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Negenborn, V.L.

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Introduction and outline of the thesis

Breast cancer is the most common cancer in women.¹ In the Netherlands, over 1 out of 8 women develops breast cancer during her life.² Fortunately, mortality rates are declining and breast cancer ranks fifth as cause of death due to a relatively favorable prognosis. Five year survival rates in western countries are currently 80%, and even up to 98% for early stage breast cancer.³ The cornerstone of breast cancer treatment is still surgical removal of the tumour. In the late nineteenth century, Halsted introduced the radical mastectomy. The entire breast, with skin and pectoralis major and minor muscle were removed.⁴ (Neo)adjuvant therapies became available as adjunct to treat local and systemic breast cancer, consisting of radiotherapy, chemotherapy, hormone therapy and immunotherapy.⁵ During the seventies, breast-conserving therapy (BCT) became an alternative to a mastectomy. BCT consists of breast-conserving surgery, and is always followed by radiotherapy. In patients that are eligible for BCT, both methods yield comparable survival rates.⁶

Radiotherapy significantly reduces the relative risk of both local and regional breast cancer recurrences after surgery. The Boost versus no Boost trial showed a significant improvement in local control of breast cancer, especially in young patients. However, no effect was seen on long-term overall survival when a radiation boost was administered following whole-breast irradiation, while radiation therapy does have negative effects such as severe fibroses and impaired cosmetic outcome.⁷ Radiation related toxicity was seen in specific cases after long term follow up (≥ 15 years), which resulted in an increased number of cardiovascular deaths. In the 21st century the use of radiotherapy advanced to decrease radiation related toxicity, including fine-tuning of the indications and decreased amount of radiation.⁸ Systemic therapies, including chemotherapy, hormone- and immunotherapy, have improved survival of patients with breast cancer.⁵ Neoadjuvant systemic therapy, i.e. before surgical treatment, was initially administered in patients with non-operable tumours. Current indications have expanded,

consisting of 1) downsizing tumour size to be able to convert to BCT, increase radical excision rates and decrease excision volume, thereby improving cosmetic outcome; 2) reduce the necessity for surgical intervention in case of complete pathological response; 3) downgrade tumour load in the axilla to prevent axillary lymph node dissection; 4) early recognition of poor- or non-responders to limit toxicity of ineffective therapy and subsequently change management.⁹ Adjuvant systemic treatment, defined as adjuvant therapy after surgical intervention, is recommended for node-positive disease and/or tumours larger than 1 centimeter.⁵ Both neoadjuvant and adjuvant systemic therapy have shown to improve overall survival, progression-free survival and time to loco-regional recurrence.^{9, 10}

Broca first reported the possibility of a hereditary cause in breast cancer in 1866 in his book 'Traité des tumeurs'.¹¹ His wife suffered from early stage breast cancer, and when he made a family tree of his wife's family, he discovered a history of several female family members with breast cancer. He suggested that there might be hereditary predisposition to cancer.¹² In 1990, the first articles on the BReast CAncer (BRCA) 1 and 2 genes were reported.¹³ The lifetime risk of developing breast cancer is up to 81% in patients with BRCA 1 and BRCA 2 genetic mutations.¹⁴ Patients with genetic mutations are candidates for bilateral prophylactic mastectomy (BPM).¹⁵ There are no prospective randomised studies available assessing the risk reduction of prophylactic mastectomy, as such research is not ethically justifiable. Based on current, retrospective studies BPM reduces the risk of developing breast cancer by 90% in BRCA gene mutation carriers and a survival advantage by BPM is suggested.¹⁴ With the advancement of our knowledge with regard to the pathogenesis of breast cancer and causative genetic mutations, the number of patients requiring bilateral BPM or a contralateral prophylactic mastectomy (CPM) increases.

Nowadays after treatment of breast cancer, there is an increased attention to secondary treatment goals as 1) the number of breast cancer survivors is growing; 2) (neo)adjuvant treatment advances; 3) treatment becomes less invasive; 4) reconstructive treatment options increase. The focus of treatment shifts from patient survival towards patient satisfaction and cosmetic outcome after the operation.

BCT and a mastectomy with reconstruction can result in comparable satisfaction rates.¹⁶ The main advantage of BCT is preservation of the breast. However, unsatisfactory cosmetic outcomes are reported in up to 40% of

the patients.¹⁷ In 1991, Toth and Lappart described the skin-sparing mastectomy to improve cosmetic outcome and facilitate post-mastectomy reconstruction.¹⁸ Currently, the skin and nipple sparing mastectomy, as reported by Hinton, has gained popularity.¹⁹ The aim of post-mastectomy reconstruction or BCT is to improve cosmetic outcome and to restore the self-esteem of women after breast cancer surgery, and thereby establishing higher quality of life at long-term follow-up.²⁰

A breast reconstruction following preventive or breast cancer surgery, can be performed immediate (i.e. in the same operation as the mastectomy) or delayed. Immediate reconstruction has proven to result in preservation of body image and reduces postoperative stress, and is thereby preferred.²⁰ Various reconstruction methods after breast cancer surgery are available and generally divided into three types; reconstruction with autologous tissue, reconstruction with implants or a combination of both.²⁰ Although all types of reconstructions are frequently performed, the optimal method is not yet determined.

The main advantage of an autologous reconstruction is the creation of a long lasting, natural breast, but it requires prolonged operation time and may result in donor side morbidity.²¹ Implant-based breast reconstruction (IBBR) is still the most performed reconstruction method, with advantages including a short operation time, no donor site morbidity, and the availability of different implant types, sizes and shapes. Patients scheduled for bilateral reconstruction are more likely to undergo IBBR.²²

In general, IBBR seems to be associated with higher complication rates compared to autologous reconstruction,²³ and complication rates up to 50% have been reported.²⁴⁻²⁶ Minor complications do not need surgical intervention and include seroma, limited necrosis that heals spontaneously and infection solved with antibiotics. Major complications require surgical intervention and include severe necrosis or infections requiring implant removal.²⁴ Several risk factors are known to influence complication rates with radiotherapy being a major risk factor.²⁵ Other factors include age, smoking habits and higher body mass index.²⁷

The conventional method for IBBR consists of a two-stage expander/implant reconstruction, in which a subpectoral tissue expander is placed during the first surgical procedure. After repeated expansion by percutaneous saline injection, the expander is replaced by a definitive implant during a second procedure. IBBR can also be performed in one stage, in

which a definitive implant is placed immediately. In both reconstruction techniques, an acellular dermal matrix (ADM) can be used as an adjunct.²⁶ An ADM is a sterile tissue matrix, derived from either human (allograft) or animal (xenograft) tissue. In Europe, only animal-derived ADMs are available.²⁸ ADMs were initially introduced for the management of full-thickness burns in 1995.²⁹ Ten years later, Breuing and Warren were the first reporting on the use of ADMs in breast reconstructive surgery.³⁰ The use of ADM was propagated mainly because it facilitates direct-to-implant breast reconstruction by augmenting the subpectoral pocket. Improvement of the aesthetic result was also suggested, by a better definition of the inframammary fold (IMF), improving lower pole projection and providing better coverage of the prosthesis. Moreover, ADMs may reduce the formation of capsular contraction at longer term follow-up.^{30,31}

Current status and gaps of evidence

The number of women surviving breast cancer and the number of women undergoing preventive breast surgery is significant, and still increases. There is growing attention to the importance of a satisfactory result after breast surgery. However, it is still unclear which surgical treatment leads to the most optimal result for each individual woman.

1. To what extent are patients satisfied with the cosmetic outcomes of BCT? And which factors contribute to this satisfaction?
2. Which breast reconstruction technique leads to the most optimal results for the individual patient? And what is the additional value of a new reconstruction technique with ADM?

Outline of this thesis

In the first part of this thesis we will address the effectiveness of ADM use in IBBR with regard to safety, cosmetic outcome, health related quality of life and cost effectiveness. In the second part of the thesis we report on the patient satisfaction after BCT.

To determine the effects of using ADMs in IBBR, the complication rate and patient-satisfaction after one-stage IBBR with ADM were investigated in two retrospective cohort studies, reported in chapter 2 and 3. In **chapter 2** the patient satisfaction was investigated using a validated questionnaire, the BREAST-Q, in one of the largest series of patients treated with ADM-assisted breast reconstruction. In **chapter 3** the first study regarding the use of a porcine ADM, EGIS, in IBBR is described. The safety of the reconstruction method was studied and clinical outcomes linked to patient satisfaction.

In **chapter 4** the safety of one-stage IBBR with ADM and two-stage IBBR was investigated in a multicenter, randomised controlled trial, the Breast Reconstruction In One Stage (BRIOS) study. Differences in clinical outcomes including surgical complications, reoperations and necessity for removal of the implant were investigated and the influence of risk factors assessed. In **chapter 5** the postoperative course after one-stage IBBR with ADM was further explored, by identifying risk factors contributing to surgical complications, reoperations and implant removal.

Porter stated that values should be defined around the customer, which in health-care means the patient.³² Patient satisfaction should play the central role in the evaluation of outcomes, but an assessment by the professional is still frequently reported as a major determinant for assessing the effectiveness of reconstruction techniques. In order to determine the most optimal reconstruction method, the patient satisfaction and aesthetic result of both one-stage IBBR with ADM and two-stage IBBR were studied in **chapter 6**.

With a high prevalence, breast cancer treatment plays a substantial part in health care. One of the current problems is how to measure outcomes in health care. Porter introduced value based health care, and defined values as health outcomes relative to the costs.³² In **chapter 7** the costs of both one-stage IBBR with ADM and two-stage IBBR were estimated based on an institutional level to determine which reconstruction technique results in lower costs.

The patient satisfaction after BCT was assessed in **chapter 8**. Factors influencing this satisfaction were explored by using data from the randomised Cosmetic Outcome of the Breast After Lumpectomy Treatment (COBALT) trial. In this trial, women scheduled to undergo BCT were randomised to undergo either ultrasound-guided surgery (USS) or palpation-guided surgery (PGS). Patients were asked to rate several factors, the overall cosmetic outcome, and the overall satisfaction with the operated breast at 3, 12 and 36 months follow-up. The role of tumour, treatment and patient-related items, and of the individual factors on the overall patient reported cosmetic outcome and satisfaction were studied.

In **chapter 9** an expert panel of four reconstructive surgeons were asked to score the cosmetic result of 109 women after BCT based on postoperative photographs. Surgeons were also asked which patients in their opinion were suitable for additional reconstruction, which reconstruction method they would use, and what the expected improvement would be.

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