Surgical risk factors of breast reconstruction and their clinical implications
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Breast conserving therapy in patients with a relatively large (T2, T3) breast cancer: Long-term local control and cosmetic outcome of a feasibility study

Based on:
Plast Reconstr Surg 2004; 113: 1607-1616
Chapter 2

Introduction

Since the late 1980's, breast conserving therapy (BCT) is widely accepted as an oncologically\textsuperscript{1,2} and psychologically\textsuperscript{3} appropriate method of primary treatment of T1 and T2 breast cancers that measure up to 5 cm. Even though large tumor size alone is not considered a contraindication for BCT in terms of local tumor control,\textsuperscript{4,5} this size plays a main role in the feasibility of BCT in terms of cosmetic results.\textsuperscript{6-8} The volume reduction associated with tumorectomy including a macroscopically tumor-free margin of approximately 1 cm is too large in some cases of T2, and in almost all cases of T3 breast cancers\textsuperscript{9}. For safe and cosmetically acceptable BCT in these cases, tumor volume has to be reduced preoperatively and lost tissue volume ought to be replaced after wide local excision.

In 1993, our group reported on the feasibility of combining preoperative radiotherapy, breast conserving surgery, and immediate tissue replacement by myo(sub)cutaneous latissimus dorsi flap transplantation in 6 patients with relatively large T2 and T3 breast cancers.\textsuperscript{5} The preliminary results of that phase-2 study were encouraging with respect to treatment toxicity and cosmetic outcome. Although the clinical tumor response after radiotherapy was difficult to evaluate, no tumor recurrences had occurred in the breast after a minimum follow-up of over 2.5 years. It was concluded that these results supported continuation of the study but that the safety of technique with regard to tumor control had to be regarded in particular. To evaluate the long-term local tumor control and cosmetic outcome we studied the results obtained in the first 20 patients after a minimum follow-up of 5 years. Oncologic safety was evaluated by means of number of loco-regional recurrences or distant metastasis, observed 5-year survival, and actuarial 10-year survival. The cosmetic outcome was evaluated by means of patients' and observers' assessment of six criteria contributing to the cosmesis of the reconstructed breast. Furthermore, the influence of each of these criteria and the latissimus dorsi donor scar on the over-all assessment of the procedure was evaluated.
Material and Methods

Patients
The inclusion and exclusion criteria for this study have been reported previously. In short, patients with cytologically confirmed T2 breast cancer previously not amenable for BCT because of relative tumor size, and those with a T3 tumor were candidates for our prospective study. Limited clinical axillary node involvement was no exclusion criterion but a negative axillary apex biopsy taken under local anaesthesia was felt required to select patients with a relatively good prognosis. There were no restrictions with regard to the site of the primary tumor in the breast. Metastatic disease was excluded by history, physical examination, chest X-ray, and blood chemistry results. Additional bone scans or liver sonography were performed when indicated. The study was approved by the Medical Ethical Committee and patients were included in the study after informed consent had been obtained.

From March 1988 through February 1996, 20 patients with a mean age of 49 years (range, 32 - 65 yr) entered the study (Table 1). Twelve patients had a T3 tumor and eight, a T2 tumor. Mean tumor size was 4.8 cm (range, 2.0 - 6.5 cm). Eleven patients had palpable axillary nodes whereas the remaining patients were considered clinically node-negative. All 20 patients completed radiation therapy and surgical procedures according to the protocol.

Therapy and follow-up
Preoperative radiotherapy
Prior to radiotherapy, the extent of the breast tumor was outlined by skin tattoos. The patients were treated by whole breast irradiation using a tangential opposing field technique with a total dose at the isocenter of 50 Gy in 25 daily fractions, and an intralaesional boost using an iridium wire implant technique. In the first 4 patients the dose of this boost was 15 Gy. Because the surgical breast specimen histologically proved to contain tumor in 2 of the first 4 patients, the dose in the remaining 16 patients was increased to 25 Gy (Table 1). All patients underwent internal mammary lymph node irradiation of 50 Gy in 25 daily fractions. The axilla was not irradiated. During radiotherapy, no tumor progression occurred in the breast or regional lymph nodes of all 20 patients. In all patients but one, radiotherapy resulted in reduction of the primary breast tumor.
Table 1: Characteristics of the 20 patients and their breast cancers

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Pt: patient; MP: pre- or postmenopausal; Size: size of bra cup; TS: preoperatively estimated size of tumor; T: tumor stage; N: lymph node stage; Boost: preoperative iridium boost; TW: weight of excisional specimen (NA: data not available); Hist: histologic type of tumor (poor: poorly differentiated; duct: ductal carcinoma, lobul: lobular carcinoma); Margins: histologic complete (compl) or incomplete (incom) resection; CT: adjuvant postoperative chemotherapy (cmf: cyclophosphamide / methotrexate / 5-fluorouracil; tam: tamoxifen; decl: declined by patient); FU: follow-up. Status: patient alive, died of disease (DOD), or died of other causes (DOOC).

Surgical treatment

Surgery was performed 3 to 4 weeks after iridium implantation and consisted of excision of the original tumor site marked by the tattoos with a minimal additional margin of 1 cm. The skin overlying the tumor was included in 2 patients. The mean mass of the 10 weighted surgical specimen was 135 g (range, 70 - 220 g). All specimen were inked to be microscopically evaluated for completeness of tumor excision. Levels I and II lymph node dissection was performed through a separate horizontal axillary incision as level III had already been proven negative by the axillary apex biopsy prior to radiotherapy. Immediate volume replacement was obtained by transplantation of the ipsilateral latissimus dorsi flap. The location of the flap's skin island was chosen...
based on tumor location and necessary pedicle length, and the size of the muscle flap and overlying skin island were designed in accordance with the breast volume to be replaced. Depending on the extent of skin excision at the tumor site the skin island was deepithelialized (n = 16), or not (n = 3). In one patient, the muscle flap was transplanted without a skin island. All flaps were tunneled subcutaneously and sutured over vacuum drains, using absorbable material.

**Histopathologic outcome, adjuvant therapy, and oncologic follow-up**

Macroscopic examination of the tumorectomy specimen showed no signs of cancer in 4 patients but, microscopically, malignancy was found in all breast specimens. Ductal carcinoma was diagnosed in 13 patients and lobular carcinoma in one (Table 1). Histology could not be defined in the 6 remaining patients because of the effects of radiotherapy. These 6 malignancies were referred to as 'poorly differentiated'. Five patients had positive resection margins and in 1 patient the completeness of excision could not be clearly assessed. The axillary lymph nodes were routinely examined for lymph node metastases and these were found in 8 patients. In three, the metastases extended extracapsularly.

Eleven patients had adjuvant therapy. Four of these 11 patients were premenopausal and they were treated with six cycles of cyclophosphamide / methotrexate / 5-fluorouracil (CMF) chemotherapy, whereas the seven postmenopausal patients were prescribed tamoxifen, 30 mg daily, for at least 2 years. One premenopausal patient and 1 postmenopausal patient received both adjuvant therapies, whereas another premenopausal patient was treated by a combination of CMF, tamoxifen, and axillary radiotherapy (Table 1). One additional premenopausal patient declined from adjuvant chemotherapy in spite of axillary lymph node metastasis. Patients were seen at the out-patient clinic every 3 months, and mammography was performed every year.

**Cosmetic assessment**

After a mean follow-up of 5 years (range, 2 - 9 years), 13 of the 14 then surviving patients were available for evaluation of the long-term cosmetic outcome at the out-patient clinic. The one remaining patient refused cooperation in this study.

Cosmetic assessment consisted of three parts: a questionnaire to be filled out by the patient, clinical examination by a plastic surgeon (LAEW) and a plastic
surgical resident (ET), and photographic assessment by a panel. The panel consisted of 6 plastic surgeons, 6 plastic surgical residents, and 2 medical students. For each of these 3 sub-assessments, an array of criteria providing a detailed description of the cosmesis of the reconstructed breast and donor area were evaluated, including symmetry, consistence, aspect of the skin, aspect of the nipple, shape of the breast, and appearance of the donor scar on the back. Finally, the over-all cosmetic outcome was evaluated.

The subjective questionnaire included a 3-level scale for judgement of each of the 6 criteria and the over-all outcome, ranging from 1 for a very poor result, to 3 for an excellent result.\textsuperscript{10} The same 6 criteria were assessed on a 3-level scale at examination by the two clinicians.

For panel assessment, 12 of the 13 patients were photographed in three standardized directions. The thirteenth patient was seen for cosmetic follow-up only after the panel had gathered. Four slides were projected of each patient: the frontal view of the patient, the left and the right sided profile, and the dorsal view showing the donor scar (Fig 1 and 2). For the slides of each patient, each

\textbf{Figure 1:} The postoperative results were photographed in four directions and these slides were assessed by a panel. Optimal cosmetic outcome of therapy as observed in patient 1.
of the 14 members of this panel filled out a questionnaire featuring all criteria except 'consistency', as this can not be judged on a photograph. Rather, the scar on the breast was scored. Before the actual procedure was started, the panel was given an impression of the questionnaire to be filled out by viewing and judging a result in an extra patient.

Statistical evaluation of cosmetic assessment

To evaluate which of the 6 criteria had the strongest influence on predicting the panel's mean score for 'over-all cosmetic outcome', all criteria and the over-all outcome were assessed by scoring on a scale from 1 to 10. The rank correlation of each possible pair of criteria and over-all outcome was tested by means of the Spearman correlation coefficient analysis. This correlation coefficient (corr.coef.) takes values between 0 and 1, a coefficient of 0 indicating no agreement at all, and a coefficient of 1 meaning that the criteria are fully synchronous. It was accepted that the rank correlation of the Spearman coefficient was used for this rather than the weighted kappa, or upsilon, provided the

Figure 2: Poor cosmetic outcome of therapy as observed in patient 6.
scores for each criterion and the over-all outcome were ordered and the scores of each pair of panelists had approximately the same mean and standard deviation. We graphically verified the linear relation between each possible pair of criteria and 'over-all outcome'.

Figure 3: Kaplan Meier curve of survival of the 20 patients. X-s indicate the postoperative follow-up of the 12 survivors to date. † indicates that patient 19 died of non-hodgkin lymphoma, 51 months after BCT.

Results

Local control

Since BCT, 7 patients have died as a result of metastasis from breast cancer and 1 patient from non-hodgkin lymphoma a mean of 60 months after surgery (range, 37 - 104 months). The actual 5-year survival rate was 0.75 (Fig 3). Although the follow-up of 5 of the 12 survivors is still less than 10 years (range of follow-up in these 5 patients, 80 to 168 months), the actuarial 10-year survival rate is 0.60. The one patient who had refused adjuvant chemotherapy was the only patient in this series to have a loco-regional recurrence. Hence, both the actual 5-year, and actuarial 10-year local control rate is 0.95.
Breast conserving therapy for T2T3 breast tumors

We did not find any correlation between histopathologic type of the tumor or microscopic completeness of resection, and the occurrence of metastases. Multi-variance analysis of additional characteristics of the patients (Table 1) showed that these, too, were not correlated with survival.

Cosmesis and statistical evaluation of cosmetic assessment

Patients’ assessment of cosmetic outcome
The average score for the subjective over-all cosmetic outcome by the 13 patients was 2.8 out of 3 (range, 1 - 3; sd, 0.58). Only one patient scored the over-all result as being poor because she felt that her breasts were asymmetrical. Moreover, her breast and nipple were retracted and the overlying skin showed changes induced by the iridium implant.

The scores given by the patients to ‘shape of the breast’ tended to correlate best with their over-all score, whereas that of the ‘scar on the back’ tended to correlate negatively with the over-all score.

Clinicians’ assessment of cosmetic outcome
The average score for the clinical over-all cosmetic outcome of treatment was 2.66 out of 3 (range, 1 - 3; sd, 0.67). The clinicians’ over-all scores correlated with the subjective over-all scores by the patients (Fig 4). Again, the over-all score tended to correlate best with that of ‘shape of breast’ and worst with that of the ‘scar on the back’.

Panelists’ photographic assessment of cosmetic outcome
No statistically significant difference was found between the scores by the specialist-members, resident-members, and student-members of the panel (p = 0.05). Hence, we averaged the scores of all panelists for each of the criteria in each of the patients. In 10 of the 12 patients scored by the panel, the panelists’ mean score for the over-all cosmetic outcome of the breast reconstruction was 6 out of 10 and over (mean over-all score, 6.3; range, 4.4 - 8.1; sd, 1.59) (Fig 4). As was true for the clinicians’ ratings, the panelists’ over-all scores correlated with those of the patients (Fig 4) even though the relative mean over-all score was lower than that of the patients (6.3 out of 10 vs. 2.8 out of 3). We found a high correlation between the 2 clinicians and 14 panelists for the mean over-all score in each patient (Fig 4). The panelists’ scores of most pairs of the criteria were strongly correlated (with the corr.coef. taking values between 0.58 and 0.79), with the exception of the donor ‘scar on the back’ (corr.coef.: 0.00 - 0.20) (Table 2). The criterion ‘scar on the back’ hardly had any influence on the
panelists' over-all rating (corr.coef.: 0.14), whereas the criteria 'shape of breast' (corr.coef.: 0.89) and 'symmetry of breasts' (corr.coef.: 0.87) had. The scatter plots confirmed the linearity of correlation between 'over-all outcome' and each of the 6 criteria with the exception of 'scar on the back'.

![Scatter plot](image)

**Figure 4**: Scores for over-all cosmetic outcome in each patient as scored by the patient (X-s), compared to the average over-all score by the 2 clinicians (circles) and the panelists (stars).

**Table 2**: Correlation coefficients for each possible pair of criteria as scored by all panel members

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Breast conserving therapy for T2T3 breast tumors

Discussion

Conventional breast conserving therapy by wide local excision and radiotherapy provides good cancer control in a majority of patients with relatively small T2 breast cancers. The increasing acceptance of such combined treatment resulted in the cosmetic appearance of the treated breast to become an essential point of interest. The cosmetic outcome of BCT may further be optimized as long as the local control is not compromised. Localization, length, and orientation of the scar and the volume of resected tissue are among the surgical factors to influence this cosmetic outcome. Likewise, radiation technique plays an important role, and an increase of external beam dose has been associated with more fibrosis and retraction of the irradiated breast. Additional internal irridium implant irradiation may decrease the external beam dose and, hence, the disfigurement of the breast. Moreover, the indications for BCT may be extended to include even larger breast tumors as long as local control is not compromised. In the series presented herein we showed that good long-term local control and cosmetic outcome could be obtained by up-front high-dose radiotherapy, breast conserving surgery, and direct autologous reconstruction in patients with relatively large tumors. Initially, the involvement of surgical margins found in 6 patients raised questions about possible risks of local tumor recurrence. Still, although cancer cells were seen in the surgical specimen of all patients and the margins were involved in 6 out of 20 specimen, breast relapse was observed after 35 months in only 1 patients. In our opinion, this adequately proves that it is unnecessary to defer the reconstruction long enough to allow the margin status to be evaluated. Apparently, the cancer cells found 4 weeks after radiotherapy are inadequate to produce viable offspring. Both the breast relapse rate and the survival rate observed in our series equals that of more radical surgical therapy of T2 and T3 breast cancers, we consider our treatment modality as oncologically safe. Still, did we prove it to also be cosmetically rewarding? To date, no consensus exists on how to assess the cosmetic result following breast conserving therapy. Ideally, such a method should detect relevant changes in breast appearance in an unambiguous way, making comparison of results possible between different treatment modalities and different treatment centers. Methods used to assess these results range from fairly objective, such as the quantitative measurement of the breast and nipple retraction,
to rather subjective, such as grading the results as either satisfactory or non-satisfactory without using strict criteria.\textsuperscript{6,8,10,18,19} The influence of the effects of treatment on the overall cosmetic outcome is yet to be fully defined and the optimal method of obtaining these measurements remains difficult. In previous studies, most authors scored cosmetic outcome in one out of 4 categories 'excellent', 'good', 'fair', and 'poor' but the reproducibility of this method varied between centers, whereas intra-observer consensus was rarely obtained.\textsuperscript{6,20} Previous procedures to assess the results of breast reconstruction have relied mainly on the subjective evaluation using a three-, four-, or five-point scale to assess standardized photographs.\textsuperscript{5,10,13,19} Inter-observer agreement was rather low in these studies and, as a result, only the average score could be used to analyze the impact of specific patient-, tumor-, and treatment-related factors on the cosmetic outcome, or to analyze the correlation of assessment results with other methods of cosmetic evaluation.

Digitizer evaluation seemed more accurate than panel evaluation in terms of intra-, and inter-observer variability and has been advocated as a more objective method of assessment.\textsuperscript{12,14} Although this is an easy and quick method to evaluate large numbers of patients in multi-center trials, it lacks the detection of disturbing scars and skin changes.\textsuperscript{14,16} As such, van Limbergen et al.\textsuperscript{12,13} concluded that digitized assessment of the breast retraction correlated less with the panel scoring in cases where the tumor was located in the medio-inferior quadrant of the breast. Since the cosmetic outcome is highly influenced by a disturbance in this location of the breast, this is a serious shortcoming of digitized assessment. Rather than for the computer, the cosmetic result of breast reconstruction ought to appear as normal as possible in the eye of the patient. Even though such a "subjective evaluation of the breast reconstruction is imperfect, it is all we have and we have to live with it"\textsuperscript{12,21}

Our questionnaire featured a number of criteria felt to contribute to the possible disfiguring effect of therapy. Each criterion may affect the over-all outcome in a different way. The shape of the reconstructed breast and its symmetry to the contralateral native breast were more influential on the quantitative assessment of over-all cosmetic result than the other criteria. Acceptance of the mean of all panelists' scores of the different criteria as independent parameters in a multiple linear regression model yielded an $R^2$ value of 0.88. This $R^2$ statistic is a measure of the 'goodness of fit' of the model (i.e. how much of the observed variation in 'over-all outcome' can be explained by our model) and an $R^2$ value
of 0.88 indicates that variation in the scores for the 6 independent criteria accounted for as much as 88% of the variation in the score for 'over-all outcome'. Hence, 12 percent of reconstructed breast disfigurement remains unexplained in our model. The percentual contribution of the respective criteria to 'over-all outcome' varies from 0.4% for 'aspect of the nipple' to 30% and 42% for 'symmetry' and 'shape' of the breast, respectively (Table 3). The latter 2 criteria were most important to influence the impression of the over-all cosmetic result and stepwise repetition of the analysis for the criteria 'shape' and 'symmetry' yields that the 88% consists of 52% for 'shape' and 36% for 'symmetry'. Still, such multivariate analysis is statistically insignificant as it is not realistic to run a regression analysis with 6 predictor variables with only 13 observations (so-called 'overfitting' of the model).

Table 3: Regression coefficients (RC) and percentage contribution (%) of each of the six criteria to the over-all outcome as scored by all panel members

<table>
<thead>
<tr>
<th>Criteria</th>
<th>RC</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symmetry</td>
<td>0.346</td>
<td>30.6</td>
</tr>
<tr>
<td>Shape</td>
<td>0.477</td>
<td>42.1</td>
</tr>
<tr>
<td>Skin</td>
<td>0.043</td>
<td>3.8</td>
</tr>
<tr>
<td>Nipple</td>
<td>0.004</td>
<td>0.4</td>
</tr>
<tr>
<td>Scar breast</td>
<td>0.088</td>
<td>7.9</td>
</tr>
<tr>
<td>Scar back</td>
<td>-0.036</td>
<td>3.2</td>
</tr>
<tr>
<td>Unexplained</td>
<td></td>
<td>12.0</td>
</tr>
</tbody>
</table>

Our observation of the importance of the symmetry and shape is in accordance with previous studies which demonstrated that quantitative measurements of asymmetry of breasts and nipple retraction correlate with subjective assessment of cosmetic outcome of BCT.13,16 Fair to good agreement was observed among the specialist-panelists, resident-panelists, and student-panelists on all criteria of the questionnaire. As the clinicians' over-all score for each patient correlated highly with that of the panelists (Fig 4), we consider the judgement of 2 clinicians representative of that of a larger group of specialists, residents, and students.

As this was a study on the feasibility of a modality of treatment, the patients were not randomized over 2 or more modalities to compare outcome. Moreover we found a highly skewed distribution of the patient's and clinician's scores and these data cannot be considered to be normally distributed. Still, the subjective
assessment of our technique compares to that of conventional BCT modalities for smaller T1 or T2 breast cancers. Even though the studies on cosmetic outcome of such treatment differed in regard of end terms and length of postoperative period before evaluation, these studies showed 66 – 96% of patients to be satisfied with the result of treatment.\textsuperscript{6,8,12,13,15} Our patients were predominately positive about the result and all appreciated to have kept their breast regardless of the cosmetic outcome. To retain their breast seems to be of more importance to women who prefer breast conserving therapy than its obvious difference in shape and size from the contralateral breast.\textsuperscript{19} Moreover, patients hardly seem to care about the additional scar on the back. Like others, we found the patients to score the over-all cosmetic outcome of treatment more favorably than physicians do.\textsuperscript{16,19,22} This might reflect the patients’ reluctance to report possible dissatisfaction in presence of the attending surgeon.\textsuperscript{14} Still, we used a questionnaire to try and overcome this bias and, moreover, the 2 clinicians who cosmetically assessed all patients had not been involved in the patients treatment. Alternatively, the favorable scores may reflect it being more convenient for the patient to accept and respect the cosmetic outcome as it is. Because the tissues that had been most intensively irradiated were excised and replaced by well vascularized tissues, late radiation-related side-effects were less when compared with the conventional technique. Clinically, moreover, we observed a remarkable absence of lymphedema of the arm. For these reasons, we consider our method of treatment of these relatively large tumors to also be cosmetically rewarding. It may be concerning that chemotherapy for patients with large tumors, many of whom are clinically node positive, is delayed until after radiotherapy and surgery. These women are at risk both for local failure and, more importantly, systemic disease. It seems hard to justify this approach when neoadjuvant chemotherapy has been used to good effect in the same setting and has the significant advantage of addressing the risk of systemic disease. Currently, patients with invasive breast cancers that are considered too large for BCT are offered up-front chemotherapy. The remission rate of such chemotherapy is about 0.80 with 0.10 histologically complete remissions.\textsuperscript{23,24} BCT can be performed in 40 to 60% of these patients and results in good local control rates. As holds true for larger tumors treated by preoperative radiotherapy, however, tumor regression is insufficient to allow for cosmetically rewarding BCT in part of these patients. In these patients alike, the combined protocol presented by us
may very well be offered as an alternative treatment modality. The major drawback of our treatment protocol was of a logistic nature. Combining preoperative radiotherapy, ablative surgery, and immediate reconstructive surgery in the tight time schedule requires a closely cooperating multidisciplinary team willing and able to carefully plan each treatment step. When jointly tuned, however, exposure of the thoracodorsal pedicle as a result of the axillary lymph node dissection enhances the immediate transposition of the latissimus dorsi flap.

We conclude that breast conserving therapy combining preoperative irradiation and immediate myo(sub)cutaneous latissimus dorsi flap reconstruction after wide local excision is an oncologically safe and cosmetically rewarding, but logistically straining treatment modality for patients with relatively large T2, and T3 breast cancers.

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Chapter 2

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Breast conserving therapy for T2T3 breast tumors


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