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Breast

The Effect of the Timing of Radiotherapy on Clinical and Patient-Reported Outcomes After Latissimus Dorsi Breast Reconstruction: A 10-Year Study

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Background: Breast reconstruction (BR) is considered to be adversely affected by radiotherapy (RT), particularly when an implant is used. The aim of this study was to compare clinical and patient-reported outcomes after expander-assisted latissimus dorsi breast reconstruction depending on the timing of RT.
Methods: Patients undergoing BR over a 10-year period (follow-up mean, 56 [14–134] months) were divided into 3 groups. Group 1, RT after mastectomy and BR, Group 2, RT before mastectomy and BR, and Group 3, RT after mastectomy but before BR. The primary endpoints were early and late surgical interventions. Validated questionnaires were circulated to all study patients and matched controls.
Results: Three hundred thirteen patients underwent 389 BRs. One hundred eighteen patients received RT, of which 65 had undergone expander-assisted latissimus dorsi breast reconstruction. Both use and timing of RT influenced clinical outcomes. Overall, use of RT resulted in a 3-fold increase in complications ($P = 0.003$). Postreconstruction RT resulted in more than double the number of complications compared with prereconstruction RT ($P = 0.008$) and delaying BR until after mastectomy and RT reduced complications to levels observed in control patients ($P =$ nonsignificant). Complications were halved in patients undergoing autologous LD reconstruction ($P = 0.0001$). Patient-reported outcomes were similar for emotional well-being, satisfaction, and shoulder symptoms, although a nonsignificant increase in chronic breast symptoms was reported by the RT group.
Conclusion: The timing and type of LD reconstruction chosen by patients receiving RT has a significant impact on the risk of subsequent complications and unplanned interventions but has little impact on longer term patient well-being or satisfaction.
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INTRODUCTION

The use of postmastectomy radiotherapy (PMRT) has been increasing slowly over the last 25 years supported by the publication of trials, demonstrating the positive impact of PMRT on overall survival.[1–5] The rate of immediate breast reconstruction (IBR) in the United Kingdom has also increased 4-fold from around 5% in 2006 to over 20% in 2011.[7,8] With the increasing demand for breast reconstruction (BR), choosing the most appropriate procedure for an individual patient is an important factor in achieving a successful outcome. Among a range of factors which may influence this decision are the patient's expectations, breast size and shape, smoking history, and comorbidities as well as the timing of chemotherapy. Previous breast irradiation or planned radiotherapy (RT) are key factors to consider, given the effect of RT on BR, especially when expanders or implants are used.[6,9–13]

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Three small prospective studies[9,10,13] have compared the incidence of complications requiring intervention in patients undergoing implant-based LD reconstruction with or without postoperative RT. Each study reported a significant increase in complications in the irradiated group. Severe capsular contracture increases with time in patients undergoing immediate implant-based reconstruction followed by RT,[9,10] with the incidence of capsular contracture escalating from 11% to 33%. An analysis of aesthetic results and satisfaction in 68 patients undergoing IBR with a tissue expander or implant reported a good/excellent level of satisfaction in 80% of irradiated patients (compared with 88% in the nonirradiated control group). Overall, 68% of irradiated patients in the same group developed capsular contracture compared with 40% in the control group.[11] Furthermore, a study looking at the sequencing of BR and RT, with respect to complications and patient satisfaction, reported a trend toward a higher rate of complications in patients undergoing RT after BR compared with patients undergoing BR after RT (32% versus 44%). General satisfaction was comparable between the RT-first and BR-first groups (68% versus 68%), and satisfaction rates with aesthetic outcomes were also similar (50% versus 62%; $P = 0.238$).[12]

A single center evaluation of clinical outcomes after 1,000 implant-based reconstructions included a subgroup of 146 irradiated patients who had LD reconstruction.[17] The authors observed no difference in complication rates in 36 patients who had RT before or after LD reconstruction compared with 110 nonirradiated patients, concluding that RT had no effect. The conflicting results of these studies prompted a review of the timing of RT on clinical and patient-reported outcomes after expander-assisted LD reconstruction (eLDR) to test the hypothesis that giving RT after eLDR will lead to worse clinical and patient-reported outcomes compared with outcomes in patients undergoing eLDR after the completion of adjuvant RT.

METHODS

Data Collection

An analysis of a prospectively compiled patient database of all BRs performed between 2002 and 2011 was carried out. All patients were discussed in a preoperative multidisciplinary team meeting, and decisions about the timing and type of BR were based on clinical factors and patient choice. Options considered included subpectoral, eLD, autologous LD reconstruction (ALD), and unipedicled transverse rectus myocutaneous (TRAM) flap procedures. Patients choosing free flap procedures were referred a unit with microvascular experience. Patients were judged suitable for ALD reconstruction without an expander when sufficient volume could be harvested by including fat from the cutaneous skin paddle, the surface of the muscle, the scapular fat pad, the anterior fatty zone, and the suprailiac fat pad. Expander-based LD procedures were recommended in those patients with insufficient flap volume to achieve a symmetrical BR.

Patients undergoing PMRT were selected based on adverse histopathological features including tumor size, multifocality, nodal status (> 3), and a positive posterior margin. Clinical data collected included patient and tumor details, timing and type of reconstruction, dose and fractionation of RT, nipple reconstruction, contralateral symmetrizing surgery, implant exchange with or without capsulotomy or capsulectomy, and time to reoperation. Tissue expanders and permanent implants were included within the RT field in patients undergoing postreconstruction RT.

Early complications including hemorrhage, infection, or necrosis were recorded when reoperation was required within 30 days of reconstruction. Late complications were recorded when unplanned revisional surgery was required for asymmetry, deformity, and capsular contracture. A group of 59 control patients matched for year of reconstruction who had undergone eLDR without RT was selected at random from the database.

Patient-Reported Outcomes

Patient-reported outcomes were assessed using a questionnaire based on the "Breast Q©" (validated Quality of Life tool[18,19]) to evaluate physical, emotional, and sexual well-being, as well as overall patient satisfaction. This was circulated to all patients in both irradiated and control groups.

RT Groups

Patients fell into 1 of the 3 groups. Group 1, patients undergoing mastectomy and IBR followed by RT. Group 2, patients undergoing RT before mastectomy and IBR. Group 3, patients undergoing mastectomy and RT, followed by delayed breast reconstruction (DBR).

Group 2 included patients with local recurrence after breast-conserving surgery (BCS) and RT as well as patients presenting with larger tumors treated by neoadjuvant RT before mastectomy and IBR.

Statistical Analysis

Fisher's exact test was used to compare differences in both clinical and patient-reported outcomes between the RT and no RT groups. A P value of < 0.05 was regarded as significant.

RESULTS

Three hundred eighty-nine reconstructions were performed in 313 women between 2002 and 2011. One hundred eighteen (30.3%) of these patients had either pre- or postoperative RT, and this group of patients were evaluated to investigate the effects of RT. Table 1 compares these

Table 1. RT Use* and Patient Demographics

	RT	No RT	*P*
n	118	59	
Age (y)	56 (36–79)	55 (35–66)	0.36
Follow-up from reconstruction (y)	5 (0.5–10)	4 (1–11)	0.45
Tumor diameter (mm)	33.9 (8–100)	26.7 (12–42)	0.37
Node positivity (%)	87 (74)	9 (15)	0.0001
Chemotherapy (%)	94 (80)	7 (12)	0.0001
Endocrine (%)	73 (62)	45 (76)	0.06

*RT dose, 50 Gy in 25 fractions.

118 patients with 59 controls selected from the nonirradiated group.

Table 2 outlines the frequency of different reconstructive procedures carried out and the sequence of RT in these 118 patients who had either pre- or post-BR radiotherapy.

Complications After Radiotherapy

Table 3 compares the early and late complications of the 65 irradiated patients undergoing eLDR with 59 control patients who underwent an eLDR without any pre- or postreconstruction RT. Overall, 44% of irradiated eLDR patients developed complications compared with 18% of controls (P = 0.003). Although there was no difference in the early complication rate between the 2 groups (P = 0.566), almost a third of eLDRs in irradiated patients required revisional surgery for asymmetry, deformity, or capsule formation at a later date (P = 0.004).

There were no cases of flap necrosis, but 3 implants were removed due to infection (implant loss following eLDR + RT versus control, 4.6% versus 1.7%; P = NS).

Table 4 compares the complications following eLDR and RT with patients undergoing autologous reconstruction and RT (26 ALD reconstructions and 17 unipedicled TRAM reconstructions). Late complications requiring intervention were twice as frequent in the eLD group, but overall complications were similar due to a higher early complication rate following autologous procedures.

Timing of RT and Complications

Complications fell from 75% in group 1 to 38% in group 2, and to 20% in group 3. Similar complication rates were observed in both group 3 and the nonirradiated control group (Table 5).

Patient-Reported Outcomes

Overall Satisfaction

High levels of satisfaction with the outcome of BR were reported by patients, regardless of RT use, with 82% (RT group) and 85% (no RT group) rating the outcomes of their reconstruction as excellent or very good (Fig. 1).

Breast and Shoulder Symptoms

Twenty-five percentage of irradiated patients reported adverse symptoms in the reconstructed breast compared with 7% in the control group (P = 0.22). The reported softness of the reconstruction was the same in both groups, with over 75% of patients reporting that their reconstructed breast felt significantly firmer than the contralateral breast, irrespective of whether they had undergone RT or not (P = 0.38). One-third reported pectoral girdle, back, and neck symptoms "most or all of the time" in both groups (Fig. 2).

Well-Being

Sexual, physical, or emotional well-being scores in patients having eLDR were unaffected by the use of RT. Overall well-being scores were similar in both groups—107.6 (RT) and 114.1 (no RT) of a maximum score of 144 (P = 0.48).

DISCUSSION

This is the largest study to date investigating whether the use and timing of RT influences the outcomes of LD reconstruction. The findings have demonstrated the detrimental effects of RT, particularly when used alongside eLD-based procedures and add to a growing body of evidence that highlights the adverse effects of RT after implant-based reconstruction. A recent systematic review of > 1,000 patients has reported reconstruction failure (defined as loss of implant or flap conversion) in 1 in 5 patients undergoing implant-alone procedures, regardless of whether they received pre- or postoperative RT.[17] Similar major complication rates have been reported following the irradiation of reconstructions combining implants with LD flaps.[9,10]

Our findings demonstrate a clear relationship between the timing of RT and the risk of late complications requiring additional surgical procedures following eLD reconstruction. Patients at the highest risk of complications underwent RT after IBR, whereas those at lowest risk (with a complication rate similar to nonirradiated patients) had reconstruction delayed until some time after completing RT. Patients at intermediate risk had undergone irradiation of the intact breast before mastectomy and IBR. This group consisted of patients who had either developed a local recurrence after previous BCS and RT or those treated by neoadjuvant chemotherapy and RT for locally advanced disease. Our findings should be interpreted with some degree of caution, as the small numbers of patients in each subgroup increases the potential for a type 1 error due to the limited sample size.

Although early postoperative complications were higher following autologous compared with eLDR in irradiated patients, late complications were significantly less in the autologous group, approaching the rate observed in the eLDR control group, in keeping with other studies.[11] These findings are also consistent with the time-dependent improvement in patient-reported outcomes following autologous reconstruction in contrast to the linear deterioration following implant-based techniques during a 10-year follow-up, after correcting for RT use.[26] Signifi-

Table 2. Type of Reconstruction Performed and the Timing of RT in Each Group

Type of Reconstruction	Group 1, Mx + IBR, Then RT	Group 2, RT before Mx + IBR	Group 3, Mx and RT, Then DBR	Total
Expander-assisted LD	24	16	25	65
Autologous LD	13	11	2	26
TRAM	2	4	11	17
Subpectoral	5	4	1	10
Total	44	35	39	118

Mx, mastectomy.

Table 3. Frequency of Complications Requiring Interventions in Patients Undergoing eLDR

	eLDR + RT (65)		Controls (59)		*P*
	n	%	n	%	
Early complications					
Hemorrhage	1	1.5	1	1.7	NS
Infection	4	6.1	2	3.4	NS
Implant loss	3	4.6	1	1.7	NS
Flap loss	0	0	0	0	NS
Total	8	12.2	4	6.8	NS
Late complications					
Asymmetry	2	3.1	3	5.1	NS
Deformity	2	3.1	2	3.4	NS
Capsular contracture	17	26.2	1	1.7	0.0004
Total	21	32.4	6	10.2	0.0041

Table 4. Comparison of Complications in Irradiated Patients Following eLDR and Autologous Reconstruction

	eLDR + RT (65)	Autologous Reconstruction + RT (43)	*P*
Early complications	8 (12)	9 (21)	0.2834
Late complications	21 (32)	7 (16)	0.0001
Total	29 (43)	16 (37)	0.5504

cantly lower long-term complication rates have also been shown to correlate with the better aesthetic outcomes reported after autologous techniques.[27]

RT has already been shown to have an adverse effect on cosmetic outcomes following both autologous and implant-assisted LD reconstruction.[13,17] We did not attempt to evaluate cosmetic outcomes but rather relied on patient-reported outcomes, which arguably provide a more holistic and meaningful assessment of outcome, including well-being and self-esteem.

Predicting the use of PMRT before surgery may in the future help to inform the optimal timing of reconstruction. Axillary node status,[1–3] and other histopathological features including tumor size, tumor grade, lymphovascular invasion, multifocality, and young age can predict the relative risk of recurrence.[28] Most of these factors can be established by preoperative core biopsy and high-quality imaging. The use of "up front" sentinel node biopsy (SNB) can also inform decision-making about the scheduling and type of reconstruction and has real potential as the popularity of IBR using implant-based techniques continue to rise.[29]

The results of the current study also suggest that "up front" neoadjuvant irradiation of the intact breast before mastectomy and IBR provides a further option for patients not willing to delay reconstruction. This approach has also been shown by others to mitigate the adverse effects of RT when used after reconstruction.[30,31] Of the 35 patients who had RT before mastectomy and reconstruction in the current series, 16 underwent eLDR procedures (group 2). Twelve of these patients had developed local recurrence after previous BCS, so nothing could be done about their historical exposure to RT. The remaining 4 patients (25%) had locally advanced tumors and underwent a full course of "neoadjuvant" RT before definitive surgery.

This is a variation of the "delayed-immediate" BR technique first described by Kronowitz et al.[32] using an implant as a "spacer" after skin-sparing mastectomy. In our patients, this approach enabled irradiation of the chest wall and skin envelope before reconstruction with a nonirradiated LD flap and expander. Only 1 of the 4 "neoadjuvant RT" patients required an early skin debridement, and one-third of those relapsing after previous BCS required revisional surgery, suggesting that adverse effects of RT can be limited by using the diseased breast as a "biological spacer" before reconstruction.

Patient-Reported Outcomes

The high overall level of satisfaction reported by our patients 56 months after surgery underlines the positive impact of reconstruction after mastectomy and confirms the findings of other studies. A national audit of > 5,000 reconstructions carried out in the United Kingdom (the National Mastectomy and Breast Reconstruction Audit [NMBRA]) compared both clinical and patient-reported outcomes in women choosing implant-only reconstruction with those choosing more complex flap-based procedures (implant/expander LD, ALD, pedicle TRAM, and free flap reconstruction).[6] The level of satisfaction reported by patients in the NMBRA 18 months following flap-based procedures was very similar to the satisfaction experienced by patients in the current study. By contrast, women choosing implant-only reconstruction in the NMBRA reported lower levels of overall satisfaction with the outcomes of their surgery than those who had undergone more complex surgery.

The finding that satisfaction was independent of the use of RT in this study is somewhat counterintuitive, as irradiated patients experienced more complications. One explanation is that those patients developing asymmetry, deformity, and capsular contracture had already undergone further surgery including capsulotomy, capsulectomy, and implant exchange. Satisfaction was measured at a moment in time, and our findings suggest that these complications can be overcome by corrective procedures without adversely affecting longer term outcomes.

Patient-reported symptom scores indicate that despite satisfaction with outcomes, a significant minority of women will continue to experience chronic breast pain or pectoral girdle symptoms, or functional disturbance, more than 4 years after LD reconstruction. Breast pain was experienced by a quarter of women following RT, and adverse shoulder symptoms by a third of respondents, regardless of RT use. Although radiation-induced breast pain is a common and unavoidable side effect of treatment,[9–11,19] the higher levels of shoulder dysfunction and pain reported in this and other studies[7] are a cause for concern. In future, earlier mobilization and targeted physiotherapy should become a standard of care to minimize distressing longer term symptoms experienced by patients undergoing LD reconstruction.[33,34]

Strategic Planning

These results suggest that if the need for PMRT can be predicted before surgery, delaying BR until a later date

Table 5. Complications Relating to Timing of RT

	Group 1, eLDR Then RT (24)	Group 2, RT Then Mx + eLDR (16)	Group 3, Mx, RT, Then DLD (25)	Controls (59)
Early complications	4 (17)	2 (13)	2 (8)	5 (8)
Late complications	14 (58)	4 (25)	3 (12)	6 (10)
Total	18 (75)	6 (38)	5 (20)	11 (18)

Mx, mastectomy.

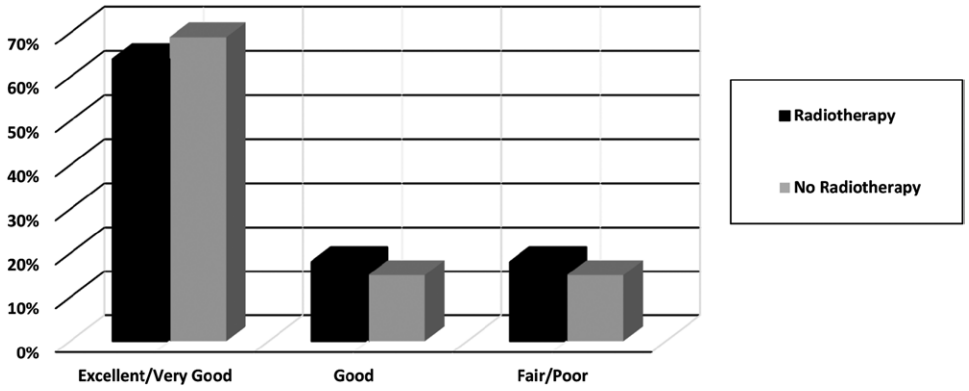

Fig. 1. Effect of RT on patient satisfaction following eLDR.

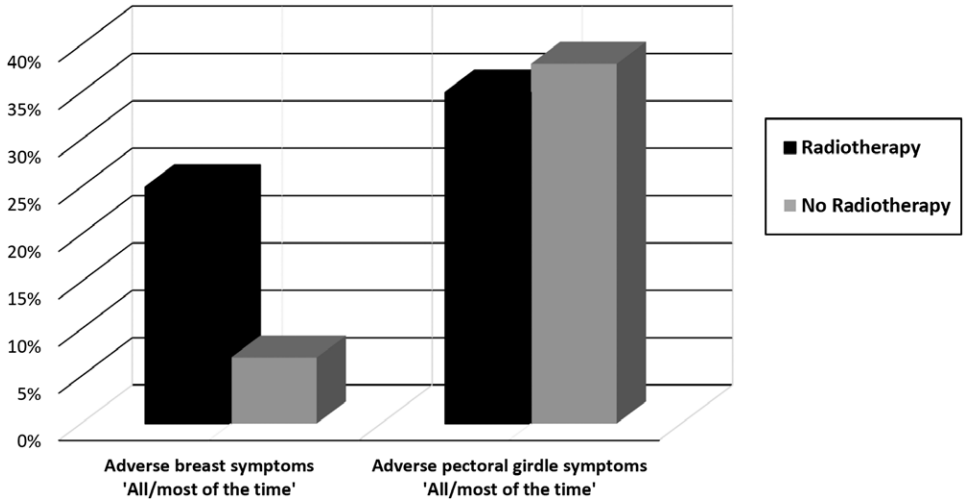

Fig. 2. Patient-reported scores for breast and shoulder symptoms.

can lead to a 3-fold reduction in the overall complications of eLDR. Six of the 24 (25%) eLDR patients irradiated after immediate reconstruction (group 1) were node negative, and RT was recommended subsequently on the grounds of multifocality, final histological tumor size, and/or the presence of lymphovascular invasion. The use of core biopsy and high-quality imaging would today help to identify most of these patients, giving them the opportunity to avoid a 75% reoperation rate by delaying reconstruction and crossing over from group 1 to group 3. The remaining 75% of patients in group 1 were irradiated on the grounds of node positivity. It is becoming increasingly possible to predict the nodal status of this group by the use of ultrasound-guided lymph node biopsy in those patients with suspicious axillary nodes and "up front" SNB in the remainder, again informing evidence-based decisions about the timing of reconstruction.[29]

Based on our findings, what steps should be taken when managing patients who opt for LD reconstruction after careful consideration of all alternatives? First, patient suitability for LD reconstruction clearly takes priority and should be based on a range of factors including comorbidities, body habitus, breast morphology, the contralateral breast, and attitude to risk. Second, efforts should be made by the multidisciplinary team to identify those patients likely to require RT and/or systemic therapy, based on local and national guidelines. Comprehensive preoperative imaging, image-guided core biopsy of breast lesions and any abnormal axillary nodes, or SNB, is essential. This will enable full histopathological and immunocytochemical characterization and staging of the tumor, which in turn will determine the use, timing, and type of systemic therapy. Lastly, identification of patients who meet the criteria for PMRT will inform a discussion about the timing

and type of procedure and a consideration of the 4 main options. First, to delay reconstruction until 6–12 months after the completion of RT, second to undergo immediate ALD or other autologous reconstruction before RT, and third to choose immediate eLDR after a clear explanation of the consequences of postoperative RT detailed above. And finally with multidisciplinary agreement, to consider preoperative neoadjuvant treatment including RT before mastectomy and reconstruction.

Lastly, patients should be reassured that if RT is required, it is unlikely to have a long-term adverse effect on quality of life or overall satisfaction with the results of reconstruction. They should be made aware that further unplanned surgical procedures may be required to resolve RT-related problems and achieve an optimal outcome.

CONCLUSIONS

This is the largest study to date investigating the impact of the timing of RT on the subsequent outcome of LD reconstruction. The findings add to a growing body of evidence pointing to the detrimental effect of RT on BR, particularly when combined with a prosthesis. The results suggest that when PMRT is anticipated, a range of strategies should be considered to mitigate the adverse long-term effects of treatment. Delaying eLDR until after RT is completed is the most effective strategy, achieving complication rates equivalent to those experienced by nonirradiated patients. Other approaches involving neoadjuvant RT or using autologous flaps can help to improve outcomes in those women who decline DBR.

In future, more detailed preoperative investigation and greater multidisciplinary input will help to inform decisions about the timing and type of reconstruction. A more integrated approach has the potential to reduce the longer term effects of RT as well as the associated cost, anxiety, and inconvenience of further surgical procedures.

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