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Delayed two-stage breast reconstruction: The impact of radiotherapy

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Abstract *Background:* Despite a trend towards immediate breast reconstruction in recent years, delayed breast reconstruction using a tissue expander remains a common procedure. Radiotherapy after mastectomy but before reconstruction is a risk factor, although studies examining the effect of this are limited. The aim of this retrospective cohort study is to evaluate the impact of pre-reconstructive radiotherapy (PRT) in patients undergoing breast reconstruction using an expander/implant.

Materials and methods: Two hundred twenty-three consecutive patients underwent unilateral mastectomy followed by expander-based reconstruction over a 10-year period (2004–2013). Fifty patients (22%) received radiotherapy before reconstruction (PRT group), and 173 patients (78%) did not (non-PRT group).

Descriptive patient data as well as data regarding the operations, hospitalisation and complications were collected.

Statistical analyses such as logistic regression, Fisher exact test and multivariate analysis were performed using R-statistics.

Results: PRT was a significant predictor of loss of reconstruction, and when adjusted for smoking and body mass index (BMI), it showed an odds ratio (OR) of 17.8 [95% confidence interval (CI): 5.7–70.6; $p<0.01$] for loss of reconstruction, with 15 (30%) in the PRT group and 7 (4%) in

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the non-PRT group. We found no difference in short-term reoperations or infections at either stage of reconstruction.
Conclusion: In patients undergoing delayed breast reconstruction using an expander/implant, radiotherapy is a significant risk factor for loss of reconstruction. It should be considered a relative contraindication for this reconstructive modality, and careful selection and advisement of the patient about the risks of complications and potential need for additional corrective surgery or later autologous breast reconstruction should be discussed.

Introduction

Breast reconstruction using an expander followed by a permanent implant is a common procedure and is the first choice of reconstruction for most patients undergoing mastectomy.[1,2] Due to increasing incidence, breast cancer is currently the most common cause of cancer among women in Europe and is estimated to account for almost 30% of all female cancers.[3]

An increasing amount of knowledge about the benefits of combined adjuvant systemic and radiotherapy has emerged through clinical trials,[4-7] leaving women with a history of breast cancer as the largest group of cancer survivors.[8] This has resulted in an increased need for reconstructions in women undergoing radiotherapy.

Several reconstructive options exist depending on the timing of the reconstruction and possible treatment with adjuvant radiotherapy, the clinical appearance of the mastectomy site, and the patient's desire.[9-11] In patients who are not expected to receive pre-reconstructive radiotherapy (PRT), immediate reconstruction with an implant and two-stage reconstruction are the most common procedures.[12]

Although a trend toward immediate breast reconstruction has been seen in recent years, delayed reconstruction is still a common procedure.[13] A number of studies have investigated the effect of radiotherapy delivered to an immediate reconstruction at either the expander or the implant stage,[14-17] but well-conducted studies evaluating the effect of PRT are scarce and often based on relatively small populations.[18,19] Although many surgeons favour autologous breast reconstruction (ABR) in this situation,[10,20] many patients still undergo an implant-based reconstruction.

The present study aims to investigate the effect of PRT on delayed reconstruction with an expander followed by a permanent implant.

Patients and methods

Patients

A retrospective review of medical records for all delayed, unilateral two-stage breast reconstructions performed at Copenhagen University Hospital, Rigshospitalet, Denmark, during a 10-year period from 2004 to 2013 was conducted. All patients had the pectoralis major muscle preserved during initial mastectomy. No cases included the use of acellular dermal matrix or any type of mesh. Two hundred twenty-three procedures were included in the study and divided into two groups: a group that received PRT ($n = 50$) and a group that did not ($n = 173$).

Data regarding age, time from mastectomy to reconstruction, adjuvant therapy, smoking, expander and implant volume, operative data and complications (reoperations, infections, implant failure and reason for implant failure) were collected.

The primary outcome was loss of reconstruction defined as removal of expander/implant. The secondary outcomes were reoperations within 30 days and major infections following the procedures. Major infections were defined as the need for intravenous antibiotic treatment. The complications were recorded separately for both stages of reconstruction (expander stage/implant stage).

Surgical procedure

The patient's skin was examined preoperatively to assess whether the patient was suitable for expander reconstruction. If the patient had previously been exposed to radiotherapy, expander reconstruction was offered only if a consultant-level plastic surgeon assessed the patient as suitable for expander-implant reconstruction. The decision was based on clinical parameters such as radiation damage, skin condition, and size of the contralateral breast.

The reconstruction was performed in two stages. During the fast stage, an expander was placed; at the second stage, the expander was removed and replaced with a permanent implant.

The standard surgical technique was incision through and excision of the mastectomy scar, dissecting the pectoralis major muscle and creating a sub-muscular pocket for inserting the expander. The expander was partially filled with a saline solution, and after approximately 2 weeks, percutaneous saline infusion to the expander began in the outpatient clinic. The standard expansion regimen included infusion of 100 mL saline every 2 weeks. In some cases, it may not have been possible to infuse 100 mL due to pain or excessive tightness of the skin. In such cases, the regimen was adjusted, typically with a new goal of 50 mL per session or how much the patient and tissue would tolerate. When the desired volume was reached, the expander was left in situ for approximately 3 months before it was replaced with a permanent implant. All reconstructions were performed using Mentor® tissue expanders and implants.

Table 1 Demographic data of PRT and non-PRT expander-based delayed breast reconstructions.

	Non-PRT group ($n=173$)	PRT group ($n=50$)	p
Age, years (avg.)	51.6 (9.8)	49.1 (11.2)	0.1
BMI kg/m^2 (avg.)	24.1 (3.8)	23.4 (2.7)	0.2
Smokers (%)	37 (27%)	1 (2%)	<0.01*
Adjuvating therapy			
- Chemotherapy	93 (54%)	42 (84%)	<0.001*
- Endocrine therapy	89 (51%)	34 (68%)	0.06
Mastectomy - reconstruction, days (avg.)	939 (1445)	1384 (1879)	0.07
Initial expander volume, mL (avg.)	151 (56)	150 (52)	0.9
Final expander volume, mL (avg.)	445 (102)	401 (84)	<0.01*
Implant size, mL (avg.)	392 (103)	362 (90)	0.1

Data presented as average (SD) or numerical (% of column) and differences are tested with *T*-tests or chi^2 test.
* Marks statistically significant difference.

Statistical analysis

The data were analysed using R-project, *R-statistics version 3.3.2*. The *t*-test and chi-square test were used for continuous and categorical variables, respectively. Univariate analysis was performed on the entire cohort to compare the non-PRT and PRT groups. Multivariable analysis was performed on the primary outcome, loss of reconstruction, for patients who received PRT and those who did not. Potential confounders were selected depending on significant difference in descriptive baseline data between our two groups and previously identified associations in the literature. Patients who experienced failure of reconstruction before insertion of the permanent implant were excluded from analysis regarding events related to the permanent implant.

Overall loss of reconstruction and loss at each stage of reconstruction (expander stage or implant stage) were determined. Statistical significance was set to p-values < 0.05. Independent variables such as smoking status, body mass index (BMI), time from mastectomy to reconstruction, comorbidities, and age were investigated for correlations with the primary outcome.

The secondary outcomes (reoperations and infections) were investigated overall and by stage of reconstruction.

Results

Table 1 shows the characteristics of the study cohort. Irradiated and nonirradiated patients were comparable regarding age, BMI, comorbidities, time from mastectomy to the first stage of reconstruction, and permanent implant size.

There were significantly more smokers in the non-PRT group than in the PRT group (27% vs. 2%, respectively, $p<0.01$), and patients in the PRT group were more likely to have received adjuvant chemotherapy than the group without radiation therapy (84.0% vs. 54.1%). Although permanent implant size did not show statistically difference between the two groups (390 mL for non-PRT and 362 mL for PRT), the patients in the non-PRT group had significantly larger volumes of the expander before the change to a permanent implant than those in the PRT group (445 mL vs. 401 mL, respectively).

The mean time from mastectomy to reconstruction was 939 days for the non-PRT group and 1384 days for the PRT group but did not reach significance ($p=0.074$).

Primary outcome - loss of reconstruction

Among the 223 patients, 22 experienced loss of reconstruction: eight because of infection, six because of suboptimal aesthetic result, four due to pain from prosthesis, two because of wound complications, and, in two cases, the exact cause could not be determined (one was performed in another country and one at a private clinic). Of the 22 patients with loss of reconstruction, 15 received PRT (30% failure rate) and 7 were in the non-PRT group (4% failure rate). The difference was found to be statistically significant ($p<0.01$). Eleven reconstructions were lost during the expansion phase (seven RT and four non-RT), and 11 were lost after insertion of the permanent implant (eight RT and three non-RT). The overall loss and loss of reconstruction by phase are shown in Table 2.

PRT was a significant predictor of loss of reconstruction, and the univariate analysis showed an OR of 10.2 (95% CI: 4.0-28.4; $p<0.001$) for loss of reconstruction compared to the non-PRT group. When adjusted for smoking and BMI in a multivariable analysis, we found an OR of 17.8 (95% CI: 5.7-70.6;$p<0.001$) for loss of reconstruction between the PRT and e non-PRT groups (Table 3).

In the multivariable analysis, BMI was a significant contributing risk factor ($p<0.05$), meaning higher BMI increased the risk for loss of reconstruction. A subgroup analysis showed that patients with loss of reconstruction and no PRT had a higher BMI than those in the PRT group, with values of 26.8 versus 24.2, respectively, although the difference was not statistically significant ($p=0.12$).

We found no correlation between smoking and loss of reconstruction ($p=0.88$).

Complications

Following expander insertion, a total of 10 patients had a reoperation within 30 days (4.4%, $n=223$), whereas 16 (7.5%, $n=212$) were reoperated within 30 days after the insertion of the permanent implant. Eighteen patients (8.7%)

Table 2 Reconstruction-related complications for expander-based breast reconstructions with (PRT) and without pre-reconstructive radiotherapy (Non-PRT).

	Non-PRT group ($n = 173$)	PRT group ($n = 50$)	p
***Re*-operations (30 days)**	19 (11%)	7 (14%)	0.6
Expander stage	6 (3%)	4 (8%)	0.3
- Hematoma	5 (3%)	2 (4%)	0.7
- Wound dehiscence	0	0	
- Explantation	1 (1%)	2 (4%)	0.13
Implant stage	13 (8%)	3 (7%)	1
- Hematoma	13 (8%)	0	0.08
- Wound dehiscence	0	2 (5%)	0.04*
- Explantation	0	1 (2%)	0.2
Loss of reconstruction	7 (4%)	15 (30%)	<0.001*
- Expander stage	4 (2%)	7 (14%)	<0.001*
- Implant stage	3 (2%)	8 (16%)	<0.001*
Major infections			
- Expander stage	13 (8%)	5 (10%)	0.7
- Implant stage	17 (10%)	6 (14%)	0.6

Data presented as average (SD) or numerical (% of column) and differences are tested chi² test.
* Marks statistically significant difference.

Table 3 Multivariate analysis for loss of reconstruction including PRT, BMI and smoking status.

	OR	95% CI
Pre-reconstruction radiotherapy	17.85*	5.68-70.64
Increasing BMI	1.17*	1.01-1.34
Active smoker	3.39	0.74-15.38

* Marks statistically significant difference.

had a major infection following expander insertion and 23 (11%) had a major infection following implant insertion. There was no significant difference between the two groups regarding overall reoperations after expander insertion ($p = 0.3$) or after placement of the permanent implant ($p = 1$), although a significant difference in the number of wound complications was seen (two in the PRT group vs. zero in the non-PRT group). No difference in infections after placement of expander ($p = 0.6$) or after implant ($p = 0.4$) was found. An overview of complications is listed in Table 2. We found no correlation between smoking and overall reoperations after insertion of expander ($p = 0.86$) or permanent implant ($p = 0.9$), nor between smoking and infections at either stage ($p = 0.75$ for expander stage and $p = 0.6$ for implant stage).

Discussion

The present study found a highly significant increased risk of loss of reconstruction in women treated with PRT. Patients who received PRT had a failure rate of 30%, whereas the non-PRT group had a 4% failure of reconstruction. When the results were further adjusted for BMI and smoking status, the OR was as high as 17.8.

Surprisingly, we found no difference in overall complications leading to reoperation within 30 days of surgery between the two groups, although previous exposure to radiation therapy has been reported as a significant risk factor for early major complications.[10,16,21]

The reason for the large difference in reconstructive failure between the two groups but not in 30-day postoperative complications is possibly because the expander is filled only with an average of 150 mL at the time of insertion, which was possible in the patients despite irradiated skin. The difficulties emerge during the expansion process, as the radiation damage does not allow the skin to expand properly, resulting in complications leading to failure.

Previous studies report elevated BMI and smoking as risk factors for complications, including loss of reconstruction in patients undergoing two-stage reconstruction.[14,15,22,23]

Our study identified increased BMI as a significant contributing risk factor for loss of reconstruction when comparing PRT patients with non-PRT patients. We found no statistically significant relationship between smoking and loss of reconstruction or complications such as reoperations and infections.

The strength of the present study is the relatively large cohort of consecutive patients investigated and the number of patients who have received PRT ($n = 50$), which to the authors' knowledge is one of the largest cohorts on the subject. Although the number is large compared to that in previous studies, the number of events of secondary outcomes remain relatively small, and care should be taken when drawing definite conclusions.

Seth et al. pointed out a potential weakness when investigating the isolated effect of PRT on delayed two-stage reconstruction: The patients included are part of the PRT cohort that has been assessed to have the highest expected chance of successful reconstruction.[24] Although the failure rate in the PRT group is found to be increased by more than ten times in the present study, previous radiation therapy might be regarded as an even higher risk factor for reconstruction, as the patients are carefully selected.

PRT is consistently reported as a risk factor for failure of reconstruction, with failure rates between 8.7% and 40%

for patients receiving PRT ahead of two-stage reconstruction.[16,18,19,24,25]

In 2012, Hvilsom et al. found failure rates of 13.1% and 6.8% in patients who did (10/76) and did not receive PRT (24/353), respectively, and although they did not report a significant difference in the two groups, a trend was seen, with a p-value of 0.06.[25]

Hirsch et al. compared delayed reconstruction in patients who received PRT with patients who underwent immediate reconstruction preceded by breast-conserving surgery and radiotherapy and found failure rates of 40% in both groups, but the delayed reconstruction group consisted of only 10 patients.[18] As a part of a comparison of immediate and delayed breast reconstructions, the same group retrospectively reviewed 74 reconstructions in 59 patients undergoing delayed reconstruction and found failure of reconstruction or conversion to flap in 8.7% of the PRT cases (2/23) and 7.8% of patients who did not receive PRT (4/51), with no significant difference in the two groups.[24]

Lin et al. found that 18 of 49 patients (37%) receiving radiation therapy either before reconstruction or during the expansion phase experienced loss of reconstruction or conversion to ABR, but they concluded that these patients are still able to undergo reconstruction by including patients who needed conversion to flap ($n = 8$) in the group that overall successfully completed reconstruction.[16]

In a recent study on the subject, Lam et al. found a significantly higher rate of reconstruction failure, 15% (3/20) versus 2% (3/150) ($p = 0.02$), in patients in the RT group than in those in the non-PRT group.[19]

We had significantly more patients with a history of chemotherapy in the PRT group than in the non-PRT group (54% vs. 84%). To the best of our knowledge, there are no reports of wound complications, impaired wound healing or fibrosis of the breast area as a long-term result of chemotherapy. A previous study found no correlation between a history of chemotherapy and functional restriction of the arm or lymphoedema of the arm.[26] Thus, there is no indication that chemotherapy results in fibrosis.

Previous studies have reported ORs between 2.2 and 4.9 for complications, including failure for smokers.[14,16]

Reviews by Voineskos et al. and Alderman et al. support the findings in these studies and conclude that careful consideration and information about the risks should be given to the patients.[22,23]

In addition to smoking, BMI constitutes a lifestyle factor and has been thoroughly examined in the literature. In the aforementioned study by McCarthy et al., BMI was found to be a significant risk factor for complications, with an OR of 6.9 for reconstructive failure in women with a BMI greater than 30 kg/m^2 as well as an increased risk in overall complications for this group.[14]

High BMI as a risk factor of complications is supported in reviews by Voineskos et al. as well as Alderman et al.[22,23]; the latter reported grade A evidence of BMI as a risk factor, meaning it is a strong recommendation to be taken into account based on the American Society of Plastic Surgeons Scale for Grading Recommendations.[22]

ABR is generally considered the alternative option for delayed reconstruction after PRT and is considered by many to be the golden standard due to its good aesthetic result and natural feel, with the deep inferior epigastric perforator (DIEP) flap being the first-choice flap in patients with a suitable donor site.[27] When comparing ABR to expander-based reconstruction, failure rates and complications must be compared with regard to radiation history.

In a recent meta-analysis based on 18 studies, Lee et al. found that in patients with previously irradiated breast areas, ABR alone as well as combined with an implant was associated with a 92% or 72% decreased risk of reconstruction failure compared to that in prosthetic-only based reconstructions without the supplement of a flap.[28]

Berry et al. found that PRT increased major complication rates from 21% to 45% in expander/implant reconstructions but did not affect the complication rate in ABR (18% vs. 21%).[29]

Previous studies report failure rates in ABRs with a DIEP flap to be 1–2%.[30,31] Although these studies do not investigate the isolated effect of PRT on the clinical outcome, a substantial number of the included patients had received radiotherapy, leaving a much higher chance for success than in the expander-based populations. These findings were supported by Jagsi et al., who found a failure rate of 19% in irradiated patients with implant-based reconstructions, compared to 1% in irradiated patients with ABR.[32] In addition, they found that patients undergoing ABR had greater satisfaction with the breast than patients undergoing implant-based reconstructions.

In addition, recent advances in enhanced recovery programmes for ABR allow a hospital stay of only 3 days for these procedures.[33] The advantages of ABR over expander-based reconstructions with regard to complications, as well as the comparable length of stay for ABR and expander-based reconstructions, should be considered when planning a breast reconstruction.

Conclusion

In patients undergoing delayed breast reconstruction using an expander/implant, PRT is a significant risk factor for loss of reconstruction. As 30% of patients are not able to complete this reconstructive process even though they represent a selected cohort evaluated to be the best possible cases for a positive outcome, PRT should be considered a relative contraindication for this reconstructive modality. We believe ABR should be the first choice for these patients. Careful advisement about the risks and potential need for additional corrective surgery or later ABR should be discussed if expander-based reconstructions are planned for these patients.

Conflict of interest

None.

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N/A.

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