Journal of Plastic, Reconstructive & Aesthetic Surgery (2019) 72, 1769–1775

Immediate versus delayed autologous breast reconstruction: A retrospective matched cohort study of irradiated patients☆

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Received 12 September 2018; accepted 30 May 2019

KEYWORDS
Radiotherapy;
Autologous breast reconstruction

Summary *Background:* The impact of radiotherapy on breast reconstructions is not completely understood. The purpose of this study was to evaluate long-term effects of radiation therapy in relation to timing of autologous breast reconstruction.
Methods: A total of 1247 patients undergoing autologous breast reconstruction at the University Hospitals of Leuven between August 1997 and October 2013 were subjected to a retrospective matched cohort study. Each patient who underwent immediate breast reconstruction (IBR) and received post mastectomy radiotherapy (PMRT) were matched with two patients receiving PMRT and delayed breast reconstruction (DBR), according to age and body mass index. Early and late complications were compared between both groups after a minimum follow-up of 3 years. The need for corrective procedures on the reconstructed and contralateral breast was also evaluated. Data were collected using patients' medical records.
Results: A total of 20 patients who underwent IR with PMRT were identified and matched to 40 patients who underwent DBR. There were two revisions in the DR group, both due to venous occlusion. Both revisions were successful and no flap failures occurred in either group. The rate of early complications did not differ significantly between the two groups. Among late complications were both the rates of fat necrosis ($p < 0.001$) and skin contracture ($p < 0.001$) higher in the IBR group than in the DBR group. Neither corrective procedures to the reconstructed breast nor symmetrizing operations in the contralateral breast, differed between the groups.

☆ Parts of this article have been presented at the following meetings/conferences: 1. 17/01/2016 Annual Meeting of the American Society for Reconstructive Microsurgery, Scottsdale, Arizona; 2. 19/05/2018 Annual Meeting of the European Association of Plastic Surgeons, Madrid, Spain.

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https://doi.org/10.1016/j.bjps.2019.05.054

Conclusion: The current study indicates that radiotherapy may contribute to adverse long-term flap-related outcome after IBR. We therefore recommend reconstructions to be delayed whenever possible in patients who will require PMRT.

Introduction

Breast cancer is the most common cancer in women and the leading cause of death from cancer among women. The important role of mastectomy in the advanced stages of breast cancer has led to a growing demand for reconstructive options. In addition, there has been an increase in the indications for radiotherapy after mastectomy in women with breast cancer. This is because of its ability to achieve both better loco-regional control and increased survival.[1,2] The current indications for postmastectomy radiotherapy (PMRT) are all T3 and T4 tumors, positive lymph nodes, lymphovascular invasion, positive sections, and triple negative tumors. This poses a challenge for the timing of breast reconstruction. Many women prefer immediate breast reconstruction (IBR) to delayed breast reconstruction (DBR) because of the aesthetic and psychological benefits. However, in the setting of PMRT, these advantages are not so clear and numerous potential adverse effects of PMRT on reconstruction are described in the literature.[3] For implant-based reconstructions, it is generally accepted that PMRT yields worse outcomes.[4,5] However, in the setting of autologous reconstructions, data are limited and often contradictory (see discussion). Due to these potential adverse outcomes, the current consensus is to delay the reconstruction until adjuvant therapy has been completed.

In our hospital, we perform IBR in some cases, especially when there is a specific patient demand. The purpose of this study was to evaluate the long-term effects of radiotherapy on autologous reconstructions by comparing the outcome between patients undergoing IBR and patients undergoing DBR in the setting of PMRT.

Patients and methods

Patient population

We retrospectively reviewed all women who underwent an autologous breast reconstruction at the University Hospital of Leuven between August 1997 and October 2014. In total, 1247 patients underwent 1556 reconstructions, performed by three surgeons (Figure 1). We excluded all cases of bilateral reconstructions to rule out the effects of operational differences between unilateral and bilateral reconstructions. In order to evaluate the long-term effects of radiotherapy, only patients that had a follow up for at least three years were included. There were 300 patients undergoing DR after radiotherapy and 39 patients undergoing IR with subsequent radiotherapy. The decision to perform an IR is made by the oncologist and depends on the possible need of adjuvant radiotherapy. Whenever this risk exceeds 90%, it is suggested to the patient to postpone their reconstruction until after completion of the RT and perform a delayed reconstruction. Only 20 of these 39 patients in the IR group underwent irradiation to the chest wall, and thus the reconstructed breast, and were included. The other 19 patients only received radiotherapy to the internal mammary nodes and could not be included. As a consequence of the significant difference in average age and body mass index (BMI) between the IBR and DBR groups, we searched for 40 matched controls in the DBR group. The criteria for matching were age (±2 years), BMI (±2 units) and, when possible, smoking habits (smoker during surgery, stopped before reconstruction, or never smoked), type of flap (deep inferior epigastric perforator (DIEP), superior gluteal artery perforator, and superficial inferior epigastric artery), and chemotherapy. Patient characteristics are listed in Table 1.

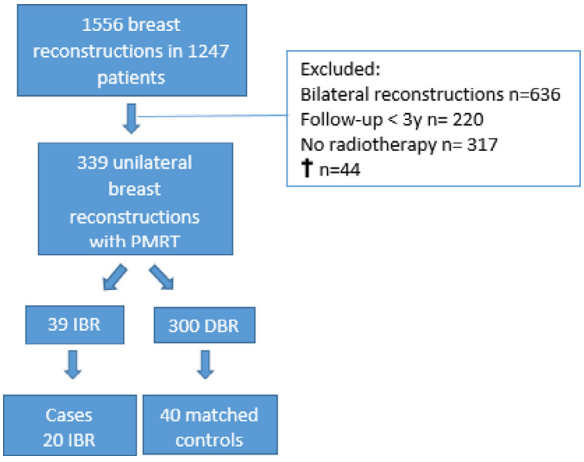

Figure 1 Flow chart for the study. IBR, immediate breast reconstruction; DBR, delayed breast reconstruction; PMRT, post mastectomy radiation therapy.

Data were collected retrospectively by reviewing hospital records and office notes that were written by the performing surgeons during the outpatients clinics. There were no disputes in stating or defining fat necrosis or contracture.

Radiotherapy

All patients underwent external beam radiotherapy to the chest wall. The total dose of 50 Gy was administered in 25 sessions of 2 Gy over a period of 5 weeks. The average time interval between mastectomy with IR and radiotherapy was 4.5 months (range, 1–10 months). In the DBR group, the average time interval between mastectomy and radiotherapy was 4.7 months (range, 1–8 months). The average time interval between radiotherapy and DBR was 2.7 years (range, 1–12 years). The cause of the large variation in the length of time between radiotherapy and DBR is often the preference of the patient or the surgeon. In our practice, we advise

Table 1 Patient characteristics.

	Immediate reconstruction	Delayed reconstruction
No. of patients	20	40
Age, years		
- Mean	46.25	46.08
- Range	35-64	33-62
BMI		
- Mean	22.9	21.5
- Range	17-33.1	19-34.2
Type flap		
- DIEP	18	37
- SGAP	1	1
- SIEA	1	2
Chemotherapy		
- Yes	15	29
- No	5	11
Smoking		
- Yes	2	4
- No	18	36
RT: 50 Gy, 25 sessions	20	40

BMI, body mass index; DIEP, deep inferior epigastric perforator; SGAP, superior gluteal artery perforator; SIEA, superficial inferior epigastric artery; RT, radiotherapy; Gy, gray.

an interval of at least six months between completing PMRT and DBR, or longer when required by the oncologist.

Complications and structural changes

Complications were assessed through review of the patients' medical records and classified into early and late complications. Infection, wound dehiscence, flap revision, and flap failure were considered to be early complications. Only infections that needed antibiotic therapy were included.

The late complications included fat necrosis and contracture. Secondary procedures to the reconstructed breast (e.g. liposuction, fat grafting, local tissue rearrangements or adding a prothesis) and corrections of the contralateral breast (e.g. breast reduction) were assessed to evaluate the symmetry and satisfaction achieved by the reconstructions and were graded according to the invasiveness of the procedure.

Fat necrosis was defined as a localized induration of 1 cm or more, determined by the physician during follow-up consultations. Contracture was defined as a generalized decrease in the volume of the breast with a reduction in the elasticity of the skin. Late complications were documented during the period of follow-up from completion of radiotherapy until the last patient contact. In the IBR group this period was 7.5 years on average (range, 3-17 years). In the DBR group, it was 8.5 years (range, 3-23 years).

Statistics

Fisher's exact was used to test for differences in categorical variables between both groups. The Mann-Whitney U test was used to test for differences in ordinal variables between both groups.

All tests were two-sided, and a 5% significance level was assumed for all tests.

All analyses were performed using SAS software version 9.3 for Windows (SAS Institute, Cary, NC).

Results

There were two revisions in the DBR group, both due to venous occlusion. Both revisions were successful and no flap failures occurred in either group. The ratio of early complications did not differ significantly between the two groups. The incidence of fat necrosis and contracture was significantly higher in the IBR group than in the DBR group. In 12 of 20 patients (60%) in the IBR group, contracture occurred in the reconstructed breast, which is significantly higher than the 2.5% fibrosis rate in the DBR group. The same proportion of patients developed fat necrosis in the IBR group, as opposed to the 12.5% fat necrosis rate in the DBR group. The early and late complications are summarized in Table 2. Regarding the secondary procedures, there were no significant differences between both groups.

Discussion

The current study is to our knowledge the first to compare differences in long-term outcome between immediate and delayed perforator flap reconstruction in a matched cohort setting. We saw a significantly higher ratio of fat necrosis and contracture in patients undergoing IBR. From the esthetical point of view, contracture of the reconstructed breast can easily be noted because of the volume loss that will result from this contracture. Fat necrosis on the other hand can only become visible when the volume of the fat necrosis lump reaches a certain dimension. Furthermore, the visibility will depend on the area where the fat necrosis is located, which is certainly the case for cranial pole located fat necrosis. But, maybe even more important, fat necrosis poses another problem for the patient. It can be extremely stressful to be confronted with the palpation or tactile awareness of a nodule or lump since this was often the initial clinical sign of disease.

Women requiring a mastectomy as part of their breast cancer therapy are offered the option of breast reconstruction. IBR has become increasingly popular over the last few years. The aesthetic benefits, maintenance of the skin envelope and less scarring resulting in a better contour and more symmetrical outcome, are the most important advantages. However, there are also psychological as well as economic advantages; the patient does not have to go through a period without a breast and only one single surgery is required.[6-8] The increasing demand for prophylactic mastectomy is the main cause for the increase in the number of IBRs. However, when the intent is to provide curative treatment, the choice between IBR and DBR is often determined by the need for PMRT. Due to the adverse effects of radiotherapy on the reconstruction, the consensus is to postpone the reconstruction until after completion of adjuvant radiotherapy. In our study, we demonstrated that patients

Table 2 Early and late complications after immediate and delayed reconstruction.

Complications	Immediate reconstruction ($n=20$)	Delayed reconstruction ($n=40$)	p-value
Early			
Infection	4/20 (20.0%)	2/40 (5.0%)	0.089
Wound dehiscence	3/20 (15.0%)	4/40 (10.0%)	0.676
Flap revision	0/20 (0.0%)	2/40 (5.0%)	0.548
Flap failure	0/20 (0.0%)	0/40 (0.0%)	
Late			
Fat necrosis*	12/20 (60.0%)	5/40 (12.5%)	<0.001
Fibrosis/contracture*	12/20 (60.0%)	1/40 (2.5%)	<0.001

Variables were analyzed using Fisher's exact test. All reported p-values are two-sided.

undergoing IBR have poorer outcomes than patients who have their reconstruction postponed until after radiotherapy.

However, the studies on this subject are limited. Various series with transverse rectus abdominis muscle (TRAM) flap reconstructions have been reported. Carlson et al. compared 25 patients with pedicled TRAM-flaps who received PMRT with 149 patients who did not receive PMRT and found a higher incidence of complications in the irradiated group (44%) than in the non-irradiated group (34%).[9] Tran et al. compared 32 patients treated with free TRAM-flap IR and PMRT with 70 patients undergoing DR after PMRT. They found a significantly higher ratio of fat necrosis (44% vs. 9%), loss of volume (88% vs. 0%), and flap contracture (75% vs. 0%) in the patients receiving IR. To correct for the effects of volume loss, an additional flap was necessary in 28% of the patients who underwent PMRT after IR compared to none in patients undergoing DR.[10]

Other series examined the effects of PMRT on different types of reconstructions. In a retrospective study, Lee et al. compared three groups with both implant-based and autologous reconstructions. The first group had a DR after PMRT ($n=57$), the second an IR with PMRT ($n=59$), and the third group did not receive PMRT ($n=665$). They found a higher rate of complications in the IR group than in the DR group.[11] Adesiyun et al. compared 75 patients undergoing DR after radiotherapy with 75 patients undergoing IR followed by subsequent radiotherapy. They saw a statistically significant higher rate of complications in the IR group (33% vs. 14%).[12]

However, different types of reconstruction may respond differently to PMRT. It has been widely accepted that implant-based reconstructions have poorer outcomes than autologous reconstruction in the context of PMRT.[4] Nevertheless, we must also distinguish between different types of autologous reconstructions to allow for a better comparison. The adverse effects of radiotherapy occur partly due to its effects on vascularization. It has been suggested that flaps with a larger number of perforators or with more abundant muscle tissue have more extensive vascularization and thus more resistance to the effects of radiotherapy.[13,14]

Therefore, we have focused on perforator flaps. The DIEP-flap has become the gold standard for breast reconstruction; however, few investigators have examined the effects of PMRT on DIEP-flaps and their conclusions have been contradictory. A case-control study was performed by Rogers et al. in which 30 patients undergoing IR and PMRT were compared with 30 matched controls not receiving PMRT. They found a significantly higher ratio of fat necrosis (23.3% vs. 0%) and fibrosis/shrinkage (56.7% vs. 0%) in the irradiated group.[15] However, a recent study by Chatterjee et al. found no differences in terms of volume loss between 22 patients irradiated after DIEP-flap reconstruction and 46 unirradiated patients.[16] Clarke-Pearson et al. examined patients who had bilateral breast reconstruction by means of a DIEP-flap with unilateral PMRT. Owing to the limited number of patients, a detailed statistical analysis was not possible. However, they did find satisfactory aesthetic results in their patients with no clinically significant fat necrosis.[17]

The consensus on postponing reconstruction in the setting of radiotherapy is also based on another major argument: the oncological safety of an IR. There are three important concerns with IR and appropriate oncological treatment. First, the reconstructed breast could potentially mask local recurrences by interfering with the clinical examination during follow-up. However, most local recurrences occur on the anterior chest skin and can easily be detected with physical examination.[18] The second concern is the potential delay in adjuvant therapy. If wound healing problems occur after an IR, they may cause a delay in the administration of radiotherapy. There are several significant studies showing poorer oncological outcomes when radiotherapy is delayed.[19,20] However, the literature is very scarce on this subject and most studies have very limited study populations. However, the same studies showed no significant delay in adjuvant therapy with an IR.[21,22] In our study, two out of the 20 patients undergoing IR had to delay the start of their radiotherapy due to postoperative wound problems. The final concern is about the delivery of the radiation to the chest wall. The reconstruction may alter chest wall anatomy and therefore distort the geometrics of the radiation field design, leading to under- or overdosing of the targeted and underlying tissues.[23] However, the main question is whether there is a difference in local recurrence or overall survival between patients undergoing IR or DR in the setting of PMRT. Huang et al. compared the incidence of local recurrence and distant metastasis for breast cancer patients with and without immediate TRAM flap reconstruction in the setting of PMRT. They reported no statistically significant differences in the incidences of loco-regional recurrence or distant metastasis between the two groups.[24] Strålman et al. demonstrated a loco-regional recurrence rate of 6% in 100 patients who had undergone mastectomy

with IR followed by radiotherapy.[25] This suggests that there is no significant decrease in efficacy or delivery of radiation after reconstruction.

Whether a reconstruction should be delayed if a patient requires radiotherapy remains a matter of debate. Studies examining the effects of radiotherapy on autologous flaps often produce contradictory results due to differences in methodology and the outcomes being measured, and small patient populations. There are no randomized controlled trials on this topic with most studies being retrospective single-center studies. The major weakness, however, is the duration of follow-up. The adverse effects of radiotherapy are commonly divided into early adverse effects (occurring weeks/months after exposure) and late adverse effects, sometimes not evident until many years after exposure.[26,27] This means that studies with follow-up times of one or two years are, in reality, of limited value. Most of these limitations are also applicable to our study. The limited sample size, lack of objective parameters and the retrospective nature are the major weaknesses. However, by using follow-up times of at least three years, more robust conclusions can be made about the long-term effects of radiotherapy, in contrast to other studies. Fibrosis and volume loss are among these late complications most commonly seen. This has led to the strategy that, already from the very early reconstructive cases, the reconstructed breast is reconstructed slightly larger than the contralateral side provided there is ample, properly vascularized autologous tissue to do so. In the cases where it was preoperatively known that radiotherapy had to follow the reconstruction, this surgical approach was even more exploited. However, the degree of fibrosis and volume loss is almost unpredictable. Some patients do not have any loss of volume at all after completion of radiotherapy.

Regarding early complications, there were no differences observed in the current study. There is no difference in flap loss nor revision rate between the IBR and DBR groups. However, two reoperations due to vascular occlusion were noted among preoperatively irradiated subjects only. Although no statistical conclusions can be drawn from this, it is noteworthy that previous chest wall irradiation has been described as a risk-factor for vascular complications in a large cohort study by Fosnot and coworkers.[28] Although radiation did not affect the overall success rate, the authors concluded that surgeons should be aware that working in a previously irradiated field carries additional technical risk. This may be of limited value for the overall outcome, but still worth taking to account when choosing between IBR and DBR.

Appropriate patient selection is crucial to obtain successful outcomes. Some patient-specific factors, such as smoking and obesity, are established risk factors for poor outcomes.[29,30] However, it still remains difficult to predict which patients will suffer from adverse outcomes following PMRT. Some patients present with volume loss after IBR followed by RT, some do not. The unpredictability of the esthetic outcome is even more enhanced by the fact that some patients do not experience any side effect at all after completion of the radiotherapy, but when they subsequently undergo liposuction (since the breast was made larger initially because of expected radiotherapy), this liposuction can induce contracture of the reconstructed breast instead of achieving symmetry. What could be hopeful in this matter is that very recent research aims to identify biomarkers that may predict individual radio sensitivity.[31,32]

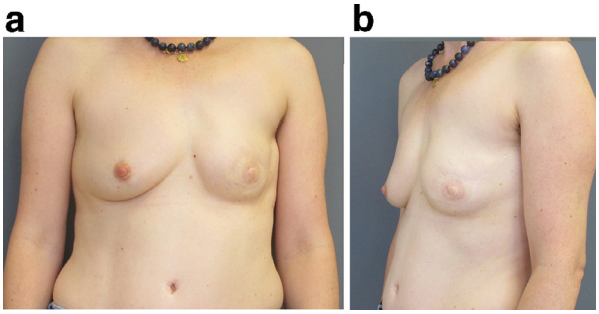

Figure 2 Patient 1, 9 years after IBR and postmastectomy radiotherapy.

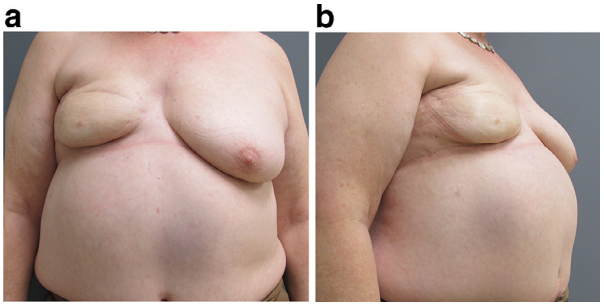

Figure 3 Patient 2, 16 years after IBR and postmastectomy radiotherapy.

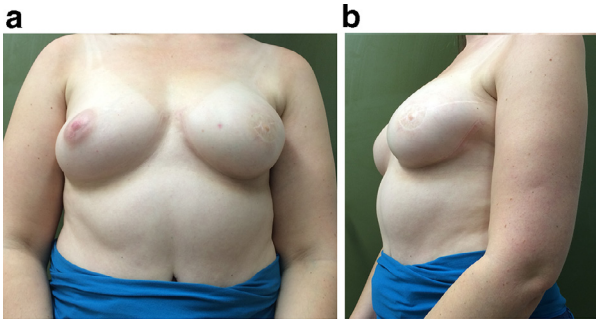

Figure 4 Patient 3, 5 years after IBR and postmastectomy radiotherapy.

We like to illustrate this in three patients that underwent breast reconstruction with PMRT. Patient 1 (Figure 2) is a 37-year-old nonsmoker who received an immediate DIEP-flap reconstruction with PMRT. Her BMI was 20.7 and she did not receive chemotherapy. Despite these favorable characteristics, she developed flap contracture for which she underwent two sessions of fat grafting. Patient 2 (Figure 3) is a 55-year-old nonsmoker with a BMI of 29. She underwent an immediate DIEP-flap reconstruction without chemotherapy and developed severe fibrosis and loss of volume. On the other hand, Patient 3 (Figure 4) is a 35-year-old patient who was a smoker at the time of her immediate DIEP-flap reconstruction, but suffered little consequences from the radiotherapy (she only had a small zone of fat necrosis.) Looking at the patients with an asymmetry post radiotherapy one

Table 3 Secondary and contralateral procedures after immediate and delayed reconstruction.

	p-value
Secondary procedures	0.432
Contralateral procedures	0.658

Variables were analyzed using a Mann–Whitney *U* test. All reported *p*-values are two-sided.

can discuss how to treat this problem. A secondary balancing operation (of the contralateral side) can be rewarding when the reconstructed breast has become fibrotic or contracted and can exist of a breast reduction or mastopexy of that contralateral side. A second way of treating the problem can be lipofilling of the fibrotic or contracted breast. But in these cases experience has shown little or no benefit of lipofilling of a breast that has become rigid or contracted due to postoperative radiotherapy. As can be seen in patient 2, who developed severe fibrosis and loss of volume, several attempts of lipofilling to augment the volume had been undertaken with hardly any benefit or volume gain. This explains why we did not see any statistical difference in secondary procedures, as demonstrated in Table 3.

Besides the difficulty of predicting how individual patients will respond to PMRT, it is not always known preoperatively if the patient will require adjuvant radiotherapy. This decision is made when the final pathologic report of the mastectomy specimen is known.

Conclusion

The current study indicates that radiotherapy may contribute to adverse long-term flap-related outcome after IBR. We therefore recommend that reconstruction should be delayed whenever possible in patients who will require PMRT. The inability to predict which patients will have a poor outcome and the risks of delaying adjuvant therapy reinforce our belief that reconstruction should be postponed unless explicitly demanded by the patient. In that case, the patient should be thoroughly informed about the risks and benefits of the procedure.

Conflict of interest

There are no conflicts of interest to declare.

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