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## Clinical results and patient-reported outcomes in breast reconstructive surgery

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# General discussion and future perspectives

As 1 out of 8 women will develop breast cancer, the impact of this devastating disease is enormous.<sup>1,2</sup> Luckily, advances in breast cancer care led to high survival rates which made focus shift towards improving the quality of life (QOL), patient satisfaction and aesthetic outcome during breast conserving- and reconstructive surgery. Breast reconstruction plays a major role after (prophylactic) breast cancer treatment. New reconstruction techniques continue to be developed with the ultimate goal of selecting the most optimal reconstruction technique for each woman on a case-by-case basis. In order to choose an optimal technique for breast reconstruction, one should be able to weigh the benefits for the individual patient against the risks of adverse outcomes and associated costs.

## IMPLANT-BASED BREAST RECONSTRUCTION

### Safety of the procedure

Today, autologous tissue, implants or a combination of both are used for breast reconstruction. Implant-based breast reconstruction (IBBR) is still the most performed reconstruction technique.<sup>3</sup> It offers several advantages, including a short operation and recovery time without donor site morbidity.<sup>4</sup> It is still under debate if it is advantageous to place a definitive implant immediately, i.e. to reconstruct in one-stage, or to first place a tissue expander and exchange it for a definitive implant during a second procedure. Surgeons usually either support the conventional two-stage reconstruction technique or believe in one-stage reconstruction.

In IBBR, adverse events are mainly caused by wound healing problems, including skin necrosis, wound dehiscence, and wound infection. In general, it is assumed that decreased tissue perfusion is a causative factor in these wound healing problems. Depending on the extent and the management of the complication, the complication may be resolved or implant removal is necessary. It is hypothesized that adverse outcomes after IBBR are a

consequence of poor skin flap perfusion, which in turn causes impaired wound healing. This line of thought finds a broad consensus within the field of breast reconstructive surgery.<sup>5</sup> However, this hypothesis is hard to objectify, since objective measures of intraoperative skin flap quality or perfusion are still being developed. In this thesis, we added to the circumstantial evidence, however, an objective method to assess the quality of the skin flap intra operatively was not used and the importance of skin flap quality in adverse outcome should be further explored.

In the last decennium, the additional use of an acellular dermal matrix (ADM) has become popular. However, its use remains controversial. An ADM can be used in the one-stage as well as in the two-stage procedure. They enable greater intra- and postoperative expander filling in a two-stage reconstruction or a larger definitive implant volume in direct-to-implant. Moreover, the use of an ADM has been suggested to give superior aesthetic results and to cause less postoperative pain by reduced traction on the pectoralis muscle. However, these advantages have yet to be proven.<sup>6</sup> Furthermore, the safety of IBBR and the use of ADMs is still under debate. Several studies, including the results in this thesis, show a high complication rate after this reconstruction method, even requiring implant removal.<sup>6</sup> We should therefore conclude that its use should be limited and performed on a case-by-case basis. The one-stage IBBR with ADM reconstruction should not be considered a 'one-and-done' approach.<sup>7</sup> We do not propose to eliminate the use of an ADM entirely, but the indication should be based on balanced judgement and its use should not be incorporated as standard care. We learned that one-stage IBBR with ADM is a delicate procedure and the conventional two-stage IBBR is a more forgiving procedure with regards to the safety. Currently, two-stage IBBR is justifiably the standard reconstruction method in implant-based breast reconstruction. One-stage IBBR should only be performed in patients with small to moderate sized breasts. Patients should also be informed about the possibility to convert to a two-stage procedure, when the surgeon questions the mastectomy skin flap quality.

Furthermore, the definitive role of an ADM in breast reconstruction is still unclear. In this thesis, two different techniques were compared (one-stage IBBR with ADM vs two-stage IBBR without ADM) and the independent effect of the ADM could not be established. Woerdeman et al investigated one-stage IBBR without the use of an ADM and also reported

a higher complication rate of 33%, leading to removal of the implant in 18% of the reconstructions (20% of the patients).<sup>8</sup> There is a high demand for a prospective trial comparing one-stage IBBR with and without ADM. The study design could be a non-randomised set-up, using propensity score matching.<sup>9</sup> This allows surgeons to use the reconstruction technique that they are most familiar with. Furthermore, it may lower barriers to participate in the trial, because patients do not need to be randomised for their treatment.

Previously, authors suggested that the experience and expertise of the surgeon are also important and state that a learning curve is present when performing breast reconstructions with implants, in particular one-stage IBBR with ADM.<sup>10-12</sup> Colwell et al reported a higher total complication rate in the surgeons' first-year experience (21.4%) compared with the 10.9% in the subsequent years, due to accurate determination of the viability of the mastectomy skin flap.<sup>10</sup> Reported surgical techniques that may improve the skin flap quality are careful tissue handling and avoiding tension during closure.<sup>13</sup> It is beyond dispute that the experience of the surgeon contributes to the outcome of the reconstruction. However, when incorporating a new technique, safety is one of the primary concerns. It is debatable if a reconstruction technique should be offered to patients, if outcomes of the reconstruction method depend that much on a surgeons' experience. Two-stage reconstruction seems a safer choice when performing IBBR. If there is any doubt regarding the mastectomy skin flap quality during surgery, surgeons should easily convert to a two-stage reconstruction by placing an expander instead of the definitive implant. Surgeons that are highly experienced with the technique reporting on single center studies show lower complication rates (< 5%) and removal of implant (1.3%).<sup>14, 15</sup> This indicates that the experience of the surgeons may contribute to the occurrence and management of complications, by either different surgical techniques or better patient selection.

In this thesis mastectomy weight was a significant predictor of adverse outcomes, which indicates that larger breast size is definitely a risk factor for one-step procedures. It is therefore recommended to perform one-stage IBBR with an ADM preferably only in patients with small to moderate sized breasts.<sup>16</sup> However, more research is necessary to identify other factors and to determine the precise role of complication management in implant-based breast reconstruction.

## Quality of life and aesthetic outcome

The main aim of breast reconstruction is to improve the QOL of women who need to undergo mastectomy. In order to assess QOL, questionnaires assessing Patient Reported Outcome Measures (PROMs) were developed. There are many different questionnaires available. PROMs are either generic, such as the EuroQol Group 5-D Instrument (EQ-5D)<sup>17</sup>, or treatment specific, which in the field of breast surgery mainly concerns the BREAST-Q.<sup>18</sup> The BREAST-Q was developed in 2009 to evaluate both QOL as well as patient satisfaction after breast reconstructive surgery. To date, procedure-specific questionnaires are available for the evaluation of a mastectomy only, breast reduction/mastopexy, breast augmentation, breast conserving therapy, and breast reconstruction with implants or with autologous tissue. PROMs are increasingly used to evaluate a treatment's efficacy, not only in clinical trials but in some clinics also in daily practice<sup>19</sup>. The use of PROMs can help detect emotional distress or insufficient supportive care. Implementation of PROMs also improves communication about symptoms and QOL. PROMs not only provide valuable insights into results for both patients and clinicians, but can also be used as a quality indicator to compare individual and institutional performance and thereby improve health care outcomes. However, there are still a number of barriers, including insufficient time to address outcomes of PROMs, lack of use and interpretation and the determination of the added value of PROMs in clinical settings. Future research is necessary to determine how PROMs should be incorporated into daily practice.<sup>19</sup>

In the BRIOS study, the QOL and patient satisfaction were comparable between one-stage IBBR with ADM and two-stage IBBR, even though more complications occurred in the one-stage group. The higher complication rate did not lead to a significant lower QOL or patient satisfaction in the one-stage group when compared to the two-stage group. At one year after placement of the final implant, the used reconstruction technique with an implant, either in a two-stage or one-stage with ADM reconstruction, does eventually not lead to large differences in the QOL and patient satisfaction. For both groups, much larger differences were seen between the pre-operative and post-operative BREAST-Q scores, in particular in the BREAST-Q 1 Satisfaction with Breasts scale. If we compare the post-operative values to patients with a mastectomy only, for example in the study by Ng et al<sup>20</sup>, patients with a breast reconstruction score remarkably higher on the Satisfaction with Breast scale (a mean score of 48.9 without reconstruction).

Hence, IBBR does lead to higher patient satisfaction, but is not yet as good as the satisfaction of a woman with her own breasts.

The incorporation of PROMs in more clinics to evaluate daily practice would be very useful, as they are essential to be able to improve patient care.<sup>19</sup> If all hospitals start evaluating each patients' treatment by a questionnaire, similar to the way complication rates are currently registered, a lot of valuable data would be gathered. We should then be able to gain even more insight in the patients' needs and expected outcomes when facing breast surgery.

Beside PROMs, the surgeons' assessment with their experience and expertise should be taken into consideration as well. There are only limited methods available for assessing these outcomes and consist of a panel evaluation based on pre- and postoperative photographs. One method for assessing photographs was first described by Visser et al. and Brinkman et al., and further developed into the Aesthetic Item Scale by Dikmans et al.<sup>21-23</sup> Several independent surgeons rate the cosmetic outcome and their scores are averaged. Such an approach provides a more objective assessment of the results than evaluation by the patient only, but is relatively time-consuming and thereby not very suitable to incorporate in daily care. An objective method to assess outcomes after breast reconstruction, such as the computer software BCCT.core for assessing cosmesis after breast conserving therapy, would be helpful in investigating the most optimal reconstruction method.<sup>24</sup> However, such computer software is not yet available for the evaluation of post-mastectomy breast reconstructions.

### **Health care costs**

Ultimately the benefits of each intervention should also be weighed against the financial costs associated with the treatment.<sup>25</sup> There are two issues that needs to be addressed. First, does the intervention yield such added value that it is justifiable to make additional costs? This mainly depends on the outcomes of the reconstruction method, which was previously discussed.

Second, is it feasible for the surgeon to provide this certain care with the current financing system? In developed countries, health care costs are rising and total costs now account for about one-sixth of the economy. The

way health care is financed varies considerably between countries. In the Netherlands, health insurance is mandatory. The payment system is based on case-mix model, which is defined as a care package of all activities and services of hospital and medical specialists for the demand for care of the patient.<sup>26</sup> Any costs that are made during this specific demand for care, should be paid out of one prefixed fee, based on so-called Diagnosis Related Groups (DRGs). This implies that the reimbursement fee does not match the actual costs and in some cases the differences between costs and reimbursement can be substantial. For instance, an ADM is quite expensive (range, £ 1292 ( $\approx$  € 1449) to \$ 4890 ( $\approx$  € 4212)).<sup>27, 28</sup> For example, the costs of the ADM direct-to-market in the Netherlands were € 2,370 each at the time of the study. If a patient undergoes a reconstruction with ADM, no extra fee is received for the use of the ADM. All these additional costs are included in one price. The sum reimbursed is payable regardless of the actual cost to the hospital providing the relevant care, which is sometimes higher and sometimes lower than the reimbursement. With no extra fee for the ADM, the reimbursement of the one-stage IBBR with ADM, especially in a bilateral reconstruction, is insufficient to cover the actual costs. Thereby, the hospital experiences financial losses if this reconstruction method is performed. The cost-effectiveness of one-stage IBBR with ADM and two-stage IBBR was investigated. When comparing the direct costs (in euros) at an institutional level, both uni- and bilateral one-stage IBBR with ADM were associated with higher costs, compared to two-stage IBBR. If this situation does not change, it is not favorable to perform this reconstruction method based on the costs.

### **Future perspectives in implant-based breast reconstruction**

In general, if a patient is scheduled for breast reconstruction, the surgeon must take sufficient time to review all surgical options with the patient and the eligibility of the individual for each of these options.<sup>29</sup> First, there is the choice between either implant-based or an autologous reconstruction. While a natural breast can be created with autologous reconstruction with a free flap, this method is associated with possible (severe) donor site morbidity. Furthermore, not all patients are eligible for this type of surgery, as sufficient donor tissue must be available for transplantation. A relative new technique with autologous fat grafting (AFG) is currently being investigated in a multicenter randomised trial, the Breast Reconstruction with External pre-expansion and Autologous

fat transfer versus Standard Therapy (BREAST) trial. The autologous fat is harvested from multiple donor sites of the body, resulting in minimal donor side morbidity. In the BREAST trial, breast reconstruction with AFG is compared to the conventional two-stage implant-based breast reconstruction. This reconstruction method is a promising alternative to other autologous reconstructions with free flaps. The results of this study are expected in the following years.

The alternative is choosing breast reconstruction with an implant. As described above, this method is also not without risk of complications and other disadvantages are that implants may need to be replaced after time and that the reconstructed breast feels different from “own” tissue.

Many other factors play a role in choosing the most fitting technique. Hence, there are studies focusing on the development of a clinical decision support system for breast reconstruction.<sup>30</sup> As there are so many surgical options for breast reconstruction, patients and clinicians face a difficult task to choose the reconstruction technique while considering all pros and cons.

Difficult issues to address are for instance whether a contralateral preventive mastectomy should be performed. The decision for an autologous or implant-based reconstruction also remains difficult. At this time, tools and applications as well as care facilities which support patients in their decision to choose the optimal reconstruction technique are direly needed.

If successful, both autologous and implant-based breast reconstruction can result in a satisfying result. When selecting the most optimal reconstruction technique for each woman on a case-by-case basis, the safety, patient indications, and value relative to costs should be considered. In order to select and improve the current reconstruction methods:

1. We need to give more attention to what the patient experiences as outcome of the reconstruction (proms).
2. We need to bring the rate of complications down (either with improved methods or better patient indication).
3. We need to provide tools that help both patient and professional to better choose the technique that matches the individual patient.
4. With the development of new reconstruction methods, it is important to be aware of the costs.

## BREAST CONSERVING THERAPY

### **Aesthetic and patient reported outcomes**

The minority of breast cancer patients require a mastectomy and in patients that are eligible, breast-conserving therapy (BCT) is a valid treatment option in patients desiring preservation of their remaining breast tissue. Although most of the breast tissue remains in situ, the aesthetic outcome varies widely. An overall decrease in patient satisfaction and cosmetic outcome is seen during the years after BCT. Several risk factors are known that influence the cosmetic outcome. In the Cosmetic Outcome of the Breast After Lumpectomy Treatment (COBALT) trial, older women and women with larger excision volumes were prone for poor cosmesis. Another important factor concerns radiotherapy, which is also called 'the gift that keeps giving'.<sup>31</sup> Radiotherapy leads to severe fibrosis and retraction, resulting in asymmetry. The breast specific factors size, shape and nipple position, which contribute to the symmetry of the breasts, were found to predict the overall cosmetic result. An option to prevent asymmetry of the breast, is oncoplastic breast surgery (OPBS). OPBS combines oncological resection with plastic surgery techniques to improve outcomes, by volume-displacement and volume replacement with autologous tissue.<sup>32</sup> However, current evidence is limited, and prospective studies are needed to determine which women are eligible for OPBS.

If only surgical excision, or even combined with OPBS, has not resulted in an acceptable aesthetic outcome, delayed reconstruction techniques are available to improve cosmesis. Volume replacement with autologous tissue (ie lipofilling or a local or free flap) can still be performed as a second procedure. Other secondary reconstructions include a reconstruction with prosthesis, revision of the scar or nipple reconstruction. Another option is reconstruction of the contralateral, healthy breast with breast reduction or mastopexy. Current literature still lacks proper comparison of all different techniques, and the performed reconstruction method is frequently based on the assessment by the surgeon and not the patient herself.<sup>33</sup> Furthermore, there are many different questionnaires available, making it impossible to compare results between studies. Recently, the BREAST-Q was also developed for BCT, which may hopefully lead to a more standardized measurement of patient-reported outcomes, especially when incorporated in daily practice.<sup>34</sup>

### **Future perspectives in breast conserving therapy**

Despite the advances in breast reconstructive surgery, the cosmetic outcome can still be improved. There is no management algorithm available to determine which patient benefits most from a secondary reconstruction after BCT, and which technique should be used in particular. Future research should focus on the assessment of the patient satisfaction, the surgeon and also compare it to an objective method such as the BCCT score, and combine these methods to determine the most optimal reconstruction technique for each patient.

Also, not all patients are aware of the fact that a secondary correction after BCT is an option. There are many surgical options available for a secondary reconstruction. The entire medical team of breast cancer patients should be aware of these techniques and a secondary correction to improve the final outcome should be offered more often at the outpatient clinic, with referral to a plastic surgeon.

### **General conclusion**

To conclude, the safety, patient satisfaction and aesthetic results after IBBR and breast conserving therapy are addressed in this thesis. A higher complication rate after one-stage IBBR with ADM was seen compared to the conventional two-stage IBBR, with comparable patient satisfaction, aesthetic results, and costs. As long as this complication rate does not improve, the two-stage IBBR is deservedly the standard reconstruction method. Cosmetic results after breast-conserving therapy can still be improved. Although current reconstructive techniques in breast surgery are advanced, there are still opportunities for further enhancements.

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