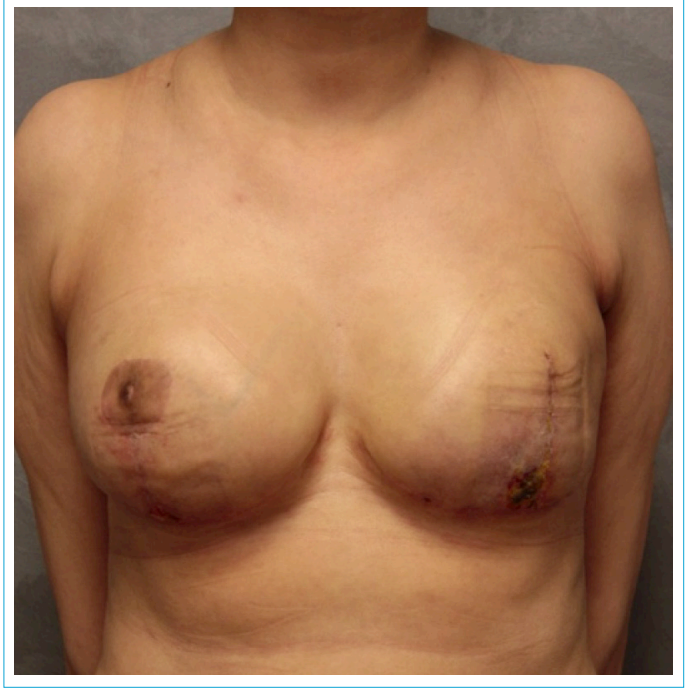

Figure 5. Postoperative image of the 52-year-old woman with BRCA mutation and a strong family history of breast cancer who underwent bilateral one stage implant-based breast reconstruction following subcutaneous mastectomy using mastopexy incisions. Subareolar frozen section analysis confirmed tumor extending into the left nipple. Nipple–areolar complex was removed and skin sparing mastectomy was performed. Topical antibiotics were used in the treatment of limited necrosis. The necrosed tissue of the mastectomy flap was shed and permitted subsequent healing by secondary intention.

Figure 6. 3 months after the initial surgery, 25 sessions of radiation therapy were completed and the appearance of the patient was as shown in the image.

Autologous reconstruction is the gold standard for patients receiving RT because it minimizes complications related to breast reconstruction surgery. The patients receiving RT after autologous reconstruction may also experience undesirable aesthetic results such as fat necrosis, skin fibrosis, and contracture formation of the autologous flap. On the other hand, Pont et al.[26] have reported that the quality-of-life measures, satisfaction with outcomes, and cosmetic results in patients undergoing immediate breast reconstruction with autologous free flap did not differ between

Figure 7. Postoperative status of the 32-year-old patient at twenty months after left nipple-sparing mastectomy with immediate implant placement and seven months after radiotherapy completion (Front).

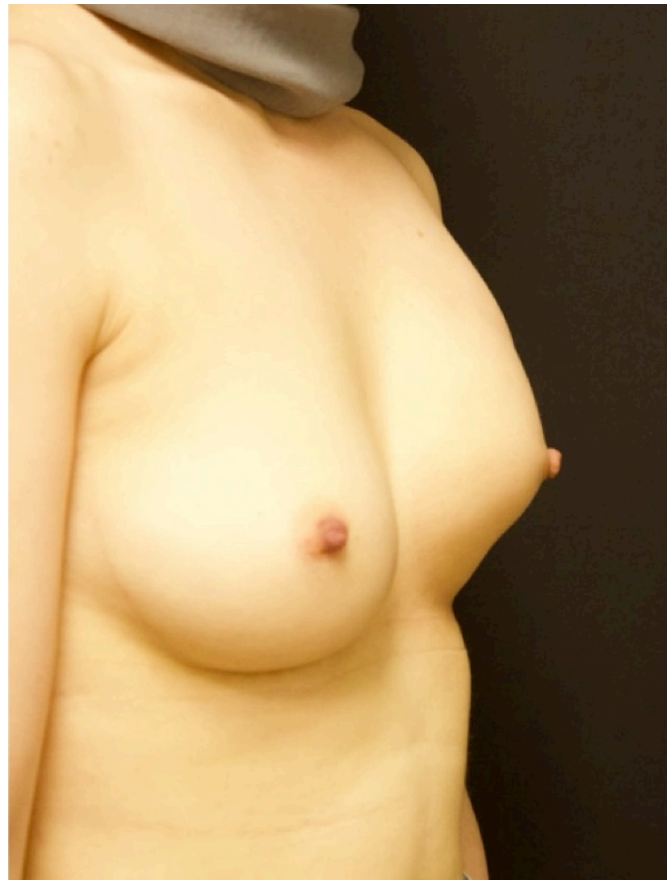

Figure 8. Postoperative status of the 32-year-old patient at twenty months after left nipple-sparing mastectomy with immediate implant placement and seven months after radiotherapy completion (Oblique).

irradiated and non-radiated breasts. In a study by Craig et al.[27], it was emphasized that no statistical difference was detected in the deep inferior epigastric artery perforator (DIEP) flap volume and projection between radiated and non-radiated sides. It has been suggested that placing the radiated flaps inferiorly, since the position of the radiated flaps were higher in response to fibrosis and contracture of the overlying skin envelope, would improve symmetry.

The main point to consider when performing autologous reconstruction is the timing of the reconstruction as delayed, delayed-immediate or immediate according to RT exposure. Previous studies indicate that delayed autologous reconstruction usually provides better cosmetic results.[28,29] In a study by Billig et al.[30] involving a total of 175 patients who received RT, in which 108 patients underwent immediate autologous breast reconstruction and 67 patients underwent delayed autologous breast reconstruction, no significant difference was found between the two groups in terms of BREAST-Q scores, and complications such as fat necrosis, dehiscence, hematoma, and seroma at 1 and 2 years postoperatively. Based on the results of this study, patients receiving RT are still suitable candidates for immediate autologous reconstruction. On the long-term follow-up, atrophy of autologous tissue may occur which can be corrected with fat injections.

Breast Reconstruction in Patients with a Previous History of Radiotherapy

Patients who have undergone breast-conserving surgery and RT appear as mastectomy candidates in two scenarios: the first is salvage mastectomy (local-regional recurrence after initial breast conservation treatment), the second is completion mastectomy (genetic mutation carriers or candidates for bilateral mastectomy with a high risk of developing contralateral breast cancer). Each patient's wound healing and response to RT are individual. First of all, it should be evaluated how obvious the signs of RT are on the patient's chest wall. If adverse signs of previous RT (pigmentation, telangiectasias, atrophy, fibrosis) are evident in the chest wall examination, it is always safer to offer autologous or hybrid reconstruction methods (implant reconstruction with flaps) as there is no ideal environment for reconstruction with implants. If these signs of previous RT

are not present, implant-based reconstruction can be performed by creating a partial retropectoral pocket. Muscle-sparing breast reconstruction with prepectoral implant is usually not preferred in patients with a history of previous RT due to the high risk of complications.[31]

In recent years, implant-based reconstruction techniques have rapidly increased in the setting of RT. In short-term results, implant-based reconstruction appears to be more useful compared to autologous reconstruction. In long-term results, autologous reconstruction appears to be superior in terms of quality of life, sensory recovery, long-term complications and reconstruction failure rate compared to implant-based reconstruction.[32] In the study of Chetta et al.,[33] which examined 4,187 breast cancer patients who were exposed to RT after mastectomy and underwent breast reconstruction, reconstruction failure occurred in 29.4% of patients with implant-based reconstruction, while this rate was 4.3% in patients with autologous reconstruction. Jo et al.[34] retrospectively evaluated the data of patients for whom they performed DIEP flaps in 27 breasts that underwent salvage mastectomy, 32 breasts that underwent completion mastectomy and 564 breasts that underwent primary mastectomy. They compared the primary and completion mastectomy groups with the salvage mastectomy group, and found that there was no significant difference in early and late complications. They also evaluated the data of patients for whom they performed DTI reconstruction in 20 breasts that underwent salvage mastectomy, 12 breasts that underwent completion mastectomy and 351 breasts that underwent primary mastectomy. They compared the primary and completion mastectomy groups with the salvage mastectomy group, and found that wound healing problems and capsular contracture were significantly increased in the salvage mastectomy group. Since the higher rates of wound healing problems and capsular contracture with DTI reconstruction, we can conclude that DIEP flap is a successful reconstruction option after salvage mastectomy.

33 patients were enrolled in the study of PRADA over a period of 2 years. Premastectomy radiotherapy (PreMRT) was implemented 3-4 weeks after neoadjuvant chemotherapy. SSM and DIEP flap reconstruction were planned 2-6 weeks after completion of PreMRT. The status of wound healing was evaluated and similar rates of breast open wounds to those reported with postoperative RT were found. In the PRADA study, RT like neoadjuvant chemotherapy was tried to be shifted to the preoperative period, but there were two important points that positively affected the safety and preoperative applicability of RT. First of all, autologous reconstruction was planned 2-6 weeks after RT, and surgery was performed as soon as the acute effects subsided and before chronic fibrosis was established. Secondly, immediate autologous breast reconstruction was preferred for reconstruction, and no implants were used in this study.[35] In the study evaluating the cosmetic results of the PRADA study, 17 out of 33 women from the PRADA study participated. 28 women formed the DIEP-RT cohort. The median satisfaction score at 12 months for the PRADA cohort was significantly better than the DIEP-RT cohort. Aesthetic outcomes of the PRADA cohort were reported to be good or excellent in 93% of cases.[36] Although this study suggests that changing the surgery-radiotherapy sequence leads to similar cosmetic results, larger-scale, multicenter and randomized studies are required. Also, switching surgery-radiotherapy sequence is not logistically possible for most patients under current conditions, and we do not have any studied data on implant application in this regard.

In a recent phase 2 randomized study by Schaverien et al.[37], the outcomes of patients who underwent PreMRT and regional nodal irradiation followed by mastectomy and IMBR were evaluated. In contrast to the PRADA study, all patients received conventionally fractionated RT, which is the standard of care for breast RT, and all patients received regional nodal irradiation, including internal mammary lymph nodes. None of the patients experienced complete autologous flap loss, and most of the patients with skin flap necrosis were followed with conservative treatment. During the average follow-up period of 29.7 months, no cases of locoregional recurrence or distant metastasis were observed in these patients. Although there is still a need for extensive studies on this subject, it strengthens the idea that PreMRT and RNI followed by mastectomy and IMBR with microvascular autologous flap is safe and feasible. In this study, it was claimed that while the chance of IMBR application increased for most patients, the delay in reconstruction due to the late effects of RT and the negative psychosocial effects of this situation on patients were prevented.

Bacilious et al.[38] reported 7 breast cancer patients with a history of mantle irradiation due to Hodgkin's disease were treated with two-stage reconstruction. The average interval time between mantle irradiation and breast cancer diagnosis was 16 years. None of the patients experienced skin flap necrosis, poor skin expansion, or implant extrusion. From this study, we can conclude that mantle irradiation does not compromise prosthetic breast reconstruction.

During RT treatment, patients should be monitored for side effects of RT. Also, the patients should be well informed about the management of side effects, and if necessary, moisturizers, NSAIDs, antibiotics, exercise, massage, physiotherapy, and pentoxifylline/vitamin E should be recom-

mended. Despite all precautions, implant losses on RT-applied surface reach up to 10% (Fig. 9, 10).[39,40] The time elapsed after RT and the localization of the boost applied after whole breast RT in the tumor bed are also important. Reconstruction strategy should be modified depending on the extent of chest wall affected by RT. Since muscle and skin expansion is painful and often impossible, two-stage breast reconstruction method and retropectoral implant position are not usually preferred in the setting of RT. ADM integration after RT is also suboptimal and increases complication rates.[41,42] Urban et al.[43] investigated the results of prepectoral DTI reconstruction in NSM without ADM or synthetic mesh with a mean follow-up period of 16.5 months. In this study, the rates of implant explantation and rippling (grades 3 and 4) were calculated 30.4% and 1.3%, respectively, and cosmetic results were reported as good or excellent in 87.3 percent of patients. Soft tissue support alternatives other than ADM also need to be evaluated for the prepectoral implant placement. New-generation implants enable us to obtain good results by using less material in the prepectoral implant position. Long-term studies are also needed regarding capsular contracture and other late complications after RT.

Conclusion

There is a high demand rate for immediate breast reconstruction due to reasons such as better aesthetic outcomes, reduction of total hospital stays, and avoidance of delayed surgery. However, collaborative planning is essential for success in immediate breast reconstruction. Appropriate patient selection, incision, implant pocket and materials should be determined with a multidisciplinary approach. RT is an essential part of breast cancer treatment. It is becoming increasingly important and the number and severity of complications related to RT are less common than before. It may affect breast reconstruction to a greater or lesser degree. There is a variety of repair methods for different complications, and detailed informing of patients and multidisciplinary work become of critical importance in this process. RT is not an absolute contraindication for implant-based or other types of breast reconstruction. Due to lower long-term risk of complications, autologous breast reconstruction can be preferred instead of implant-based breast reconstruction in patients scheduled for radiotherapy.

Figure 9. Postoperative view of the 46-year-old patient at two months after radiotherapy completion. After getting COVID-19 infection, dehiscence of the wound occurred on the third week.

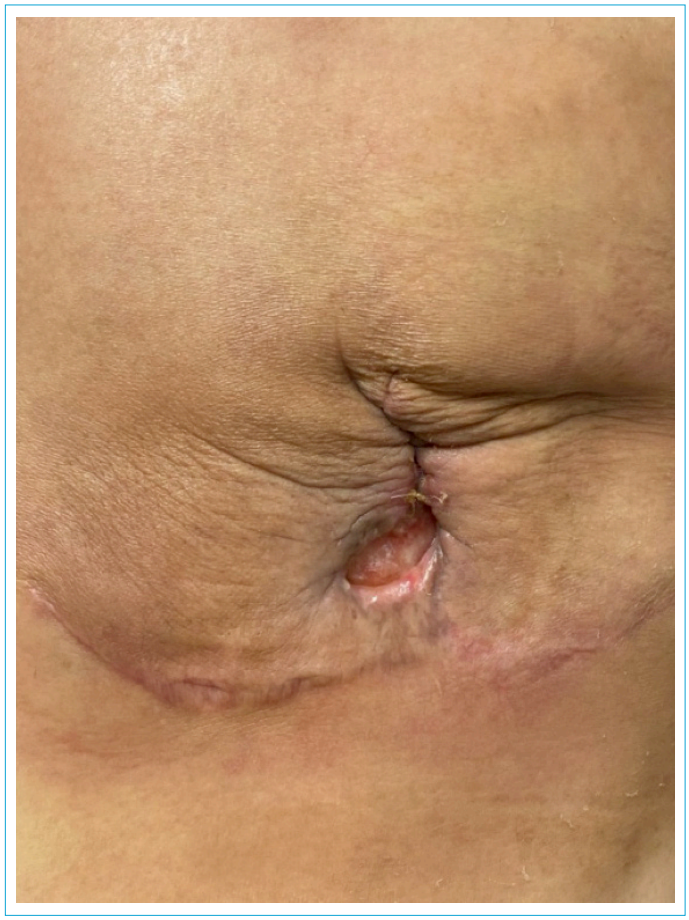

Figure 10. Wound dehiscence could not be managed with wound care and debridement, and the patient underwent implant removal.

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