Review Article

Radiation and free flaps: what is the optimal timing?

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Abstract: The debate over when to perform flaps in patients undergoing radiation remains an ongoing dilemma without definitive resolution. Classically, reconstructive surgeons recommended avoiding exposure of autologous flaps to radiotherapy due to concerns over surgical complications and poor aesthetic outcomes. However, delayed reconstruction carries its own risk profile and aesthetic limitations, given the irreversible changes to the breast envelope. Immediate reconstruction not only confers psychosocial benefits but allows for preservation of the native breast skin and footprint. In recent years, a growing body of evidence suggests that with modern radiation techniques, long-term outcomes of immediate *vs.* delayed autologous reconstruction may be more similar than previously thought. This review examines the advantages and disadvantages of each treatment algorithm and critically evaluates the existing literature on autologous breast reconstruction in the setting of post-mastectomy radiotherapy. Importantly, radiation regimens have varied widely over time and between institutions, introducing significant heterogeneity in published outcomes of flap contracture or fat necrosis after immediate reconstruction. While delayed autologous reconstruction remains a reasonable pathway, the benefits of immediate reconstruction should not be dismissed. Our findings ultimately corroborate the view that immediate flap reconstruction is a sound treatment option that can be safely offered to patients. The decision regarding which pathway to pursue should ultimately be patient-centric and driven by multidisciplinary consensus, rather than by prior dogma.

Keywords: Radiation timing; autologous reconstruction; post-mastectomy radiation therapy (PMRT); breast flap; patient outcomes

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Introduction

Background

In light of the growing popularity and prevalence of autologous breast reconstruction, the optimal timing of radiation therapy has become an increasingly salient question. Post-mastectomy radiation therapy (PMRT) has been shown to decrease locoregional disease and improve overall survival rates, making it a critical component of breast cancer treatment (1,2). Criteria for PMRT are based on pathologic features and nodal involvement, including greater than four positive axillary lymph nodes, tumor size greater than five centimeters, stage T4 disease, and positive margins. Following the Early Breast Cancer Trialists' Collaborative Group meta-analyses, which showed improved disease-free and overall survival after PMRT in women with one to three positive lymph nodes, these indications further expanded (3,4). The guidelines for PMRT continue to evolve as cancer care progresses towards less invasive surgical interventions and more refined risk-profiling.

Rationale and knowledge gap

The negative impact of radiation on tissue vascularity and

cellularity is well-documented. Ionizing radiation triggers an inflammatory cascade that leads to fibrosis, vascular thrombosis, and atrophy of the skin and subcutaneous tissue (5,6). In the breast reconstruction patient, this often clinically presents as breast pain, delayed wound healing, contracture, asymmetry, and even reconstructive failure. Numerous studies have reproducibly demonstrated high complication rates in implant-based reconstruction with radiation (7-9), thus autologous tissue is widely favored in this setting. However, the literature regarding the effects of radiation on flap reconstruction remains mixed. Older studies have shown higher rates of late complications with immediate flap reconstruction followed by PMRT compared to delayed flap reconstruction after completion of radiation, whereas more recent reports demonstrate equivalent outcomes between immediate and delayed autologous flaps. As the ultimate goal of any autologous breast reconstruction is to create a soft, natural breast mound, it is imperative to understand how radiation impacts flap success both acutely and in the long-term.

Objective

Expanding indications for PMRT and increasing acceptance of immediate breast reconstruction have prompted a need to re-evaluate the optimal sequence. In this article, we set out to compare outcomes of free flap breast reconstruction when performed before or after radiotherapy, to better characterize each treatment algorithm.

Delayed reconstruction: overview and rationale

Historically, radiation following immediate autologous breast reconstruction has been believed to create suboptimal outcomes. Since early reports that radiation adversely affected cosmetic results, symmetry, and flap contracture, further clinical studies were conducted to illustrate these effects (10,11). Many experts therefore recommended delaying flaps until after PMRT to optimize not only aesthetic outcomes, but cancer treatment efficacy. Certain oncologic concerns previously supported delaying autologous reconstruction, such as avoiding delay in time to radiation initiation and avoiding compromise of radiation delivery to the chest wall by maintaining a planar field (12). Regardless, the oncologic safety of immediate reconstruction has now been reliably demonstrated. Numerous studies have shown equivalent locoregional recurrence and distant metastasis rates in patients undergoing radiotherapy with or without immediate reconstruction, suggesting there is no decrease in efficacy of radiation when reconstruction is performed (13,14).

As a bridge between delayed and immediate pathways, Kronowitz *et al.* proposed the concept of "delayed-immediate" breast reconstruction whereby a tissue expander is placed at the time of mastectomy while awaiting final pathologic results (15). If PMRT is deemed necessary, delayed reconstruction is pursued after completion of therapy. If patients do not require adjuvant radiation, definitive breast reconstruction is performed 2 weeks following expander placement. While this approach is intended to decrease complications associated with radiotherapy, it delays reconstruction in patients that do not need PMRT. It also commits all patients to a second surgery, with the associated increased healthcare costs, peri-operative risks, and personal costs of two recovery periods. Implementation of this protocol found lower rate of overall flap complications in delayed-immediate patients compared to standard delayed patients (24% *vs.* 38%); however, no comparison was made with immediate autologous reconstruction (16). Furthermore, approximately one-third of tissue expanders were lost in the delayed-immediate group, representing a significant source of additional morbidity.

Delayed reconstruction is often grouped as a monolithic category when contrasted with immediate reconstruction; however, timing of delayed reconstruction is not standardized, with various recommendations provided in the literature. Delayed-immediate reconstruction originally described waiting 3 months after completion of radiation to proceed with a flap (16), whereas other protocols have been reported ranging from several months to over a year. One study of flap reconstruction after PMRT separated patients based on completion of radiation greater or less than 12 months prior to reconstruction and found a significantly higher rate of total flap loss and re-operation in the less than 12 months cohort (17). In contrast, other studies found no statistically significant difference using a similar time cutoff, or when 6 months was used as the threshold (18,19). These findings may be consistent with the unpredictable and biphasic nature of radiation injury. Ionizing radiation triggers an acute inflammatory phase over days to weeks, then a delayed fibro-atrophic response that can extend from months to years after treatment (20). The variable extent and duration of radiation-induced damage may thus complicate establishing reliable cutoffs. The question of optimal timing thus persists within delayed reconstruction.

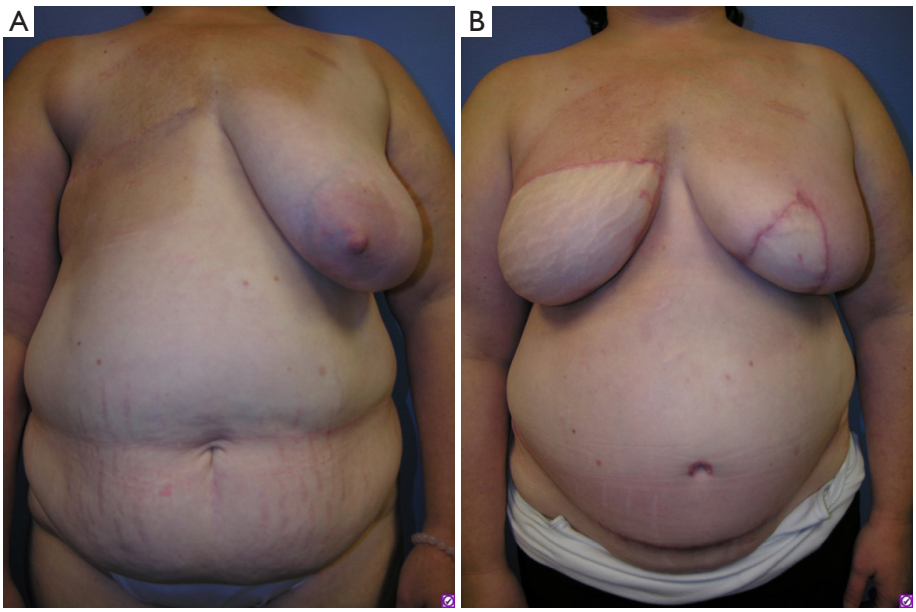

Figure 1 A patient who underwent right-sided delayed autologous reconstruction and contralateral immediate reconstruction, illustrating the aesthetic differences in final breast contour and skin paddle size between the breasts. (A) Pre-operative photo following right mastectomy and post-mastectomy radiation therapy. (B) Post-operative photo after delayed reconstruction of the right breast and immediate left breast reconstruction.

Anecdotally, many surgeons, including the senior author, defer to clinical assessment of breast skin quality and laxity when deciding when to offer reconstruction in the post-radiation setting. This avoids re-operating on a site that is still acutely tight, inflamed, and predisposed to complications.

Immediate flap reconstruction: overview and rationale

There are many well-described benefits to immediate breast reconstruction, across aesthetic, logistic, and psychosocial domains. Immediate reconstruction allows preservation of the skin envelope and breast footprint, creating a more natural-appearing breast. An immediate autologous flap can generally be buried with a small skin paddle that may be excised at a later date or used for nipple reconstruction, as opposed to the larger skin paddle required in delayed reconstruction once the skin has retracted and scarred. This difference in skin paddles is clearly demonstrated in *Figure 1*. Scar burden and unfavorable breast shape can thus initially be minimized when performing immediate reconstruction. The addition of radiotherapy has the potential to complicate these cosmetic advantages, as will be discussed in the next section comparing data on outcomes such as fat necrosis and flap shrinkage.

Importantly for patients, immediate reconstruction has been shown to enhance psychosocial well-being. In a large retrospective analysis of 577 patients who underwent either immediate or delayed reconstruction, the immediate group demonstrated higher scores for body image, self-esteem, and patient satisfaction (21). Other prospective studies following women years after mastectomy showed women with delayed reconstructions felt significantly higher levels of overall distress and depressive symptoms than those with immediate reconstructions, as well as less comfort with physical intimacy (22,23). Satisfaction with breast reconstruction was specifically evaluated in one prospective study using the BREAST-Q validated questionnaire. The authors compared patient-reported outcomes in 175 women undergoing delayed or immediate autologous reconstruction in the context of PMRT and found significantly lower pre-reconstruction scores for satisfaction with breast, psychosocial and sexual well-being in the delayed population (24). Notably, overall complication rates and satisfaction levels at 2 years post-operatively were similar between groups, suggesting breast aesthetics and quality of life were not compromised by flap

radiation as evaluated from the patient's perspective. By offering immediate flap reconstruction despite the need for PMRT, patients may obtain the same quality of life benefits and avoid waiting a prolonged period of time without a true breast mound.

Discussion: outcomes data

Multiple large studies and meta-analyses have been conducted in recent years to quantify the true effects of PMRT on autologous reconstruction. Reported complications encompass acute events such as flap loss or vessel thrombosis, and delayed events such as fat necrosis or flap contracture, as well as long-term patient-reported outcomes. While no standardized scale is applied across the literature, major complications are commonly defined as those requiring operative intervention, whereas minor complications resolve with conservative management, i.e., local wound dehiscence.

When evaluating aesthetics and volume changes, older reviews suggest worse outcomes when PMRT is given after flap reconstruction. An often-cited 2001 series compared immediate and delayed abdominal flaps with extended follow-up of 3 to 5 years and found a significantly greater incidence of late complications, consisting of volume loss, fat necrosis, and contracture of breast mounds, in the immediate reconstruction group (87.5% *vs.* 8.6%). Rates of flap loss or early vascular complications did not differ, but 28% of patients in the immediate cohort experienced flap distortion severe enough to require a second flap (25). Another study found flap shrinkage in approximately 30% of patients treated postoperatively with radiation, and 10% of patients went on to require a salvage procedure using an additional flap or an implant (26). A similar report documented fat necrosis or parenchymal fibrosis in 19.7% of flaps after radiation, necessitating revision surgeries (27). These types of findings led the authors to conclude that although immediate breast reconstruction with autologous tissue was a feasible option, it subjected patients to higher rates of fat necrosis and diminished aesthetics. Delayed flap reconstruction thus became standard practice for many plastic surgeons.

However, many of these studies consisted of small sample sizes and inconsistent outcome evaluations. One classic study of 625 abdominal-based flaps found irradiated flaps demonstrated a significantly higher rate of fat necrosis compared to non-radiated flaps (22.5% *vs.* 9.2%). However, the irradiated flaps were a far smaller sample size, only 40 patients, and there was no difference in re-operations for fat necrosis between the two groups, which raises the question of the clinical significance of the finding (28). Another large single-center review corroborated these findings, demonstrating a significantly higher incidence of volume loss and fat necrosis in flaps exposed to PMRT compared to non-radiated flaps, yet no difference in revision procedures (29). One small but interesting study used patients undergoing bilateral deep inferior epigastric perforator (DIEP) reconstruction with unilateral PMRT as internal controls to compare radiated *vs.* non-irradiated flap outcomes. There was no difference in fat necrosis between radiated or non-irradiated flaps, and aesthetic results based on photographic review were found to be satisfactory in all patients (30). These conclusions are consistent with our own clinical experience with immediate reconstruction and the quality of the cosmetic outcomes achieved (*Figure 2*).

More recently, several large subsequent studies have shown no impact of postoperative radiation on major complications in autologous reconstruction. A retrospective review of over 1,000 patients undergoing breast reconstruction with radiation delivered either before or after reconstruction (32) used multivariate analysis to show no significant difference in rates of major surgical complications and re-operations in autologous reconstruction patients who received postoperative radiotherapy (17.9% *vs.* 20.5%). Additional publications, including a prospective cohort study, found no differences in fat necrosis, wound healing, or need for surgical revisions for volume deficiency in hundreds of patients with either radiated or non-radiated free flap breast reconstructions (33,34). These findings were mirrored in a meta-analysis of 44 studies comparing complication rates between immediate and delayed breast reconstruction in the setting of PMRT. The authors demonstrated statistically equivalent rates of fat necrosis, flap loss, thrombosis, and infection (35). When specifically evaluating postoperative volume changes after unilateral DIEP reconstruction, measured as a volume ratio relative to the contralateral breast, a study using objective three-dimensional imaging found PMRT did not affect the volume ratio even at 12 months postoperatively (36).

Furthermore, concerns about delayed wound healing or increased surgical site complications due to postoperative radiation have not been borne out in the data. In a systematic review of outcomes associated with autologous breast reconstruction performed prior to or after chest wall radiation, complication rates were not significantly different (37). Pooled incidence of wound

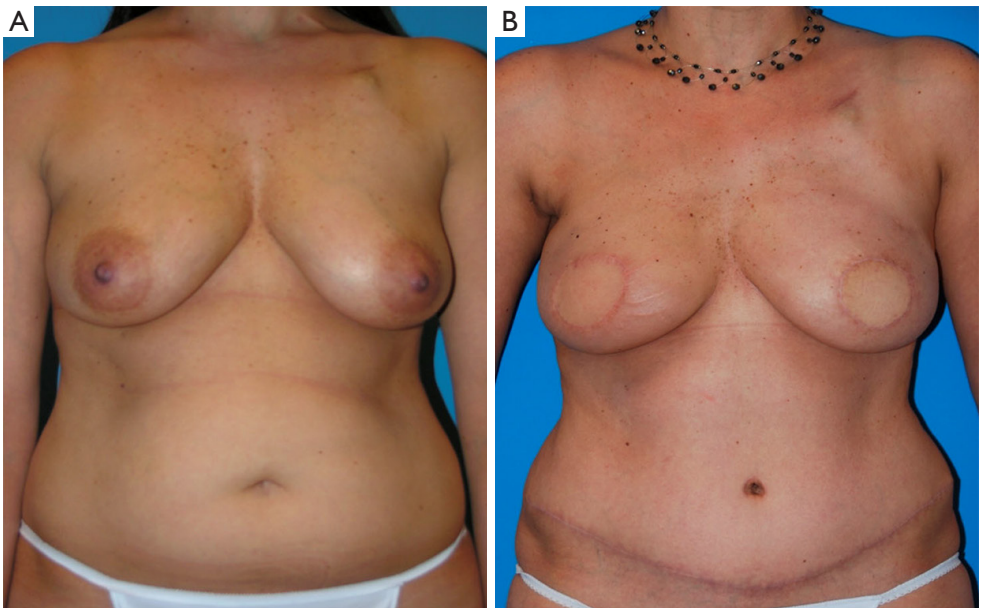

Figure 2 Pre- and post-operative images of a patient who underwent bilateral immediate autologous reconstruction and unilateral PMRT, demonstrating excellent symmetry [from: Wu *et al.* (31)]. (A) Native breasts with right sided malignancy. (B) 6 months' post-radiation to the right reconstructed breast following bilateral skin sparing mastectomies and immediate DIEP flaps. PMRT, post-mastectomy radiation therapy; DIEP, deep inferior epigastric perforator.

healing complications was 14% in flaps exposed to PMRT compared to 10% in flaps delayed after radiation, incidence of infection was 6% compared to 4%, incidence of hematoma was 1% compared 2%, and seroma rates were 4% in both groups. Furthermore, a follow-up paper to previous work by this senior author (Chang DW), providing an update on immediate *vs.* delayed autologous breast reconstruction paradigms, also found no difference in rates of surgical site infections, wound dehiscence, or fat necrosis (31). The number of revisions was in fact lower in the immediate reconstruction group than in the delayed group. Significantly lower volumes of fat grafting and fewer contralateral breast mastopexies were performed in the immediate cohort. This finding of fewer revisions has been reproduced in other studies (33,38) and is attributed to better baseline results obtained from immediate flap reconstruction. Importantly, wound complication incidence after immediate reconstruction has been shown to be relatively low and most complications minor in nature, so concerns about unreasonable delays in critical adjuvant oncologic treatments are not supported by the evidence (26,37,39).

Regarding microvascular complications, evidence initially suggested increased risk of thrombosis in delayed *vs.* immediate flap reconstruction, due to radiated recipient vessels. In a comparison of 226 radiated to 799 non-irradiated flaps, Fosnot *et al.* found prior radiation led to an increased rate of intraoperative microvascular complications (14.2% *vs.* 7.6%, P<0.003) and total vascular complications (17.3% *vs.* 9.6%, P<0.001), with statistical modeling showing radiotherapy was an independent risk factor (40). Rates of total flap loss, fat necrosis, and delayed wound healing in the radiation group were not significantly increased. Other investigations reported similar findings, showing increased likelihood of intraoperative vascular complications and need for arterial anastomotic revision (8% *vs.* 3%, P=0.04) in abdominal flaps transplanted to radiated *vs.* non-radiated chests (19). Such conclusions are difficult to translate however, without detailed information regarding radiation regimens and timing of surgery. Subsequent studies examining vascular complications have demonstrated no increased incidence of thrombosis or flap loss (24,31,37). A meta-analysis of observational studies identified no difference in early complication rates, or need for future revision surgery, when comparing immediate autologous breast reconstruction with and without PMRT (41).

Differences between findings in earlier *vs.* more recent studies may in part be attributed to advances in radiation

techniques. Current methods use three-dimensional computed tomography planning, rather than the two-dimensional fields used previously. Variable beam angles, field sizes, and beam energies are implemented to optimize target penetration while minimizing dosage to surrounding tissues (42). Consequently, chest wall radiation damage is limited more than in the past, while maintaining oncologic efficacy. Nonetheless, radiation regimens vary widely by patient and by institution. One systematic review found many studies did not provide dosage details, and of those that did, regimens varied between 45 to 60 Gray given over a range of 3 to 6 weeks (43). Questions of internal mammary node radiation and bolus doses to the skin currently remain up to the discretion of each radiation oncologist. Some centers are also attempting to improve outcomes of reconstruction in early-stage breast cancer by using hypofractionation, which has shown promise in reducing the volume loss associated with standard PMRT (19,20). Subtle differences in dose delivery may have a meaningful impact on acute and late consequences of radiation damage.

Strengths and limitations

There are broad limitations to much of the evidence on this topic. Many studies involved limited sample sizes, single-surgeon experiences, and retrospective perspectives. High-quality data regarding the preferred sequencing of radiation and breast reconstruction are still lacking, partly due to the inherent lack of feasibility of patient randomization in this sensitive context. The heterogeneity between studies in methodology and reporting makes outcomes challenging to compare and precludes validation of any treatment strategy. For instance, "flap contracture" or "fat necrosis" is often defined without reproducible metrics and at various thresholds depending on the provider. The nuances of fat necrosis dimensions and symptomatology that are integral to the patient's experience are lost with binary documentation of presence or absence.

Additionally, aesthetic outcomes are subjectively evaluated by surgeons, patients, or reviewers without standardization between studies, at times based solely on photographs. Statistical evaluation of cosmetic results between different grading scales consequently becomes impossible. Determining satisfactory or unsatisfactory results must take into account evaluations from patients themselves using validated questionnaires such as the BREAST-Q. Few existing studies of autologous breast reconstruction and PMRT apply validated patient-reported outcome measures.

These intrinsic methodological and statistical shortcomings consequently undermine the utility of the findings in current systematic reviews. Despite the amount of research on this subject, there is a limited amount of extractable data to pool. Aggregate information about radiation protocols and timing is also typically unavailable, and length of follow-up is limited across individual studies. Another inconsistency is that certain meta-analyses consider donor and recipient site complications together, although only recipient sites receive radiation. In the same vein, many reviews compare early wound healing complications in immediate *vs.* delayed groups, attributed to PMRT, however early complications may have occurred prior to the initiation of radiation in patients undergoing immediate flap reconstruction. Parenchymal changes of the breast flap are particularly of interest yet are non-uniformly reported in the literature. Few studies quantify or qualify the clinical severity of findings such as flap fibrosis, which can vary widely in its significance to patients and long-term consequences. Globally, clearer answers on this topic will require moving away from underpowered observational studies and towards multicenter prospective trials with objective, reproducible assessments.

Conclusions

In this review, we re-evaluate the paradigms recommending against immediate breast free flap reconstruction for patients who require PMRT. There are clear detrimental effects of radiation on soft tissue fibrosis, with unpredictable manifestations. Regardless, these possibilities must be weighed against the known adverse psychosocial effects of delaying breast reconstruction. The existing body of research suggests that, within limitations of heterogeneous reporting and variable radiation protocols, immediate free flap breast reconstruction in patients receiving PMRT can be performed without increased morbidity compared to delayed reconstruction.

It is this author's opinion that immediate flap reconstruction followed by radiation can achieve satisfactory outcomes while avoiding the detrimental psychological effects of an absent breast and while maintaining cost efficacy. Recent evidence supports this as a successful reconstruction sequence that may reduce the number of surgical procedures required. A potentially higher risk of fat necrosis or flap contracture may persist but does not necessarily translate into clinical morbidity requiring re-operation.

Ultimately, the decision regarding surgical timing must be made individually between each patient and their surgeon. Patient satisfaction will be determined by a complex interplay between personal preferences, context, and objective outcomes, rather than by aggregate data. Many institution-specific variables should be considered as well, particularly the anticipated radiation regimen. Multidisciplinary discussion between the surgical oncologist, plastic surgeon, and radiation oncologist must reach a consensus about best practice for each patient's unique pathology. When both immediate and delayed flaps are feasible, it is the role of the plastic surgeon to thoroughly discuss risks and benefits, guide the patient in their choices, and obtain maximally informed consent.

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Footnote

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