Immediate post-mastectomy breast reconstruction followed by radiotherapy: risk factors for complications

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CLINICAL TRIAL

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Abstract The objective is to prospectively determine the factors responsible for reconstruction failure and capsular contracture in mastectomized breast cancer patients who underwent immediate two-stage breast reconstruction with a tissue expander and implant, followed by radiotherapy. This is a multicenter, prospective, non-randomized study. Between February 1998 and September 2006, we prospectively examined 141 consecutive patients, each of which received an implant after mastectomy, followed by chest wall radiotherapy at 46–50 Gy in 23–25 fractions. Radiotherapy was delivered during immediate post-mastectomy reconstruction. Patients were evaluated by both a radiation oncologist and a surgeon 24–36 months after treatment. The median follow-up duration was 37 months. According to Baker's classification, capsular contracture was grade 0, 1, or 2 in 67.5% of cases; it was grade 3 or 4 in 32.5% of cases. In total, 32 breast reconstruction failures required surgery. In univariate analysis, the following factors were associated with Baker grade 3 and 4 capsular contraction: adjuvant hormone therapy ($P = 0.02$), the surgeon ($P = 0.04$), and smoking ($P = 0.05$). Only one factor was significant in multivariate analysis: the surgeon ($P = 0.009$). Three factors were associated with immediate post-mastectomy breast reconstruction failure in multiple logistic regression analysis: T3 or T4 tumors ($P = 0.0005$), smoking ($P = 0.001$), and pN+ axillary status ($P = 0.004$). Patients with none, 1, 2, or all 3 factors have a probability of failure equal to 7, 15.7, 48.3, and 100%, respectively ($P = 3.6 \times 10^{-6}$). The model accurately predicts 80% of failures. Mastectomy, immediate reconstruction (expander followed by implant), and radiotherapy should be considered when conservative surgery is contraindicated. Three factors may be used to select patients likely to benefit from this technique with a low failure rate.

Keywords Mastectomy · Immediate reconstruction · Radiotherapy · Capsular contracture · Reconstruction failure

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Introduction

The relevance of post-mastectomy radiotherapy (RT) of the chest wall for breast cancer has been documented in large tumors and tumors with lymph node involvement on the axillary dissection site [21–23]. RT has been shown to increase local control and overall survival in these patients [23].

The use of immediate post-mastectomy reconstruction (IPMR) after breast cancer has markedly increased in recent years. Many patients select post-mastectomy reconstruction because it reduces the psychological and cosmetic impact of the mastectomy [12]. Furthermore, the cost of immediate reconstruction is lower than that of delayed reconstruction [14].

It is now recognized that IPMR is not associated with higher carcinogenic risks than delayed reconstruction, without retarding the implementation of adjuvant treatments [1, 31]. RT dose is not affected by the presence or absence of an expander, but the expander may complicate the RT technique [20].

Two reconstruction techniques are frequently performed. The first technique uses a myocutaneous flap, either from the *latissimus dorsi* or the *rectus abdominis* (transverse *rectus abdominis* myocutaneous [TRAM]) [3, 8]; the second uses a temporary expander placed in the retropectoral position, which is later replaced by a permanent implant (tissue expander/implant [TE/I]). The tissue is expanded using an inflatable expander and then replaced by an implant a while after treatment. Several research teams argue that the TE/I technique when used in conjunction with postoperative irradiation leads to more frequent complications and lesser cosmetic results than the TRAM technique [8, 13]. However, it should be noted that the TRAM technique is often contraindicated due to patient comorbidities, which creates a selection bias.

Many authors have reported that patients undergoing RT after breast reconstruction had an increased risk of complication in comparison with those undergoing reconstruction surgery without RT [3, 10, 13, 16, 18]. Yet, very few studies have established predictors of failure for either IPMR technique.

The main goal of our study was to further investigate predictors of IPMR failure with the TE/I technique followed by RT, in order to improve the selection of patients who may benefit from this technique.

Materials and methods

This was a prospective, multicenter, non-randomized study conducted between February 1998 and September 2006, including 141 patients who had undergone mastectomy for breast carcinoma followed by immediate breast reconstruction using the TE/I technique. The patients were operated on by eight surgeons from five different centers. The indications for mastectomy were tumor size, multifocality, unhealthy excision margins, or the association of an in situ and invasive carcinoma. Patients who had received conservative treatment were not included.

The standard technique consisted of modified radical mastectomy (MRM) of the entire breast tissue without areolar preservation, followed by placement of a tissue expander after detachment of the *pectoralis major* muscle. The MRM procedure was performed by a first surgeon, specialized in breast oncology, while the reconstruction part of the surgery was completed by a second surgeon, specialized in plastic surgery. There were no skin sparing mastectomies. After the intervention, the expander was inflated transcutaneously as quickly as possible every week, so as to rapidly reach the desired volume, when possible prior to irradiation.

During RT, the expander inflation was discontinued in order to maintain dose homogeneity throughout the treatment. Upon completion of the adjuvant treatments, the expander was replaced by a permanent implant, usually associated with areolar reconstruction or symmetrization surgery.

Radiotherapy treatment

The RT protocol uniformly delivered 46–50 Gy in 23–25 fractions over 5 weeks of treatment (2 Gy per day) using a conformational technique, after performing a dosimetric CT-scan. The dose was delivered to the ICRU point [7], with the reconstructed chest wall receiving 95–107% of the prescribed dose. No bolus was used. The irradiated areas were the homolateral chest wall, including the subclavicular and internal mammary lymph nodes to varying degrees. The definition of the areas to be irradiated was the responsibility of the radiation oncologist. The patients were treated using tangential 6–18 MV photon beams depending on dosimetry requirements.

Follow-up

The data pertaining to IPMR failure and patients' carcinogenic progression were retrieved from the medical files. Capsular contracture (CC) was assessed by both a surgeon and a radiation oncologist in a prospective fashion at 24–36 months after the initial surgery. At least one of them had been involved in the treatment of the patient. The cosmetic results were evaluated during the last consultation using a simple question: Are you satisfied with the cosmetic result of your IPMR? "Yes" and "no" were the only possible answers. On the same occasion, patients were

given a five-page quality of life questionnaire, the results of which will be reported in a separate publication.

Complications

IPMR failure was defined as the need for a second intervention consisting in ablation or replacement of the prosthesis. CC was graded according to Baker's modified classification [25], but for a better understanding, we called Baker 1a and 1b, respectively, grade 0 and grade 1 throughout the text. Acute complications were presented partly in a previous article [27], and as they often resolved quickly, they were not presented in this report.

Univariate statistical analysis

Any reconstruction failure requiring surgery was analyzed in relation to the patient characteristics and the treatment variables. The chi-square test was used to cross examine these variables. A value of $P < 0.05$ was considered statistically significant. Data were entered and processed statistically using the SEM software [17].

Multivariate statistical analysis

A multivariate analysis was conducted on the factors found significant in univariate analysis. Logistic regression was used to determine predictors of IPMR failure. The probability of IPMR failure was investigated using the predictors of failure discovered in univariate analysis.

Results

Patient characteristics

The characteristics of patients, tumors, and treatments are summarized in Table 1. The median patient age was 49.8 years (range: 25–75 years). Mean tumor size was 34 mm, and distribution of size across population was as follows: T1: 33%; T2 < 30 mm: 21.5%; T2 ≥ 30 mm: 22%; T3–T4: 23.5%. Of the 141 patients, 103 were non-smokers, 31 were smokers, and for seven patients this data were unavailable. Most patients (78%) were treated with neoadjuvant or adjuvant chemotherapy (CT), and 66% with adjuvant hormone therapy (HT). Of those treated with HT, 43% were prescribed tamoxifen, 15% anti-aromatase drugs, and 7% both in sequential order. The median delay between IPMR and RT was 4.2 months in patients with CT (range 1–17 months), and 1.9 months in patients without CT (range 0.8–4.2 months), ($P < 0.0001$). Half of the patients were postmenopausal at the beginning of their treatment ($n = 71$). The histological cancer type included

Table 1 Characteristics of patients, tumors, and treatments

Characteristics	n (%)
Median age (years)	49.8
Menopause	71 (50.3%)
Smoking	31 (23.1%)
Multifocality	74 (52.5%)
Resection performed	131 (91.6%)
pN+	77 (54.6%)
Histology	
Invasine ductal carcinoma	106 (74.7%)
Invasive lobular carcinoma	33 (23.2%)
Other	2 (1.4%)
Associated carcinoma in situ	80 (57.5%)
Tumor grade	
1	25 (18%)
2	78 (56.1%)
3	36 (25.6%)
Chemotherapy	110 (78%)
Neoadjuvant	25
Adjuvant	85
ER or PR >10%	100 (71.4%)
Hormone therapy	92 (66%)
Tamoxifen	61
Anti-aromatase	21
Tamoxifen then anti-aromatase	10

invasive ductal carcinoma in 74.7% of cases, invasive lobular carcinoma in 23.2% of cases, and a different histological type in 1.4% of cases. For 57.5% of cases, the cancer was in situ. The tumor was multifocal at diagnosis in 52.5% of cases. Regarding tumor grade, 18% were grade 1, 56% grade 2, and 26% grade 3. An axillary dissection was performed in 91.6% of patients, 54.6% of which presented with pN+.

In all cases where CT was indicated, RT was delivered after CT. The delay for permanent reconstruction depended on the type of adjuvant treatment (RT alone vs. RT + CT) ($P < 0.0001$).

Capsular contracture

Capsular contracture, classified according to Baker classification, was grade 0, 1, or 2 in 67.5% of cases, and grade 3 or 4 in 32.5% of cases (Table 2). Only five (3.5%) patients presented a severe grade 4 CC. In a univariate analysis, the factors associated with Baker 3 and 4 CC were: surgeon ($P = 0.04$), adjuvant HT ($P = 0.02$), and smoking ($P = 0.05$) (Table 3). In multivariate analysis, the association was significant for the surgeon ($P = 0.009$) only.

Table 2 Late complications after IPMR using the TE/I technique followed by radiotherapy

Complication types	n (%)
Failures	32 (22.7%)
Luxation	12 (8.5%)
Extrusion	7 (5.0%)
Infection	7 (5.0%)
Severe capsular contracture	6 (4.3%)
Capsular contracture according to Baker's classification	
Grade 0	35 (24.9%)
Grade 1	20 (14.2%)
Grade 2	40 (28.4%)
Grade 3	41 (29.0%)
Grade 4	5 (3.5%)

Table 3 Capsular contracture classified as Baker grade 3 and 4 (univariate analysis)

	P
Surgeon	0.04
Hormone therapy+	0.02
Smoking	0.05
Menopause	0.13
Chemotherapy	0.73
Multifocality	0.26
Associated carcinoma in situ	0.28
Mean size S	0.90
pN+	0.47
Mean delay between IPMR and start of radiotherapy	0.83

Reconstruction failure

IPMR failure defined as requiring exeresis or replacement surgery occurred in 32 patients (22.7% of cases). The events that led to failure were extrusion of the prosthesis in seven (5%), luxation in 12 (8.6%), infection in seven (5%), and severe CC in seven (4.3%) patients (Table 2).

In a univariate analysis, reconstruction failure was significantly linked to smoking ($P = 0.0009$), initial tumor size ($P = 0.000016$), and positive lymph node status ($P = 0.037$) (Table 4). Patients with an A or B breast cup-size had more failures than patients with a cup size of C, D, or E (35.9% vs. 16.7%, $P = 0.009$). However, cup-size was missing for 32 patients and therefore was not included in the multivariate analysis because of the risk of loosing other information. The mean delay between IPMR and the start of RT was not connected with failure ($P = 0.23$). Timing of placement of the permanent implant was not associated with failure. Grade 3 or 4 CC rates were not significantly correlated with higher failure rates ($P = 0.70$), neither were adjuvant nor neoadjuvant CT

Table 4 IPMR failures (univariate analysis)

	P
Surgeon	0.08
Hormone therapy	0.05
Cup size	*0.009*
Smoking	0.00091
Menopause	0.41
Chemotherapy	0.30
Multifocal tumor	0.93
Associated carcinoma in situ	0.33
Mean tumor size	0.000016
pN+	0.037
Baker grade 3 and 4	0.70
Mean delay between IPMR and start of radiotherapy	*0.23*

($P = 0.30$). The three positive factors established in the univariate analysis were included in the multivariate model. They were all linked to IPMR failure with relative risks (RR) of 6.1 (2.2–17) for T3 ($P = 0.0005$), RR = 5.9 (2–17) for smoker status ($P = 0.001$), and RR = 5 (1.7–15.5) for lymph node invasion ($P = 0.004$). The association of these three co-variables allowed for IPMR failure prediction, with varying relevance (Table 5): patients with none, 1, 2, or all 3 factors had a probability of failure equal to 7, 15.7, 48.3, and 100%, respectively ($P = 3.6 \times 10^{-6}$).

Patient status

After a median follow-up period of 37 months (range 10–107 months), 97 (68.9%) patients were alive and in complete remission, 21 (14.9%) had cancer recurrence in the form of metastases, 13 (9.2%) were lost to follow-up, 6 (4.3%) had died, and 4 (2.8%) had local recurrences.

Patient satisfaction

When questioned about the post-IPMR cosmetic result, 51 patients stated that they were satisfied with the results of IPMR, 72 were not satisfied, and 18 provided no answer. Among the patients who responded, the satisfaction rate

Table 5 Probability of IPMR failure according to the number of predictors (smoking, T3 or larger tumors, and pN+) ($P = 0.0000036$)

Failure yes/no	Risk factors (n)				
	0	1	2	3	
No	40	54	15	0	109
Yes	3	10	14	5	32
Total	43	64	29	5	141
Failure probability	7%	15.7%	48.3%	100%	

Table 6 Patient dissatisfaction (univariate analysis)

	P
Type of surgeon	0.000073
Hormone therapy	0.08
Smoking	0.54
Menopause	0.0006
Chemotherapy	0.38
Mean tumor size	0.07
Baker grade 3 and 4	0.05
Failure	0.40
Delay between IPMR and initiation of radiotherapy	0.57

was 41.4%. Patient insatisfaction was not the result of IPMR failure ($P = 0.40$), but was significantly related to the existence of grade 3 or grade 4 CC ($P = 0.05$). Patients who were not postmenopausal ($P = 0.0006$) were statistically less satisfied with IPMR. The satisfaction of each patient depended on the surgeon ($P = 0.000073$) (Table 6). The complete results of the QOL questionnaire will be reported separately.

Discussion

IPMR using the TE/I technique after breast cancer offers cosmetic and psychological advantages [12] for both the patient and the surgeon, with only a few contraindications.

Our study involved a sizeable and homogenous population of patients who underwent IPMR using the TE/I technique followed by RT. IPMR failure rate was 22.7%, with a median follow-up duration of 37 months. Higher failure rates were reported by other authors (Table 7). Chawla et al. [8] found a failure rate of 48% in 18 patients who underwent IPMR with the TE/I technique. These high rates may be due to a selection bias between the two reconstruction techniques, which were compared without any randomization.

In addition, the sample size was small. Furthermore, RT was at times performed prior to the mastectomy, resulting in an inhomogeneous patient population.

Performing the reconstruction after RT raises the risk of skin fibrosis, which renders tissue expansion more difficult, even in selected patients [15]. Krueger et al. [16] from University of Michigan reported a failure rate of 37% in 19 patients. In contrast, in larger patient populations, the reported failure rates when using the TE/I technique are in accordance with data obtained in our study [2, 13, 27].

Anderson et al. reported a 4% failure rate in their series involving 50 patients. Yet these results must be interpreted with great caution, as the follow-up period was much shorter compared to the other series (28 months). Additionally, Whitfield et al. noted a low failure rate (8%), although, in their study, RT fractionation was different (40 Gy in 15 fractions), comparable to that used in the British START trial [4]. In their series, Cordeiro et al. [10] reported an 11% failure rate in 81 patients. However, in this study, the treatment sequence differed, with irradiation delivered after the permanent implant was placed (4 weeks), while the implant was placed 4 weeks after the end of CT. Thus, the delay between surgery and RT was longer (at least 8 weeks after the end of CT). Although this delay may account to some extent for the low reconstruction failure rate, it could also jeopardize the carcinogenic efficacy of irradiation [19].

It should be noted that the failure rate we observed in our study is high, higher than that reported with the TRAM technique [8]. This high failure rate may be due to a patient selection bias, as patients with less comorbidities and sufficient intra-abdominal fat are often treated with the TRAM technique. The identification of risk factors of TE/I failure, however, may improve patient selection.

Capsular contraction after IPMR is a complication dreaded by surgeons as it has cosmetic consequences and may require re-intervention. In our series, the rate of grade 3 and 4 CCs was 32.5% (of which 3.5% were severe grade 4 CCs, which is in line with published literature). The fact

Table 7 IPMR failure with TE/I technique followed by external radiotherapy

Institution/first author	n	% failure	Median follow-up (months)
Fox Chase/Anderson [2]	50	4%	28
IPC/Tallet [27]	55	24%	25
Massachusetts/Chawla [8]	18	48%	32
Columbia/Ascherman [3]	27	18.5%	Not reported
University of Michigan/Krueger [16]	19	37%	31
Long Island/Jhaveri [13]	69	20%	38
Memorial/Cordeiro [10]	81	11%	34
Bordet/Vanderweyer [28]	6	100% complications Baker grade 3 and 4	64.5
Cambridge, UK/Whitfield [30]	41	8%	51
Present study	141	22.7%	36

that capsular contracture seemed associated with the surgeon needs to be explained. This finding was linked mainly to one of the surgeons involved in the mastectomies, but not with the plastic surgeon who usually did the reconstructions with him. This plastic surgeon also worked with other surgeons. The explanation given by the plastic surgeon was that this particular surgeon performed a more hemorrhagic surgery and did more injury to the underlying aponevrosis. This could have an influence on vascularization and needs to be confirmed in further studies.

Evidently, the rate of CC was related to patient satisfaction with the cosmetic results ($P = 0.05$), and not with the risk of failure ($P = 0.7$). Grade 3 and 4 CC rates were significantly related to the surgeon. Smoking tended to be associated with grade 3 and 4 CCs ($P = 0.05$), possibly due to the impact of tobacco on healing. The association with HT appears to be statistically significant, without any clear explanations. Nevertheless, CC remains difficult to assess, as illustrated by the high variance of data found in literature (17–68%) [12, 18, 24–26]. This may be explained by differences in patient follow-up: rate of CCs increases with increasing duration of follow-up [30]. Of note is that in our series patients were assessed by both a surgeon and a radiation oncologist, of which at least one was involved in the treatment of the patient, which may have resolved major differences in patient assessments.

Besides the IPMR technique used (TRAM or TE/I), which was found to be a predictor in most studies comparing both techniques [8, 16], no other predictor of IPMR failure when using TE/I technique was consistently reported by most authors (Table 8). Krueger et al. [16] identified tamoxifen as a significant risk factor; for Anderson et al. [2], the type of cutaneous bolus used was a risk factor; lastly, Tallet et al. [27] and Ascherman et al. [3] found CT to be a risk factor. In our study, no cutaneous bolus was

used, and CT was not found to be a significant prognosticator ($P = 0.3$).

We found three factors that were statistically linked to IPMR failure using the TE/I technique: smoking, T3–T4 tumors, and lymph node invasion. The effects of smoking on microvascularization may explain these results, as a similar relationship had already been observed for the TRAM reconstruction technique [6]. Initial tumor size and lymph node status were significant predictors, probably because of the extent of surgery in larger tumors. Unfortunately we could not go further in the analysis of the extent of lymph node dissection because the information was not reported prospectively in our database. One of the explanations of a high rate of failure could be the number of lymph nodes removed, and as to verify this, we will analyze the pathology reports in a retrospective approach and report the results later on. Histological data was not considered to be a risk factor of failure in the published literature, which requires further investigation. Breast cupsize could be an interesting result of this study, although unfortunately the information was missing in 32 patients. If one hypothesizes that larger expansion would be associated with more complications, large tumors in small breasts may require a larger skin sacrifice and therefore may be more difficult to expand. This should be investigated in further studies as well as the amount of expansion.

HT was associated with a higher failure rate, achieving borderline significance ($P = 0.05$). Other authors have observed this trend when considering complication rates [16] or cosmetic results [29]. The induction of transforming growth factor-beta (TGF-β), a peptide which modulates fibrosis by controlling cell proliferation, may be a possible explanation in patients receiving tamoxifen. Tamoxifen and RT were shown to be associated with TGF-β secretion [5, 9]. In our study, among the 92 patients who received

Table 8 Significant predictive factors of IPMR failure/complications with the TE/I technique followed by external radiotherapy (univariate analysis)

Institution/first author	Variable	Failure/complication	P
Fox Chase/Anderson [2]	Bolus type	Major complications	0.05
IPC/Tallet [27]	Chemotherapy	Failure	0.04
	Smoking	Failure	0.01
Massachusetts/Chawla [8]	IPMR type	Failure	<0.01
Columbia/Ascherman [3]	Chemotherapy	All complications	<0.01
University of Michigan/Krueger [16]	Tamoxifen	Failure	0.03
Long Island/Jhaveri [13]	IPMR type	Failure	0.007
Memorial/Cordeiro [10]	Not tested	Not tested	Not tested
Bordet/Vanderweyer [28]	Not tested	Not tested	Not tested
Present study	Smoking	Failure	0.0009
	Tumor size	Failure	0.0000016
	pN+	Failure	0.037

HT, 61 were prescribed tamoxifen, whereas only 21 were treated with anti-aromatase drugs (10 in sequential treatment). The current routine use of anti-aromatase drugs as adjuvants in postmenopausal women may decrease the relevance of this observation [11].

IPMR failures were linked to local recurrences in only four cases. The procedure appears to be more complex in the case of a larger tumor mass. In fact, in large tumors, obtaining healthy margins requires the resection of a large portion of skin. Consequently, skin expansion becomes more complex, possibly leading to complications and failures.

Our study results allowed us to create a mathematical model aimed at predicting the probability of IPMR failure. According to our model, in the absence of all three identified predictors, the probability of IPMR failure is 7%; with one factor, it is 15.7%; with two factors, it is 48.3%; with three factors, it is 100%. No other authors reported similar results, likely due to insufficient sample sizes.

This model may be useful in common clinical practice prior to proposing IPMR to patients. However, there is the problem of preoperative assessment of tumor size and lymph node status, because their determination prior to the operation is difficult. When IPMR associated with RT is considered, it may be useful to accurately determine tumor size before the procedure. Preoperative assessment of lymph nodes with ultrasound-guided biopsies needs further investigation as well as the extent of lymph node dissection.

Many authors have questioned the treatment sequence and the role of RT. Some have suggested that RT prior to IPMR would improve the complication rates [26], while others stated the opposite [10]. In our study, all of the patients underwent RT after the expander was placed. RT has proved to be effective on carcinologic results when delivered after surgery.

Patient satisfaction is a difficult criterion to assess because it is subjective, and the response to a simple question may result in a low satisfaction rate, which has previously been described [8, 10, 27]. In addition, our series did not include a control group, for example, women who underwent mastectomy for intraductal carcinoma without requiring RT. Understandably, lower satisfaction was found in patients with grade 3 or 4 CC. The patients' perception of the cosmetic result of their IPMR is a subjective factor which fluctuates with time, and the longer the follow-up period, the more reliable the outcome becomes. The IPMR insatisfaction rate in young non-postmenopausal patients may be due to the importance they attach to their appearance, in comparison to postmenopausal patients. The control of technical expertise remains a major factor, both in regard to CC rates and patient satisfaction. Patient dissatisfaction was part of a much larger quality of life study

which is still under analysis. We cannot give a proper analysis of this dissatisfaction before all the data are investigated. The complete data will be reported separately.

Conclusion

Our study identified three predictors of IPMR failure using the TE/I technique followed by RT: smoking, T3 or T4 tumors, and axillary lymph node invasion. Two of these factors are related to histological data. Based on these three factors, we created a predictive probability model of IPMR failure with the TE/I technique. In common practice, this model may be useful when proposing the aforementioned treatment to patients scheduled to undergo mastectomy. It could potentially help the patient and surgeon with regards to the usefulness of performing IPMR with the TE/I technique. A preoperative imaging assessment of tumor size is usually required, and some information on the axillary status of the patient could help in the decision of associating IPMR with radiotherapy.

Conflict of interest None.

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