Technical consideration for breast reconstruction in patients requiring neoadjuvant or adjuvant radiotherapy: a narrative review

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Background and Objective: Surgical considerations for breast reconstruction (BR) in patients requiring neoadjuvant radiotherapy (NART) or adjuvant radiotherapy (ART) cannot be understated. The management of irradiated tissue leads surgeons to face several challenges. Therefore, it is essential to comprehensively understand the proper patient selection and preoperative planning to ensure the best outcomes and minimize the risk of complications. This narrative review aims to provide an update and summary of the most important technical considerations every breast surgeon must contemplate reconstructing the irradiated breast.

Methods: The search strategy was performed on January 10th, 2023. The PubMed, Embase, Cochrane Library, and Web of Science databases were queried to capture all publications regarding surgical considerations in BR of patients undergoing NART and ART.

Key Content and Findings: This review shows that the effects of radiotherapy (RT) on BR are still being studied. RT represents an essential factor for overall patient survival, and its use is increasing. However, the range of RT treatments across different cancer centers complicates the creation of a single treatment protocol. BR improves women's quality of life, so finding the proper integration of BR and RT is essential. When deciding on the reconstructive method, there are several factors to consider, such as the patient's body characteristics, tumor stage, RT protocol, and chemotherapy. To achieve the best surgical results and the most satisfied patient, using less aggressive and safer RT methods in the treatment sequence is recommended.

Conclusions: The timing of the radiation will influence the selection of the best reconstructive methods to be employed in the breast cancer patient. However, there is clear evidence of preference for immediate autologous-based BR in cases due to the low rate of complications in the long term. But patient individualization is the key. Therefore, the benefits and risks of immediate versus delayed and autologous versus implant-based reconstruction must be weighed in every single case.

Keywords: Radiotherapy; adjuvant therapy; breast cancer; implant-based breast reconstruction (I-BBR); autologous-based breast reconstruction (A-BBR)

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Introduction

Background

Breast cancer is the fifth leading cause of death worldwide (1). In the United States, 1 in 8 women will be diagnosed with invasive breast cancer, with an estimated 287,850,000 new cases diagnosed in 2022 (2). Surgery, radiation, and systemic treatment remain the crucial components of treatment, with approximately 8 out of 10 patients receiving ionizing radiation at some point (3). Additionally, breast reconstruction (BR) after mastectomy has improved patients' satisfaction and well-being, reduced overall treatment costs, and provided better aesthetic results (3,4). Therefore, to ensure the best patient recovery, a perfect integration between these two procedures is essential.

Rationale and knowledge gap

Surgical considerations for BR in patients requiring neoadjuvant radiotherapy (NART) or adjuvant radiotherapy (ART) cannot be understated (5). To successfully manage irradiated tissue, surgeons must have a comprehensive understanding of the proper patient selection and preoperative planning to ensure the best outcomes and minimize the risk of complications (6,7). To this end, a multidisciplinary team of surgeons, oncologists and radiation oncologists should be involved in the decision-making and postoperative care of these patients (4,8,9).

Several reconstructive options have been described, and they must be tailored to the patient's needs and anatomy (9). The timing of the reconstruction is also a critical factor, as it must be performed before or after the completion of radiotherapy (RT) (7). Knowing the current evidence about the effects of RT, and its possible complications related to BR will allow the breast surgeon to understand better the different available options, indications, and contraindications to guide their decision-making. Additionally, having an updated knowledge of this topic will help when interacting with patients, as they should be informed of the potential risks and complications associated with the procedure and be counseled regarding the possibility of issues, such as an implant extrusion, capsular contracture, or flap failure, which may require further reconstructive surgery.

Objective

This narrative review aims to provide an updated summary of the essential technical considerations for breast surgeons reconstructing an irradiated breast. We will examine various surgical techniques used in NART or ART scenarios, such as implant-based breast reconstruction (I-BBR) and autologous-based breast reconstruction (A-BBR), along with their recommended timing of performance. Additionally, strategies to reduce complications and maximize patient outcomes will be discussed. We present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-23-1052/rc).

Methods

This narrative review was conducted to assess the current literature regarding surgical considerations in BR of patients undergoing NART and ART. The search strategy is outlined in *Table 1*.

Basic concepts in breast reconstruction

The complexity of treating breast cancer patients necessitates the involvement of a multidisciplinary team, comprising a medical oncologist, radiation oncologist, and surgeons, to provide the most meticulous care (4,9). In addition, the plastic surgeons are tasked with presenting the best reconstructive option suited to each case, considering factors such as breast shape and size, donor site availability, age, comorbidities, adjuvant therapy, and, most importantly, patient preferences (4).

The breast surgeon must be equipped to tailor the best reconstructive option to the patient at every stage of their journey. After a mastectomy, patients can choose a one-stage [immediate breast reconstruction (IBR)] or two-stage [delayed-immediate breast reconstruction (D-IBR)]. The one-stage (IBR) procedure offers numerous advantages, such as a decreased need for a second operation, shorter hospital stays, reduced postoperative recovery period, cost savings, more aesthetically pleasing results, and less requirement for symmetrical surgery than delayed BR (10,11). However, before to the operation, patients should be aware that a two-stage (D-IBR) procedure using an expander may be necessary due to the possibility of surgery,

Table 1 The search strategy summary

Items	Specification
Date of search	January 10th, 2023
Databases and other sources searched	PubMed, Embase, Cochrane Library, and Web of Science
Search terms used	A combination of the following MeSH terms was implemented to perform the search: "Breast reconstruction", AND "irradiated breast", OR "radiotherapy", OR "neoadjuvant", AND "adjuvant"
Timeframe	The search was limited to studies published in the last 10 years
Inclusion and exclusion criteria	Inclusion criteria: studies written in English that reported the outcome of breast reconstruction in patients undergoing radiotherapy
	Exclusion criteria: studies without a control group and studies that did not report results of breast reconstruction
Selection process	Three authors performed an independent search. The articles were evaluated for the quality of evidence, the validity of results, and their significance to the current practice. After the study collection, all the duplicates were eliminated. The first author completed the first filtering of the studies centered on titles and abstracts following the eligibility criteria. Next, the rest of the studies were screened based on full-text readings. Simultaneously, the second and third authors performed an independent search. Finally, a fourth author resolved any conflicts between the first two and third authors to accomplish a consensus among the authors
Any additional considerations, if applicable	The data from the included studies were extracted and categorized according to the type of radiotherapy administered, the breast reconstructive technique used, and the timing of the reconstruction. The results were further summarized in a narrative synthesis of the findings

and further complementary procedures may be needed for cosmetic purposes in the long run (9).

The reconstruction of the affected breast can be achieved through either A-BBR, which uses the patient's tissue, or I-BBR, which involves the use of silicone or saline breast implants. In most cases, I-BBR is performed in two stages, with a tissue expander (TE) first inserted to stretch the skin before placing the final implant (9). Both techniques are excellent reconstructive options (12,13). The choice of one method over the other depends on several factors, including the tumor type, cancer stage, remaining defect, available tissue after surgery, the patient's age, medical history, body type, and preferences (14-17). A retrospective analysis in a single center recently showed that age should not be a limiting factor when considering BR following mastectomy, as it was not associated with an increased risk of surgical complications. Notably, RT and smoking history were significant predictors of surgical complications (18).

Regarding breast cancer treatment, tumor characteristics, the type of surgical procedure, and chemo and RT can influence the breast cancer mortality ratio (3). Hence, the indication of RT after a total mastectomy in patients with positive lymph nodes decreases breast cancer mortality and distant/locoregional recurrence, contrary to patients with negative nodes (19,20). Furthermore, the drop of around half the death rate from breast cancer in high-income countries has demonstrated improved therapeutic options available nowadays (2).

Different approaches to applying radiation to the affected tissue have been established based on time (5,21,22). Therefore, RT can be classified as an adjuvant (23) (given to the patient after the surgery to eliminate any remaining cancer cells and reduce the risk of recurrence), and neoadjuvant (24) (provided before the surgery to shrink the tumor size, facilitating its removal). The type of RT selected will depend on factors such as tumor size, cancer stage, and the patient's overall health and preferences (25).

Although favorable results have been reported on patient survival rates with radiation as part of the breast cancer treatment protocol, the adverse effects on adjacent healthy organs and soft tissue are a reality (5). A recent systematic review, which included high-quality clinical data to evaluate the risk and benefits of breast cancer treatments reported an increase in non-breast-cancer mortality related to RT in a dose-response manner. The leading causes of death were esophageal cancer [risk ratio (RR) =2.51; 95% confidence interval (CI): 1.08–5.72], thromboembolism (RR =2.10; 95% CI: 1.11–3.90), lung cancer (RR =1.64; 95% CI: 1.22–2.21), and heart disease (RR =1.30; 95% CI: 1.15–1.46) (5).

Breast RT is a commonly used treatment for breast

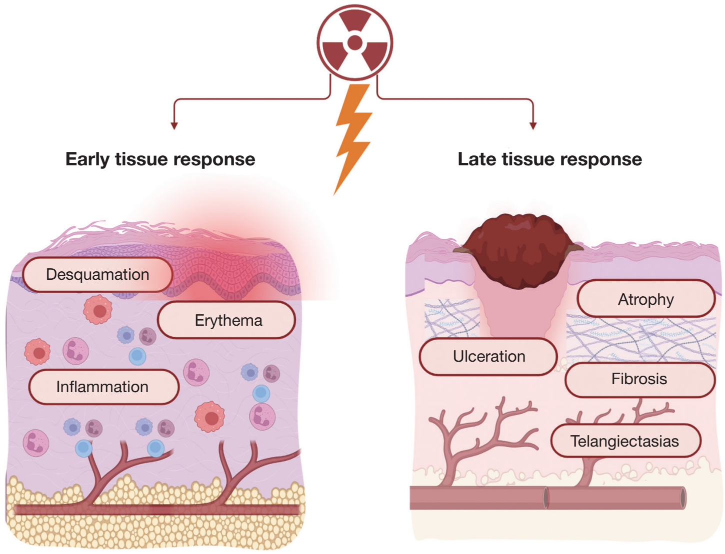

Figure 1 Radiotherapy induced-skin damage. The early skin radiation effects start around 2 to 3 weeks after beginning the treatment, characterized by inflammation, erythema, and moist and dry desquamation. In a late phase of treatment, the skin presents extensive fibrogenesis, potentially caused by a persistent wound-healing response that leads to excessive fibroblast replication and matrix deposition. Other late effects include vascular damage, neural damage, tissue atrophy, necrosis, ulcerations, and radiation-induced second malignancies. Created with BioRender.

cancer patients; however, it can have a negative impact on BR outcomes (4,26). Delayed wound healing, implant-related complications, changes in breast shape and size, an increased risk of capsular contracture, difficulty in detecting cancer recurrence, and an increased risk of lymphedema are some of the complications associated with RT in the setting of BR (13,20,27).

The tissue changes caused by RT are due to various mechanisms such as macrophage activation, cytokine secretion, impaired vascularization, hypoxia, tissue destruction, chronic wound healing, and fibrosis (26). In the skin, radiation impairs barrier functions, angiogenesis, and collagen deposition, resulting in burns, swelling, discoloration, desquamation in the short term, hardening of the skin and subcutaneous tissue, and chronic ulceration over the long term (*Figure 1*) (28-30). This adversely affects the wound healing process, in addition to causing normal tissue toxicity. Therefore, patients need to be aware of these potential risks.

Despite these potential risks, the benefits of RT are widely recognized to outweigh them (23). As such, ongoing and evolving efforts have been made to improve its efficacy and reduce its harmful effects. Indeed, modern RT techniques have been shown to reduce exposure to normal tissue, thereby minimizing the risk of adverse effects and shortening recovery time (23). Poppe *et al.* (31) reported a low complication rate and excellent local control when implementing a novel 15-day hypofractionated postmastectomy RT in patients with stage II–IIIa breast cancer. During this phase 2 multi-institutional prospective trial, 12% of patients receiving 3.33 Gy daily in the chest wall and regional lymphatics experienced mild side effects such as pain, fatigue, and lymphedema, with overall survival (OS) of 90% (31).

The new evidence resulting from the FAST-forward trial demonstrating that a 26 Gy regimen of five daily fractions is an effective and well-tolerated method of tumor control supports the recent decision of the European Society for Radiotherapy and Oncology (ESTRO), which recommends the implementation of moderately hypofractionated RT for patients who require radiation to the whole breast, chest wall (with or without reconstruction), and regional lymph nodes. Furthermore, ultrafractionation, defined as 26 Gy in 5 fractions, might be considered a standard treatment in the future; however, more randomized studies must be performed (32,33).

The recent finding that RT to the axilla can serve as a substitute for axillary lymphadenectomy (ALND) in selected patients has the potential to impact BR. Evaluations of ALND and axillary radiotherapy (AxRT) in patients with cT1-2, node-negative breast cancer, and a positive sentinel node biopsy showed a low axillary recurrence rate, with no difference in OS and disease-free survival (DFS) after either treatment (34). These outcomes can benefit patients undergoing BR after mastectomy, as it reduces morbidity related to axillary surgery and improves cosmetic outcomes, as seen in the study published by Zheng *et al.* (35). They demonstrated that replacing aggressive ALND with tailored RT represents an excellent alternative to prevent breast cancer-related lymphedema and upper extremity dysfunction in female patients presenting early breast cancer (35).

In addition, a multicenter randomized phase III clinical trial (TAXIS trial) is currently evaluating whether ALND can be safely omitted for breast cancer patients with neoadjuvant systemic treatment or in upfront surgery settings. Instead, tailored axillary surgery is offered, followed by AxRT treatment for any remaining nodal disease. The trial's primary endpoint is DFS, with morbidity and quality of life as secondary endpoints. It is planned to be finished by 2025, contributing significantly to the surgical de-escalation of the axilla for the highest-risk spectrum of breast cancer patients (36).

In summary, breast RT can have significant implications for breast BR outcomes. As described, it is associated with various potential risks and complications that patients must be aware of when considering BR after breast cancer treatment. Therefore, breast surgeons must have open discussions with their patients to fully explain these risks before deciding on the reconstructive method. The impact of breast RT on BR will vary depending on individual patient cases and the specific treatment protocols employed. Close collaboration between surgical and radiation oncology teams is imperative to ensure optimal breast cancer treatment and reconstruction outcomes.

BR in NART scenario

Radiation before surgery has been described since the 1980s. Riet *et al.* (37) demonstrated the effectiveness of this protocol in a retrospective study of 187 patients who only received preoperative hypofractionated radiation followed by a modified radical mastectomy, showing a 25-year DFS of 30% (24–37%) and a 25-year locoregional control rate of 89% (93–82%) (37).

Traditionally indicated in a patient with locally advanced breast cancer (24,38,39), NART is now a feasible therapeutic option in early-stage breast cancer cases (I, IIA and IIB, and IIIA) in which the disease has not extended beyond the axilla) (8) avoiding ART's drawbacks and displaying a low toxicity profile (40,41). Although NART has not been proven to decrease overall patients' survival (42), the benefits have been demonstrated by the improvement in DFS in estrogen receptor-positive tumors (42). Significantly, the stereotactic RT approach provides a more accurate target for tumor treatment, leading to an increase in the percentage of conservative breast surgeries (43).

In most aggressive cases (stage IIIA–C), the combination of NART and chemotherapy, followed by mastectomy and IBR, has demonstrated a 78.3% 5-year recurrence-free survival and 88.4% 5-year OS rate (44). Similarly, Ciérvide *et al.* (41,45), evaluated the feasibility and tolerability of primary concurrent radio-chemotherapy in breast cancer patients with localized triple-negative (TN) or $HER2^+$ tumors. The treatment combined three strategies simultaneously: fractionated RT in 15 sessions, tailored computed tomography (CT) based on tumor phenotype, and local planning using positron emission tomography (PET) imaging. The 70.8% pathological complete response (pCR) rate confirmed the effectiveness of this strategy. Additionally, a retrospective analysis of 356 patients treated with NART demonstrated a 45.1% OS after 25 years of follow-up in high-risk patients (46). Nevertheless, the patient's age, tumor receptor stage, nodal invasion, chemotherapy type, and NART scheme are outcome-modifying factors (46,47).

The reconstructive options offered to patients after NART will depend on the tissue's radiation exposure. For partial-breast radiation, the unirradiated breast tissue can be used for repair, yielding better cosmetic outcomes. In contrast, with whole-breast radiation, skin replacement is usually required due to contracted deformity and skin retractions. Thus, a delayed repair is often recommended, involving flap transfer to aid recovery. For patients with small breasts and skin retractions, autologous fat grafting combined with percutaneous needle release of scar bands is a commonly used solution; however, multiple surgical operations may be necessary.

I-BBR

Using NART has somewhat the potential negatives associated with using ART in postmastectomy implant-based breast reconstruction (PMI-BBR) or reconstruction using autologous tissue (48,49). In a prospective pilot study, a low rate of postoperative complications, such as wound breakdown and implant removal due to wound infection, was reported in 50% of cases in the NART group, compared to the postmastectomy radiotherapy (PMRT) group (48). Interestingly, no statistical significance in postoperative complications was reported (P=0.117) (48). Similarly, no increase in the risk of lymphedema development has been associated with NART (P=0.683) (50). On the other hand, a significant difference was reported in the time from diagnosis to treatment completion in the NART group, with a mean of 245.63±44.16 days, compared to 291.15±38.69 days in the ART patients (P=0.001) (48).

A-BBR

On the other hand, A-BBR after NART has been demonstrated to be a safe and reliable reconstructive alternative (51). In 2019, a systematic review of 16 studies evaluating available data related to NART concluded that it could be safely administrated before IBR with an interval of 6 to 8 weeks (47). No intraoperative complications were reported concerning reconstruction. I-BBR and A-BBR were associated with a low range of postoperative complications, such as less than 5% partial flap loss. No failure to complete reconstruction due to radiation was reported. No failure to complete reconstruction due to radiation was described (47).

Thiruchelvam *et al.* (51) demonstrated comparable results in a prospective, non-randomized study exploring the feasibility of NART, followed by skin sparing mastectomy (SSM) and deep inferior epigastric artery perforator (DIEP) flap reconstructions. After 3–4 weeks of chemotherapy, hypofractionated NART was applied to the breast and regional node patients, and the selected reconstructive procedure was performed 2–6 weeks later. Of the 33 enrolled patients, 12% experienced an open wound greater than 1 cm, and no serious complications were reported (51).

The rate of postsurgical complications using the Clavien-Dindo classification of surgical complications (52) was recently published by Lin *et al.* (53). Following sequential neoadjuvant chemotherapy (NACT) and NART, mastectomy with or without axillary surgery and immediate autologous BR were performed. Results showed that NART did not raise the risk of open breast wounds when compared to post-mastectomy RT. They concluded that this safety and efficacy favors a single-stage mastectomy and IBR with higher rates of distant metastasis-free survival (83.6%), OS (95.3%), and locoregional recurrence-free survival (98.1%) after 3-year follow-up compared to the standard gold treatment.

The surge of clinical trials focused on combining NART with immunotherapy has consolidated the future implementation of radiation before surgery (41). These studies, based on immunotherapy, have enabled the identification of potentiation of the tumor-specific immune response (54,55). This robust radiosensitive anti-tumor immune response activation, which is lost in the ART scenario, can eliminate micrometastasis and distant focus (56), establishing an immune memory that is one of the most favorable advantages of NART in the development of the anti-cancer vaccine therapy (57).

BR in ART scenario

The typical therapeutic sequence established by national guidelines for locally advanced breast cancer (stage III) is systemic chemotherapy, surgery, and radiation (4,9). By performing the restoration before radiation therapy, the remaining local breast tissue is preserved, resulting in a more natural outcome as the texture and color of the breast are preserved (4). However, PMRT has been associated with increased post-surgical complications and suboptimal cosmetic result (58).

In 2017, Chetta *et al.* (59) conducted a large national claim-based database study to evaluate the morbidity associated with BR after radiation. Of the 4,781 patients, they found that I-BBR was the most commonly used method, being utilized in 80%. However, they reported a higher complication rate in radiated patients who underwent implant reconstruction, with these patients having two times the odds of complications and eleven times the odds of failure compared to those who opted for autologous reconstruction. Consequently, from a patient safety standpoint, they recommended that implant-only reconstruction be considered an exception, due to the lower rate of failure and complication observed in the autologous flap reconstruction group (59).

I-BBR

The increased use of preventive bilateral mastectomy has expanded the selection of the I-BBR one-stage technique as the preferred reconstructive method (60,61). One reason is that skin sparing mastectomy and nipple sparing mastectomy (SSM/NSM) incisions in the inframammary fold or lateral breast crease favor implant colocation over autologous options, in which access to the recipient's vessels would be limited (62). Even in cases of early-stage cancer patients undergoing PMRT, this approach is not an absolute contraindication (4).

In 2021, due to the lack of high-quality clinical evidence, the Oncoplastic Breast Conservative Surgery expert panel was unable to draw any conclusions regarding the type of implant, the ideal location, and the usage of an acellular dermal matrix (ADM) to cover it and reduce the risk of complications (4). The panelists had mixed views on the link between pre-pectoral I-BBR and an increased risk of complications and failure rates compared to sub-pectoral I-BBR regarding PMRT, with several publications supporting this. Still, no differences are revealed in terms of the implant's position (with only a slight preference for pre-pectoral implantation) (63-65).

Due to most of the studies being single-center and retrospective in design, the importance of developing phase III randomized clinical trials to address these contentious topics was highlighted (4). However, the importance of the incision location and the maintenance of the thickness of mastectomy flaps was agreed upon, with the need to avoid radial incisions adjacent to the NACT was emphasized, as this could compromise the blood supply (4). Furthermore, the use of intraoperative fluorescence imaging to ensure adequate perfusion of the skin before the implant insertion was recommended (62,66).

The National Oncoplastic Guidelines for Best Practice stipulated that the implant loss rate must be maintained below 5% at 3 months postoperatively (9). Knight *et al.* (67) reported a considerable reduction of the implant loss rate after I-BBR when pre-, intra-, and post-operative measurements were implemented, some of which restricted patient selection to no more than one risk factor, use of implants with a volume less than 500 cc, intravenous antibiotics at induction, and the use of expanders in high-risk patients [smokers, body mass index (BMI) >30 kg/m^2, those who have undergone RT, and diabetics] (67).

The I-BBR two-stage or delayed-immediate approach requires the insertion of a TE immediately after mastectomy. This TE can either be fully inflated during the surgery or rapidly in the postoperative weeks. However, concerning PMRT, there is controversy over whether the expander exchange should be performed before or after radiation (68,69). A meta-analysis by Lee *et al.* (68) concluded that a lower risk of severe capsular contracture was achieved by delivering RT on the expander (RR =0.44; P<0.001) (68). However, more recent publications reported a lower rate of reconstructive failure when the radiation was applied on the permanent implant (RR =1.71; 95% CI: 1.06–2.75; P=0.03) (69).

Maintaining the TE during RT can preserve skin-breast volume and allow tissue recovery once the radiation is completed. Therefore, typically after 6 months of the last dose of RT, the second stage is initiated with the TE replacement by an implant. At this time, there is an opportunity for scar revision, the release of radiation-induced contracted capsule, and the repositioning of a dislocated inframammary fold (70). It is essential to maintain the expander size both when planning CT and during the irradiation process, as the dose given is based on the volume (71). By maintaining TE volume during RT, a reduction in capsular contraction and seroma formation can be achieved. Nevertheless, some authors have reported good results with partially deflating the TE to 50% of its volume during radiation. They stated that this maneuver facilitates RT delivery superomedial aspect of the chest, improving the geometry of the breast. The TE returns to its initial volume 2 weeks after RT completion (62).

Autologous fat grafting to the mastectomy tissue pocket around the irradiated expander after 6 weeks of RT completion combined with implant/expander exchange 3 months after lipofilling has been demonstrated to decrease capsular contraction and improve the shape and symmetry of the reconstructed breast (72-74). Similarly, using ADM has shown a reduction of TE capsular contraction rate (75). Thus, covering the whole TE with an ADM and sewing the pectoral muscle over its mesh can create a bed for the fat graft. The main goal is to reduce the risk of delayed wound recovery and implant exposure during the second stage of the surgical procedure by enabling the application of fat grafts into the inferior mastectomy flap, which is not always possible without the matrix. Furthermore, it facilitates the closure of the mastectomy incision with greater security and the formation of a tissue plane for injecting fat grafts into the breast skin envelope during the exchange for a permanent implant (62).

A-BBR

A prospective multicenter cohort study conducted between 2012 and 2015 to compare complications and patient-reported outcomes undergoing I-BBR and A-BBR included 1,625 non-irradiated and 622 irradiated patients (58). Results indicated that PMRT did not increase the risk of complications in patients who underwent A-BBR [odds ratio (OR) =0.47; 95% CI: 0.27–0.82; P=0.007]. Additionally, a higher BREAST-Q satisfaction score was reported in the A-BBR than in the I-BBR group (63.5 *vs.* 47.7; P=0.002) (58). Less reconstructive failure, a better quality of life, and sensory recovery have been found in patients who underwent immediate A-BBR (P<0.001) (7,59).

Comparably to I-BBR, A-BBR can be done directly

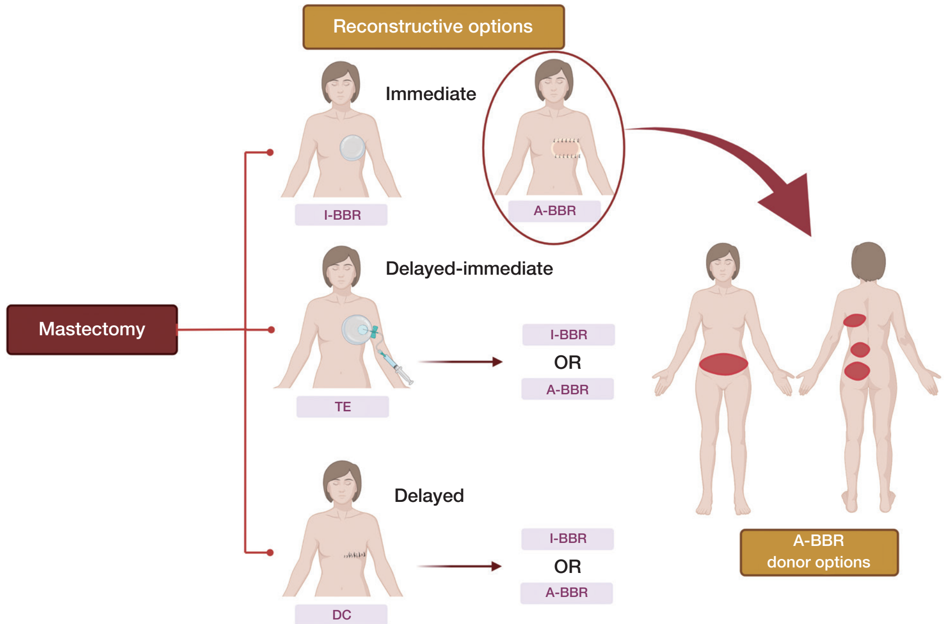

Figure 2 Graphic representation of breast reconstruction types based on timing. After the mastectomy, immediate breast reconstruction can be done using breast implants or the patient's tissue. If a TE is used immediately after the mastectomy, the permanent breast reconstruction will be performed by changing the expander with an I-BBR or A-BBR; this method is known as delayed-immediate. Finally, the delayed reconstruction method takes place in patients without additional procedures after the mastectomy. Still, several months later, after the radiotherapy is completed, they can undergo a definitive breast reconstructive procedure. Different donor sites from the body can be used for an autologous based-breast reconstructive procedure already described. Created with BioRender. I-BBR, implant-based breast reconstruction; A-BBR, autologous-based breast reconstruction; TE; tissue expander; DC, direct closure.

after surgery, or by an immediate-delated or IDEAL method (Delayed-immediate AutoLogous) (76,77). It is an alternative for patients who do not wish to have implants using their own tissue to recreate the breast (9).

The latissimus dorsi flap is a pedicled flap used frequently (7), while the most utilized free flap is the DIEP flap (9). However, in cases were DIEP flaps are not appropriate, other autologous options include the muscle-sparing transverse rectus abdominis myocutaneous (MS-TRAM) (78). Lumbar artery perforator (LAP) (79), profunda artery perforator (PAP) (80), transverse upper gracilis (TUG) (81), superior gluteal artery perforator (SGAP) (82), and inferior gluteal artery perforator (IGAP) flaps (76,83). Nonetheless, the DIEP flap is currently considered the gold standard for free autologous total BR, with a re-operation rate of 15.9% (84) and a total flap failure rate of 2.2% in unilateral reconstruction (*Figure 2*) (9,15,85).

Of note, in patients with insufficient tissue volume who agree to having implants, the combination of A-BBR and implants can provide a safe option to increase the volume (86). As an alternative, Kronowitz described a modification of the gluteal artery perforator (GAP) flap called the boomerang flap, which provides a larger volume to the lateral and superior aspect of the breast. This is indicated for the reconstruction of large-breasted patients for whom the DIEP flap is not possible, such as those with a previous cosmetic abdominoplasty, a history of an unsuccessful transverse rectus abdominis myocutaneous flap reconstruction, or not enough laxity or tissue in the abdominal musculofascial system (87). Therefore, it can be safely concluded that immediate A-BBR with PMRT is viable from an oncologic perspective, despite any worries that the amount of tissue present may prevent the desired delivery of chest wall RT (88).

The detrimental effects of ART on autologous tissue do not depend on the time of reconstruction (89,90). Lower, even comparable, rates of complications have been reported in patients who underwent immediate A-BBR compared to delayed-immediate reconstructions, with a similar overall satisfaction rate observed in both groups (25,91). Some authors have reported higher revisional surgeries associated with immediate procedures (OR =0.15; 95% CI: 0.05–0.48; P<0.001) (92). Nevertheless, differences in RT protocols in different facilities may influence the results of studies on the impact of radiation on flaps, making it difficult to generalize. Furthermore, most current studies offer short-term follow-up information, while the effects of radiation usually take many years to manifest (59).

The type of mastectomy the oncologist surgeon performs will determine the chosen reconstructive methods (9). In the case of a partial mastectomy, an immediate repair can usually be completed when the tumor's free margin is confirmed, leading to the best cosmetic outcomes. Reconstructive methods may include the arrangement of surrounding breast tissue, rotation or advancement flaps, or local de-epithelialized flaps (such as intercostal perforator, latissimus dorsi, or thoracodorsal artery perforator). Fat grafting is typically employed once radiation therapy has concluded to improve volume loss (62). Conversely, if there is a total loss of breast tissue due to a total mastectomy, immediate reconstruction will be done using any of the above-mentioned flaps, taking into account the patient's body characteristics, comorbidities, and preferences to make the decision.

The Delayed-Immediate approach after ART is used to preserve the skin envelope using a TE (93). This two-stage approach has been successfully utilized in early-stage breast cancer (stage I and IIA) to perform an SSM/SNM, resulting in a smaller flap skin island, improved aesthetic outcomes, and reduced donor site morbidity (94,95). Although in locally advanced disease, the skin envelope cannot be saved due to the high risk of local recurrence, a protocol suggested by Kronowitz *et al.* (96) demonstrated that delayed reconstruction with skin preservation could be indicated in IIB and III-stage breast cancer (96). Adjuvant chemotherapy, SSM, and deflation of the TE during ART are all valuable methods for keeping the skin for the definitive treatment (96,97). The TE should be removed 3 months after completion of RT, and then a definitive flap can be performed. The results of this protocol showed no increase in locoregional recurrences or postoperative complications (96).

The DIEP flap technique can be modified to treat thin patients who lack donor sites for A-BBR or underwent delayed reconstruction and need substantial skin replacement (62).

A bi-pedicled or double-DIEP flap utilizing the anterograde and retrograde mammary artery is indicated for these patients. Three distinct insets are advised for the specific type of breast: a rotated inset, which is beneficial for those with extensive breasts; an axillary extension, which is helpful for those requiring axillary tissue replacement; and a vertical inset, which is ideal for patients with medium to large breasts who have undergone total mastectomy and axillary sentinel lymph node biopsy and require IBR (62).

Notably, routine computed tomographic angiography (CTA) should be performed to identify the functioning blood vessels in the flaps, thus facilitating their selection and dissection and reducing the surgical time (9). Additionally, indocyanine green angiography used intraoperatively to evaluate the tissue perfusion of the skin flaps, can help detect perfusion problems and prevent flap necrosis and wound dehiscence in the postoperative stage. This complication should be avoided since it has been associated with an increased risk of locoregional recurrence (98). Therefore, a more extended follow-up period should be considered for patients with postoperative problems, as they may be at a greater risk of late recurrence (98).

The heterogeneity of breast cancer treatments and protocols from institution to institution and country makes it challenging to draw definitive conclusions on various topics associated with BR in the RT setting (*Figure 3*). Despite the vast number of publications on the subject, numerous confounding factors hinder the generalizability of the published results. Therefore, the best strategy to obtain level I evidence to bridge the gaps and contribute to the standardization of protocols that will benefit patient outcomes is to continue to develop multicenter, prospective, randomized clinical trials on controversial topics in breast cancer treatment.

Conclusions

This review suggests that the evidence surrounding BR in NART and ART is still developing. The benefits of RT in improving overall patient survival mean that its use is increasing. However, the variety of radiation treatment sequences used by different breast cancer institutions makes it difficult to establish a single treatment protocol. BR is known to improve women's quality of life, yet it is still necessary to find the perfect integration between BT and RT. Certain factors can complicate the process of determining the best approach, such as the timing of the radiation, which will influence the selection of the best reconstructive methods for the patient. Evidence suggests that immediate A-BBR is preferred due to its low rate of

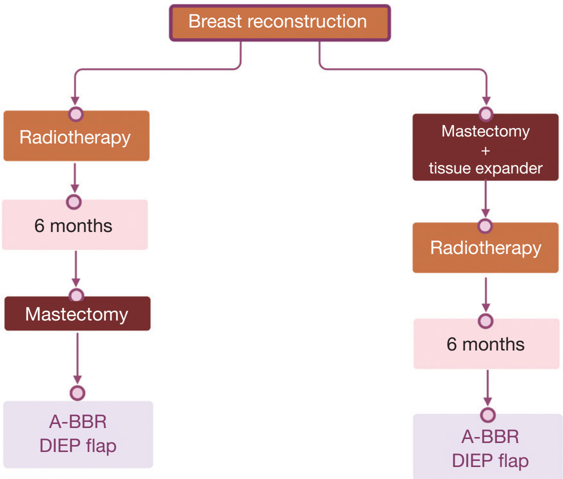

Figure 3 Management algorithm for breast reconstruction in patients who underwent radiotherapy. This algorithm describes the author's preference for breast reconstruction in patients diagnosed with breast cancer. Patients receiving neoadjuvant radiotherapy will undergo a definitive mastectomy with definitive breast reconstruction 6 months after radiotherapy. On the order hand, in the case of postmastectomy radiotherapy, a tissue expander will be inserted immediately after mastectomy and maximum inflated with saline solution. The tissue expander is maintained during radiotherapy, and 6 months after finishing, a definitive reconstructive technique will be performed. The A-BBR is the preferred reconstructive method implemented by the author, with the DIEP flap as the ideal option. Created with BioRender. A-BBR, autologous-based breast reconstruction; DIEP, deep inferior epigastric artery perforator.

long-term complications. However, individual patient characteristics must be considered when deciding which reconstructive method to use. These include the patient's body characteristics, tissue quality, previous scarring, donor site availability, comorbidities, treatment preferences, and life expectancy, as well as the tumor stage, radiation protocol, and chemotherapy. Lastly, integrating less aggressive and safer radiation methods into the treatment sequence can lead to better surgical outcomes and a more satisfied patient.

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