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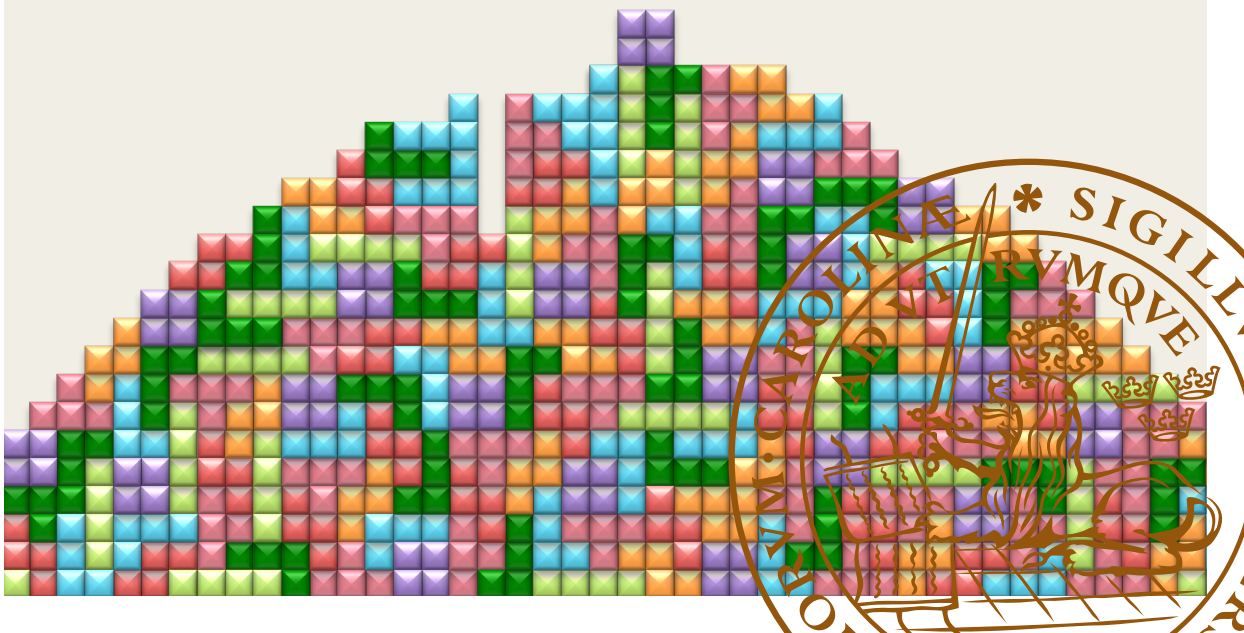
Breast-conserving surgery in the treatment of breast cancer

Aesthetic results, shared decision-making and health-related quality of life

CECILIA DAHLBÄCK | FACULTY OF MEDICINE | LUND UNIVERSITY 2019



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CECILIA DAHLBÄCK currently works as a surgical resident (ST-läkare) at the Department of Surgery, Skåne University Hospital.

In this thesis, patients treated with breast-conserving surgery for breast cancer were studied. Aesthetic outcome was evaluated with three different methods and the results were analysed in relation to long-term health-related quality of life. The patients' perception on the possibility of shared decision-making was also studied.

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Breast-conserving surgery in the treatment of breast cancer

Aesthetic results, shared decision-making and health-related quality of life

Cecilia Dahlbäck

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Abstract

Currently, there is no ideal method to evaluate, in a standardised way, the aesthetic results after breast cancer surgery. The aim of this thesis was to evaluate aesthetic outcome after breast-conserving surgery (BCS), using three different modalities, and to relate the results to long-term health-related quality of life (HRQoL). Additional aims were to identify factors with a potential influence on the aesthetic result after conventional BCS and also to investigate patient involvement in the decision-making process.

Women considered eligible for BCS at Skåne University Hospital Malmö, were consecutively included in the study over a period of four years (2008-2012). At a one-year follow-up visit, the participants were photographed and asked to complete a study-specific questionnaire (SSQ). The photos were subsequently evaluated with the BCCT.core software and by a panel of assessors. In 2015, the patients were asked to complete the HRQoL-questionnaire Breast-Q™.

Many of the patients (53%) had not, or had only partly, perceived any possibility to be involved in the decision-making process and this was associated with less satisfaction. These patients more often reported inadequate preoperative information regarding the expected aesthetic result. The main factors associated with the aesthetic results after conventional BCS in this study population were body mass index, excision volume in relation to preoperative breast volume, axillary clearance, re-excision, and postoperative infection. The results support an upper limit of 20% of the preoperative breast volume excision for conventional BCS. If the estimated excision volume exceeds this, other surgical techniques should be considered.

The photo panel evaluation showed low intra- and inter-observer agreement, and was both time- and resource-consuming. There was a statistically significant association between a higher score with BCCT.core and higher HRQoL scores. Of the three evaluation methods, the SSQ best predicted long-term HRQoL. These results indicate that to find patients at risk of having poor HRQoL long-term, patient-reported outcome measures are most important. If the aim is to compare aesthetic results between hospitals, use of the BCCT.core software is a promising method, particularly since it does not require any expensive equipment and is easy to use for surgeons in their daily practice.

Key words Breast-conserving surgery; Aesthetic result; Shared decision-making; Health-related quality of life

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“Not all those who wander are lost”

J.R.R. Tolkien

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Original papers

This thesis is based on the following original papers, which are referred to in the text by their Roman numerals:

I Dahlbäck C, Manjer J, Rehn M, Ringberg A. Determinants for patient satisfaction regarding aesthetic outcome and skin sensitivity after breast-conserving surgery. *World Journal of Surgical Oncology* (2016) 14:303-313

II Dahlbäck C, Manjer J, Rehn M, Ringberg A. Patients undergoing breast-conserving surgery can benefit from the opportunity to participate in choosing their surgical technique. *World Journal of Surgery* (2017) 41:734-741

III Dahlbäck C, Heiman Ullmark J, Rehn M, Ringberg A, Manjer J. Aesthetic result after breast-conserving therapy is associated with quality of life several years after treatment. Swedish women evaluated with BCCT.core and Breast-Q™. *Breast Cancer Research and Treatment* (2017) 164:679-687

IV Dahlbäck C, Ringberg A, Manjer J. Aesthetic outcome following breast-conserving surgery assessed by three evaluation modalities in relation to health-related quality of life. *British Journal of Surgery* (2019) 106:90-99

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Thesis at a glance

Paper	Aims	Patients and methods	Main results
I	To study patient satisfaction with postoperative aesthetic result and skin sensitivity after conventional breast-conserving surgery (BCS) and to identify factors associated with the results.	Study-specific questionnaire (SSQ) completed by 297 women one year after conventional BCS and completed radiotherapy (median 16 months after surgery).	84% were satisfied with the aesthetic result of the operated breast. >20% of preoperative breast volume removed and axillary clearance were associated with less satisfaction with the aesthetic result. 68% were satisfied with symmetry. High body mass index was associated with less satisfaction regarding symmetry. 67% were satisfied with skin sensitivity. Several factors were associated with less satisfaction with skin sensitivity, such as re-excision and postoperative infection.
II	To investigate if patients perceive a possibility to take part in the decision-making process and if this is associated with patient satisfaction.	SSQ completed by 324 women one year after BCS and radiotherapy.	53% of the patients had not, or had only partly, perceived a possibility to participate in the decision-making process. These patients were less satisfied with the aesthetic results and had more often reported inadequate preoperative information.
III	To determine whether the aesthetic results evaluated with the BCCT.core software correlate to long-term health-related quality of life (HRQoL).	Photos of 216 patients from a one-year follow-up visit analysed with BCCT.core. The Breast-Q™ questionnaire was completed median 5.5 years postoperatively.	A poor/fair BCCT.core score was associated with lower HRQoL, i.e. Q-scores below median regarding the Breast-Q™ domains “Satisfaction with breasts” and “Psychosocial well-being”.
IV	To investigate how different evaluation methods of aesthetic result after BCS predict HRQoL long-term	Evaluation of the aesthetic results one year after BCS and radiotherapy, by an SSQ (n=324), a photo panel evaluation (n=215), and the BCCT.core (n=310) in relation to the Breast-Q™ results.	The photo panel evaluation showed low intra- and inter-observer agreement. The SSQ predicted results of the Breast-Q™ domains “Satisfaction with breasts” and “Psychosocial well-being” best.

Abbreviations

AUC	Area Under the Curve
BCCT.core	Breast Cancer Conservative Treatment. cosmetic results
BCS	Breast-Conserving Surgery
BCT	Breast-Conserving Therapy (BCS with adjuvant radiotherapy)
BMI	Body Mass Index
CI	Confidence Interval
CIS	Cancer in Situ
DCIS	Ductal Cancer in Situ
EPBVE	Estimated Percentage of Breast Volume Excision
ER	Oestrogen Receptor
FISH	Fluorescent in Situ Hybridisation
HER	Human Epidermal Growth Factor Receptor
HRQoL	Health-Related Quality of Life
IHC	Immunohistochemistry
INCA	Information Network for Cancer Care
IQR	Interquartile Range
LCIS	Lobular Cancer in Situ
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
NAC	Nipple-Areola Complex
NHG	Nottingham Histologic Grade
NST	No Special Type
OPBS	Oncoplastic Breast Surgery
OR	Odds Ratio
PgR	Progesterone Receptor
pME	partial Mastectomy
PROM	Patient-Reported Outcome Measure

QST	Quantitative Sensory Testing
ROC	Receiver Operating Characteristics
SDM	Shared Decision-Making
SSQ	Study-Specific Questionnaire
TNM	Tumour, Node, Metastases
3D-SI	Three-Dimensional Surface Imaging

Introduction

More than one in ten Swedish women will be diagnosed with breast cancer during their lifetime. Even though the incidence of breast cancer has increased in the last few decades, mortality rates have decreased due to early detection and improved therapies (1). Numerous women thus continue to live for a long time after the breast cancer treatment, making health-related quality of life (HRQoL) an important outcome measure in breast cancer research. In 2015, there were over 100 000 women with a previous or current diagnosis of breast cancer living in Sweden (2).

Most women diagnosed with breast cancer are subjected to surgical treatment (1). The aesthetic result after breast cancer surgery has been shown to correspond to HRQoL (3, 4), making evaluation of the postoperative aesthetic outcome essential. However, evaluation of the aesthetic result is difficult and valid methods are scarce. Studies of possible methods to measure the aesthetic result in a standardised and reproducible way are warranted.

Many breast cancer tumours are diagnosed when they are still small, which enables breast-conserving therapy (BCT), i.e. a partial mastectomy with adjuvant radiotherapy (1). In Sweden, about 70% of newly diagnosed women with breast cancer can be offered BCT (5).

The aims of this thesis were to study the aesthetic result, using different evaluation methods, and HRQoL following BCT.

As the importance of patient involvement and shared decision-making (SDM) is being increasingly discussed (6), an additional aim was to investigate whether patients perceive a possibility to participate in the decision-making process.

However, first a glance back in time in honour of our predecessors…

Background

A brief history of breast cancer surgery

Breast cancer has been of interest to medical practitioners for many centuries, not to say millennia. Since a breast tumour reaching a certain size is easily detected, the need for a cure was evident even in the earliest days of medical history. The Edwin Smith Surgical Papyrus from ancient Egypt, written around 3000 years BC, is believed to be the earliest documentation of breast cancer (7). There is no evidence that tumours of the breast were then surgically treated, as there is of abscesses being treated with cauterisation (8).

Hippocrates (460-377 BC) stipulated that breast cancer was caused by an excess of black bile, in accordance with his beliefs that diseases arose due to an imbalance of the four humours: blood, phlegm, yellow bile, and black bile (8). Hippocrates did not recommend surgical treatment since his experience was that the patients died faster after being subjected to surgery (9).

Galen (approximately AD 130-219) hypothesised that a breast tumour was coagulated black bile, which was collected in the body but in the female was released through the monthly period. He thereby explained why breast malignancies were more common in postmenopausal woman. Galen recommended some form of surgical treatment if the tumour could be easily removed, but also different types of interventions to improve the humoural balance, such as different diets, phlebotomy, and purgation (8).

Leonides of Greece worked at the Alexandrian School in Egypt in the first century AD and is thought to have been the first to surgically remove a breast. However, during the medieval period in Europe (approximately AD 500-1400) religion came to play an important role in many areas of society. Breast amputation was used as a method of torture and punishment, whereas surgical treatment was considered barbaric and was practically banned. Between the fall of the Roman Empire and the Renaissance, the progress of surgical treatment was halted since both Christianity and Islam prohibited anatomical dissection and any opposition towards the teachings of humoural pathology was considered heresy. Despite this, there are multiple examples of physicians using surgical treatment of breast cancer during this time, but not until the anatomist Vesalius in the 16th century discarded

the doctrines of Hippocrates and Galen, did the surgical methods start to evolve more clearly (8).

Vesalius is the author behind *De Humani Corporis Fabrica*, published in 1543. He recommended ligation of vessels instead of cauterisation, which had been the traditional method, due to a belief that ligating the vessels would cause the cancer to spread. Johannes Scultetus (1595-1645) was a leading surgeon in Germany and also a talented illustrator. He described a method of swift breast removal after the base of the breast had been penetrated with large needles carrying ligatures, in order to compress the wound after surgery (8, 9).

The development of breast surgery was fast during the 17-18th century; however there was a slight backlash during the first decades of the 19th century. Some physicians were now again advocating treatments according to the teachings of Galen, including leeches, repetitive bleeding, and emetics, since relapses after surgery were so frequent (10).

The evolution of breast surgery again gained speed in the later decades of the 19th century. In 1846, general anaesthesia was introduced, revolutionising the possibilities of surgery. The radical mastectomy was popularised by William Halsted (1852-1923), who was active at the Johns Hopkins Hospital (9). He advocated "en bloc" removal of the entire breast tissue, underlying pectoral muscle and ipsilateral axillary clearance (11). Halsted was able to show significantly lower recurrence rates than those of his European colleagues. All the different parts of the radical mastectomy had been described and practised earlier, such as removal of the pectoral muscle, which had been described being done since the 16th century, and also occasionally before this (10). However, it was Halsted who managed to make this technique the gold standard for all types and sizes of breast tumours, until the modified radical mastectomy was introduced by Patey in the 1930s (12).

Radiotherapy was used in the treatment of breast cancer as early as 1896, only a year after its discovery by Roentgen (9). One pioneer in using radiotherapy in breast cancer treatment was Mustakallio, head of the Department of Radiotherapy at the University and General Hospital in Helsinki. Mustakallio was an advocate for conservative surgical treatment. He described in 1945 how he had in fact carried out himself, as a radiologist, lumpectomy on women who had refused radical surgery, of course in addition to radiotherapy. The results were not inferior to those seen in women treated with radical surgery (13, 14). Since then, several clinical trials elaborating and evaluating different aspects of radiotherapy have led to new and enhanced techniques (15).

In 1957, the National Surgical and Adjuvant Breast Project (NSABP) was initiated, with the aim of prospectively studying the treatment of breast cancer

with randomised studies. The NSABP B-06 trial started in 1976 and compared mastectomy to partial mastectomy with or without radiotherapy when treating tumours less than four centimetres in diameter. No difference in mortality rates was shown after five years. However, women treated with breast-conserving surgery (BCS) without radiotherapy had a higher frequency of local recurrence (16, 17). Recruitment of patients to a similar study in Milan began in 1973, and in 1981 Veronesi et al. were able to present the early results (18). Long-term follow-up showed that the patients treated with conservative surgical treatment and radiotherapy had equal survival rates to those treated with radical surgery (19, 20). Other studies showed similar results (21) and in 1990, the National Institutes of Health consensus conference recommended BCT for small tumours (stages I-II) (9).

Surgery of the axilla has also undergone a revolutionary development. Complete axillary clearance had, since the days of Halsted, been standard treatment in patients with breast cancer (9). In 1960, Gould published his observations of a "sentinel node" when performing a parotidectomy (22). Morton described a way to locate the lymphatics with blue dye in cases of melanoma in 1992 (23) and in 1993, the technique was described for breast cancer by Krag et al. (24). Since then, the sentinel node technique has been elaborated: after injection of blue dye or a radionucleotide, the sentinel node is identified visually or by a gamma detector and removed. In cases with a negative sentinel node, no axillary clearance is performed. The sentinel node technique is today a gold standard staging procedure in patients with early breast cancer with no clinically detectable axillary metastases (1). The frequency of false negative sentinel nodes can be decreased with serial sectioning and immunohistochemical (IHC) staining (25).

The development of effective adjuvant treatment for a proportion of breast malignancies with hormonal therapy and chemotherapy has also revolutionised breast cancer management. The effect of oestrogen was proposed in the early 19th century and in 1895 Dr George Beatson in Glasgow performed a bilateral salpingoophorectomy on a 33-year-old woman with metastasised breast cancer and recorded a dramatic response (12). Tamoxifen, a selective oestrogen receptor modulator, was discovered in the 1960s and was approved as breast cancer treatment in the 1970s. Aromatase inhibitors, which inhibit the conversion from androgens to oestrogens, were discovered in the early 1970s. Their role in the treatment of breast cancer was established in clinical trials during the 1980s (26).

Concerning chemotherapy, it was discovered during the world wars that mustard gas had an effect on malignant cells (12). Since then, several chemotherapeutic agents have been identified and have been shown to have an inhibitory effect on tumour cells (27, 28). There has also been a development towards the use of neoadjuvant chemotherapy, i.e. administration of chemotherapy before surgical

intervention. Neither disease-free nor total survival rates differ when comparing chemotherapy administered before and after surgery, but tumours may be downsized by neoadjuvant chemotherapy, enabling more patients to be treated with BCT (29, 30).

In the 1960s, a trial was initiated in New York investigating the effect of screening for breast cancer through clinical investigation and mammography (31). In 1976, the population-based randomised Malmö mammography trial was launched (32). After these early trials, much effort and research was applied to test and elaborate the method (33). Mammography screening is today offered to Swedish women between 40 and 74 years of age (1). Other techniques to examine the breasts have also been developed. Ultrasound, magnetic resonance imaging (MRI), and tomosynthesis can improve the accuracy of diagnostic examinations (34).

Techniques of surgical treatment have continued to evolve. The technique of tumour removal called "conventional" BCS in this thesis refers to a method where the tumour is excised with adequate margins (partial mastectomy). If indicated, the surrounding breast tissue is then mobilised in order to fill the cavity (35).

During the 1990s, surgeons from several different centres were independently developing various methods, originating from plastic surgery, for extirpation of tumours in situations when non-acceptable aesthetic results could be anticipated with conventional techniques (36, 37). Techniques for breast reduction had been developed by plastic surgeons during the 20th century (38). To use a reduction mammaplasty technique for removal of a tumour in a caudal position was described in 1995 (39). The technique was then elaborated to enable excision of tumours located in other parts of the breast (40). The concept of using techniques of plastic surgery in breast cancer treatment is now widely known as oncoplastic breast cancer surgery (OPBS). It includes, apart from adequate removal of the tumour, reconstruction of breast shape and/or volume to correct defects by using displacement, reduction or volume replacement techniques, and if appropriate a contralateral procedure to achieve symmetry (40, 41).

With the use of OPBS, larger excisions of breast tissue could be made without compromising the aesthetic result. Since the techniques often require more extensive incisions than conventional BCS, complication rates have been proposed to be higher (42). However, it was concluded in a review article in 2016 that the complication rates for the different surgical techniques were similar (43). So far, there have been no indications that OPBS would be less oncologically safe than conventional BCS (44).

To conclude, important research progress has led to the various treatment options available for women with breast cancer today.

Clinical management of breast cancer (in Sweden)

Diagnostics

When a lesion of the breast is suspected, either by clinical symptoms such as a palpable lump or by mammography screening, three diagnostic tools are used to determine if it is malignant: palpation, imaging (mammography, ultrasound and/or MRI), and fine needle aspiration and/or core needle biopsy (1).

During the diagnostic process, it is preferable to obtain as much information as possible, including molecular biomarkers (see page 22), to enable an optimal treatment recommendation. Analysis of cell morphology through fine needle aspiration can show if malignant cells are present, but it cannot analyse the cells' positions in relation to each other. A core needle biopsy is needed to analyse tissue morphology and to determine invasiveness, i.e. to see if the malignant cells have invaded through the basal membrane or not. If the cells respect the basal membrane, the tumour is by definition a cancer in situ (CIS), which can be ductal (DCIS) or lobular (LCIS) (45).

Breast cancer is defined as tumours originating from the terminal duct lobular units of the breasts. There are different types of invasive breast cancer. The most common type is invasive cancer of no special type (NST), previously called "ductal" breast cancer, which accounts for about 70% of all breast cancer. Approximately 30% of patients with breast cancer are thus diagnosed with "special" types of breast cancer, of which lobular breast cancer is the most common (46). The special trait of lobular breast cancer tumour cells is the loss of E-cadherin, an adhesive protein binding cells together. These tumours grow in so-called "Indian files" (47).

When results from the triple diagnostics are available, a multidisciplinary team (MDT) conference is held to discuss the optimal treatment option for the individual patient. A breast surgeon, an oncologist, a pathologist, and a radiologist should be present. Which treatment to recommend will depend on various factors, including characteristics of both the patient and the tumour (1).

Tumour staging - TNM classification

Tumour stage is determined with the tumour/node/metastasis (TNM) system (48). There are two separate systems inherent in the TNM: the clinical TNM system (cTNM), in which the tumour is classified prior to treatment, and the pathological TNM (pTNM) system, based on the histopathological examination.

In the staging process, each of the following aspects of the malignancy: T (tumour), N (node) and M (metastasis), are determined based on the following criteria:

T=extent of invasive breast cancer. Tis: CIS; T1: ≤2 cm; T2: >2-5 cm; T3: >5 cm; T4: Involving chest wall or skin, irrespective of size.

N=nodal involvement. N0: No local nodal metastases. N1: Palpable mobile ipsilateral axillary nodes. N2: Palpable fixed nodes in the ipsilateral axilla. N3: Involvement of ipsilateral supra/infraclavicular axillary nodes or internal mammary nodes in addition to ipsilateral axillary nodes.

For pTNM the classification of nodal involvement is as follows: pN0: No nodal involvement. pN1: micro or macrometastases in 1-3 ipsilateral axillar nodes. pN2: metastases in 4-9 ipsilateral axillar nodes. pN3: Metastases in 10 or more of the ipsilateral axillar nodes.

M=Metastases. M0: No clinically detectable metastases. M1: Presence of distant metastases for example in the lung, liver or bones (49).

The tumour stage is an important prognostic factor and is used to determine which treatment to recommend (1).

Surgery

Most patients undergo surgical intervention if the diagnostic process has confirmed a malignancy. In some cases where the tumour is extensive, neoadjuvant chemotherapy can be discussed to downsize the tumour before surgery. Before chemotherapy is administered, it is important to collect a biopsy from the tumour and perform axillary staging before the treatment since the treatment can in some cases eradicate the tumour completely (1).

If the tumour is relatively small (<3-4 cm), unifocal, and with no palpable axillary nodes, the MDT conference will recommend BCS, sentinel node biopsy and adjuvant radiotherapy. The recommendation is presented by the surgeon to the patient and discussed with her. On this visit, the surgeon will decide whether it is preferable to use some other form of surgical intervention, considering the patient's medical condition, personal preferences, and breast and body configuration.

In cases of a non-palpable tumour, a preoperative indication of the location can be made with a hook-wire placed stereotactically. Another technique for preoperative indication, which is not used in Malmö, is charcoal suspension. The line of incision is decided by the attending surgeon and the tumour is excised with a macroscopic margin of about one centimetre. In cases of a non-palpable mass,

perioperative mammography of the excised tissue is recommended to make sure the tumour is removed. According to regional guidelines, the surgeon often places metallic clips in the wound cavity after the tumour has been removed to guide postoperative radiotherapy (1). Using the technique that in this thesis is called "conventional BCS", the remaining breast tissue may then be mobilised at the level of Scarpa's fascia and the pectoral fascia to fill the cavity and to avoid tension when suturing. Different minor OPBS techniques, for example repositioning of the nipple-areola complex (NAC) or usage of local flaps, are increasingly used among breast surgeons to obtain an optimal aesthetic result (45). In Malmö, when the patient is eligible for more advanced OPBS techniques, perhaps with a contralateral breast reduction or a perforator flap, a plastic surgeon is often involved.

After a BCS procedure, the remaining breast tissue of the cancer-affected breast is treated with radiotherapy, as it has been shown to reduce loco-regional recurrence and increase survival rates (50).

A mastectomy, i.e. removal of the breast, is usually recommended if the tumour is extensive or multifocal. The procedure is undertaken by excision of the entire breast tissue at the level of Scarpa's fascia and of the pectoral fascia. The NAC is most often removed. If the reconstruction procedure is immediate and the patient has small breast volumes, a permanent implant is mostly used. In more voluminous breasts and in delayed reconstruction procedures, tissue expander implants are often used. If the woman has undergone radiotherapy, reconstruction with autologous tissue may be a better option to avoid the risk of capsular contracture and a firm breast. During this procedure, tissue with intact blood supply (a flap) is moved from a donor site to the chest. Pedicled flaps include the latissimus dorsi, the thoracodorsal artery perforator, and the lateral intercostal artery perforator flaps. An example of free flap surgery is the deep inferior epigastic perforator flap (1).

Histopathology, prognostic factors and adjuvant treatment

The postoperative histopathological analysis renders much information concerning the prognosis of the individual patient and determines to a large degree which adjuvant treatment she will be recommended. When the histopathological examination of the excised tumour and breast tissue is complete, a postoperative MDT conference is held to discuss which adjuvant treatment the patient should be offered.

If there is "tumour on ink", i.e. if there are tumour cells at the margin of the excised tissue, additional surgery is usually recommended (1). Since DCIS can grow with skip lesions, the distance from DCIS tumour cells to the margin should

be greater. According to the St Gallen consensus meeting in 2017, the lower limit should be set at 2 mm (51), and this is also recommended in the Swedish national guidelines (1).

Sentinel nodes

The excised sentinel node/-s can be examined perioperatively with frozen sections. If metastases are found, the axillary clearance can be performed in the same session. If no malignant cells are found, the axilla is left without further surgery. The excised nodes are then thoroughly examined with histopathological analyses. Small metastases (≤ 2 mm), so-called micrometastases, can be missed with a frozen section (1). At the time of the current study, micrometastases were also considered to be an indication for axillary clearance in all cases (52).

Histological grade

The histological grade of the tumour is determined with microscopic analysis by a pathologist. The most often used grading system is the Nottingham Histologic Grade (NHG) (also called the Elston-Ellis modification of Scarff-Bloom-Richardson) grading system, in which cell differentiation, pleomorphism of the nucleus and mitotic activity are graded. Each of these three parameters are then assessed according to specific instructions and given a grade in the range of 1-3. The different grades are summed to form a total, which then corresponds to a specific NHG grade (table 1) (1). To determine the histological grade of invasive malignancies can expose differing prognoses of women with tumours of the same stage (53).

Table 1. Converting guide: NHG grade

Total grade	NHG
3-5	1
6-7	2
8-9	3

Molecular biomarkers

Immunohistochemistry (IHC) analysis of specific traits, or biomarkers, of the tumours is routinely performed. During this analysis, proteins on the cells' surfaces are detected by the use of antibodies binding to their specific antigens. Four biomarkers are used in clinical practice to guide adjuvant treatment and to estimate the prognosis for an individual patient.

Receptors for oestrogen (ER) and progesterone (PgR) on the surface of the tumour cells are found in approximately 75-85% of patients. The presence of these receptors on more than 10% of the tumour cells indicates that the patient can benefit from hormonal treatment (1, 45).

The human epidermal growth factor receptor (HER2) can be overexpressed by gene amplification in breast cancer malignancies. These tumours can be treated with antibodies targeting HER2. The proportion of tumours overexpressing HER2 differs between 10 to 30% between studies. HER2 is routinely tested both on protein level with IHC analysis and on gene level by fluorescent in situ hybridisation (FISH) (54).

A fourth biomarker is Ki-67, which gives an indication of how fast the tumour cells divide. It is investigated through microscopic assessment made by the pathologist. Ki-67 is a prognostic marker in which a higher proliferation index correlates to worse prognosis (55).

Joining the dots

The prognosis and which adjuvant treatment an individual patient should be recommended is a result of the sum of the factors presented above. An example of how the tumours can be profiled and subgrouped is presented in figure 1.

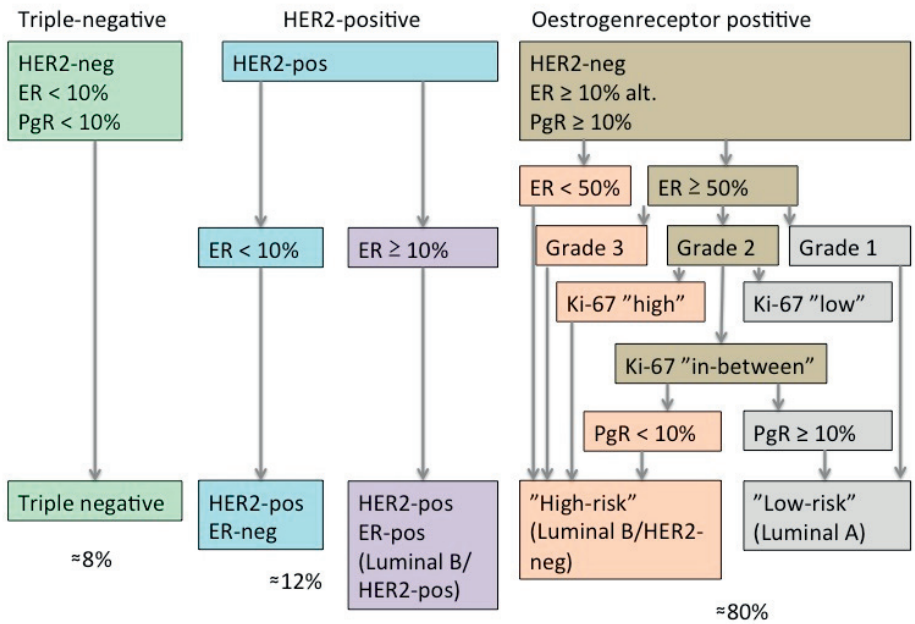


Figure 1. Subgroups of breast cancer. Adapted from (not published) original by M.D. Henrik Lindman, Uppsala University Hospital. With permission.

National Swedish guidelines, with certain regional adaptations, are available at the postoperative MDT conference to guide individual treatment recommendations concerning adjuvant treatment.

For example “triple negative” tumours, which lack overexpression of ER, PgR, and HER2, and are more frequent in younger women, indicate worse prognosis. Adjuvant treatment options for this type of breast cancer have been limited to chemotherapy (51). However, new types of immunotherapy, which uses the patient’s own immune system to fight tumour cells, are emerging. This is a rapidly growing research area and promising trials have been undertaken for women with triple negative breast cancer (56, 57).

Aesthetic result after breast-conserving surgery (BCS)

After this outline of how breast cancer is managed in the clinic, this thesis will now focus on BCS. How does the surgeon determine which surgical technique to offer the patient? When should the surgeon instead of conventional BCS recommend OPBS or even a mastectomy with or without reconstruction? Increased knowledge of which factors affect the postoperative aesthetic result could enhance the quality of preoperative decision-making regarding the surgical approach.

Even though the postoperative aesthetic result is an important outcome measure following BCS, there is still no gold standard for how the evaluation should be performed (58).

Patient self-evaluation

Asking the patient to evaluate the postoperative aesthetic result is perhaps the most important method, since it is the woman herself who must live with the postoperative result. However, a large number of factors can affect the patients' ratings, such as her expectations, demographic characteristics (59), and functional status (60). As such factors vary between populations, self-evaluation of aesthetic outcome is difficult to compare between studies (58).

Another difficulty with patient self-evaluation is how it should be performed. If a surgeon asks a patient at a follow-up visit to grade the aesthetic result, she might feel obliged to rate the result rather highly, to avoid disappointing the surgeon (59). The use of questionnaires, which enables patients to rate the results in the comfort of their own home, requires other methodological considerations. First of all, not all women will return the questionnaire, potentially leading to selection bias (61). Are the responders more or less satisfied than the non-responders, i.e. is the study sample representative of the population it is intended to study? Secondly, it is important to use a questionnaire that has appropriate and well-formulated questions, which the patients understand. Such a questionnaire should also be validated to ensure adequate reliability (the results should be reproducible) and validity (the instrument should measure what it is intended to measure) (59).

Photo panel evaluation

The method of a panel, including one or several physicians, health care workers, or laypersons, evaluating the postoperative aesthetic result has been frequently used. Often, there has been no preoperative photo to compare with, so the evaluation has often been made by considering achieved similarity to the contralateral breast (62-64).

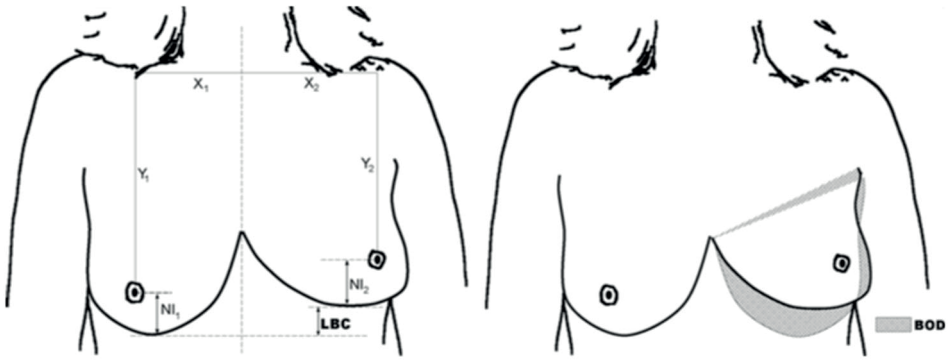
Studies have shown poor agreement between different observers (65, 66). In "Recommendations for the aesthetic evaluation of breast cancer conservative treatment", a group of experts stated that one expert assessor of aesthetic result is sufficient (58). Other authors have recommended having several assessors in the panel, such as Vrieling et. al. who proposed a panel comprising at least five persons (67).

It has been proposed that a panel of assessors with experience of breast cancer surgery is preferable, since agreement between inexperienced observers has been shown to be inferior (68).

Computerised assessment of patient photos – the BCCT.core

The software BCCT.core (Breast Cancer Conservative Treatment. cosmetic result) was created by a research group in Portugal. The first publications introducing the software were published in 2007 (69). The algorithms on which the software is based were presented as early as 2005 (70). The aim was to obtain an objective evaluation tool for aesthetic outcome after breast surgery. The BCCT.core is a semi-automatic instrument in which the assessor first manually marks out the jugular notch and a calibration mark, as well as the nipples and breast contours. Thereafter, the software evaluates the photo according to a specific algorithm. The evaluation is based on asymmetry measurements, the colour difference between the breasts and scar visibility.

Calculations of measured distances in the photos are performed to form a symmetry assessment (figure 2) which is based on relative breast retraction (BRA), lower breast contour difference (LBC), relative upward nipple retraction (UNR), relative breast compliance evaluation (BCE), i.e. the difference between nipple position and mammary fold, breast contour difference (BCD), relative breast area difference (BAD), and breast overlap difference (BOD).



pBRA	$\frac{BRA}{(\sqrt{X_1^2 + Y_1^2} + \sqrt{X_2^2 + Y_2^2})/2}$
pLBC	$\frac{LBC}{(Y_1 + NI_1 + Y_2 + NI_2)/2}$
pUNR	$\frac{UNR}{(Y_1 + Y_2)/2}$
pBCE	$\frac{BCE}{(NI_1 + NI_2)/2}$
pBCD	$\frac{BCD}{(L_1 + L_2)/2}$
pBAD	$\frac{BAD}{(\text{right area} + \text{left area})/2}$
pBOD	$\frac{BOD}{(\text{right area} + \text{left area})/2}$

Figure 2. Measurements of symmetry from article by Cardoso et al. (69) Printed with permission ©Elsevier.

Colour difference is calculated by removal of the background ("foreground/background segmentation") and thereafter performing histogram equalisation, i.e. a process of contrast adjustment. So-called RGB values, i.e. red, green, and blue light functioning as additive colours to form a colour model, reproducing various nuances of colour, can be extracted from most types of pictures. These are converged in the software into a colour model more suitable for calculation of colour difference. Colour differences in different parts of the breasts are then compared, calculating the global colour dissimilarity rate. Scar visibility, on the other hand, is assessed by examining local colour differences (69).

The developers of the software used the Delphi method to reach a consensus in a systematic way concerning how the aesthetic result should be classified: "Excellent", "Good", "Fair", or "Poor". In all, 24 physicians from 13 countries assessed photographs of 60 women from four angles. After the results of the first round were collected, the assessors were asked to redo the assessment, but now with prior knowledge concerning how others evaluated the photos. Consensus on the results for each patient was considered to have been obtained when 50% of the assessments were equal. In their sample 12% were classified as excellent, 57% as good, 21% as fair, and 10% as poor (69).

Other methods

Other attempts to create more objective evaluation tools are for example the Breast Analysing Tool (BAT® software) (71), which was constructed with the same purpose as the BCCT.core, and the three-dimensional surface imaging (3D-SI), which has attracted interest in the last decade for its potential preoperative use in surgical planning and the postoperative evaluation process (72, 73).

Timing of evaluation

When is the optimal time to evaluate the aesthetic result after breast surgery? Time should pass in order to let the scars of surgery mature and the direct effect of radiotherapy wear off. Immink et. al. showed that the effect of radiotherapy can be on-going even after three years (74). However, others, for example Volders et al. evaluated the aesthetic result with patient, panel, and BCCT.core evaluation at 3, 6, 12, and 36 months after surgery and showed that no significant difference was seen in aesthetic results after 12 months (3). Hennigs et al. evaluated patients up to six years after BCS and noted no difference with increased time from surgery in the BCCT.core results on a group level (75). In the "Recommendations for the evaluation of breast cancer conservative treatment", a follow-up visit at least a year after radiotherapy was recommended in order to obtain an impression of the final aesthetic result. It was stated that ideally, follow-up visits should also be performed after five and ten years (58).

Factors affecting the aesthetic outcome after conventional BCS

Studies of postoperative aesthetic results have been undertaken since the introduction of BCS in clinical practice (76, 77) and during those first decades, it was confirmed that BCS was no guarantee of an acceptable aesthetic result (78, 79). However, techniques of surgery and radiotherapy have evolved greatly since

then. Apart from improved surgical techniques, adverse effects of radiotherapy on the skin and breast tissue have diminished with enhanced precision of the treatment (80).

A number of factors have previously been shown to have a potential effect on the postoperative aesthetic result after conventional BCS.

Patient-related factors such as age and body mass index (BMI) are potential determinants. High age has in some studies (81, 82), but not in others (63, 83), been shown to be associated with inferior postoperative aesthetic result. It has been proposed that a higher ratio of fat in the breast, which is associated with increasing age, could impair the healing process and thus the final aesthetic result (84). Obesity has been associated with more pronounced postoperative breast asymmetry (85).

Tumour-related factors such as tumour position have also been shown to influence the postoperative aesthetic result (64, 86). Central, medial, and inferior tumour positions may cause a worse aesthetic result if treated with conventional BCS (45). Large tumour size (85) and high specimen weight (63, 64) have also been associated with inferior postoperative aesthetic result.

The above-mentioned studies have varied in sample size and study design. Given the rapid evolvement of breast cancer treatment, more studies of aesthetic outcome are needed to establish optimised up-to-date guidelines.

Skin sensitivity in the operated breast

Apart from obtaining an optimal aesthetic result, another aim with BCT is to preserve the function of the breast, such as skin sensitivity. Skin sensitivity is important for aspects of HRQoL, such as psychosocial and sexual well-being (87, 88).

Breast surgery affects skin sensitivity in different ways depending on the type of surgical procedure. For example, a breast reduction as treatment for macromastia, which often impairs the skin sensitivity of the operated breast (89), has in some cases been shown to improve skin sensitivity in women with very large breasts (90, 91). Skin sensitivity after a mastectomy, with or without reconstruction, has been shown to be significantly impaired (92, 93), but to what extent varies greatly between patients and time since operation (94, 95). The capacity for nerve regeneration is dependent on different factors, such as patient age and distance from the nerve cell body to the site of nerve injury (96).

Studies focusing on skin sensitivity after BCT are scarce (88) and studies investigating risk factors for impaired skin sensitivity after BCT are lacking. Potential factors affecting skin sensitivity after BCT, based on research conducted in other study populations, are for example patient age (95) and radiotherapy (97). It is possible that OPBS, which often includes more extensive tissue excision, could impair skin sensitivity further. As these techniques are increasingly used, it is important to assess the effect on postoperative skin sensitivity to make it possible to give the patient adequate preoperative information in the decision-making process regarding surgical method.

Evaluation of skin sensitivity

Patient self-evaluation is an often-used method to study skin sensitivity (92, 94, 97). The questionnaires have most often been study-specific and comprised different sets of questions with different rating scales. Issues inherent in this method have been discussed previously (page 25). The patients' subjective experience could be influenced by other factors, such as her expectations and demographic characteristics (59).

Other methods to evaluate skin sensitivity in a more objective way can test various functions of sensitivity. In the skin, different types of receptors react to divergent types of stimuli. After being activated, the receptors transmit the signal through afferent neurons to the brain for processing. Cutaneous mechanoreceptors are divided into low- and high-threshold receptors, based on how they react to harmful stimuli (98). The signal is relayed through neurons of different width, with

different levels of myelination, which cause them to conduct with different velocity. Large Aβ-fibres rapidly respond to touch and are often tested in a clinical setting, for example by examining the patient's ability to detect vibration (using a vibration fork), by a sharp and blunt pin test, and by two-point discrimination. Slower neurons, namely Aδ and C-fibres, are more frequently occurring in the skin and react to mechanical or thermal noxious stimuli. These can be evaluated with quantitative sensory testing (QST), which can test tactile and thermal sensitivity. In skin biopsies, epithelial nerve fibre density can be investigated and sensitivity can also be evaluated by somatosensory evoked potentials with neurophysiological recordings (95).

Shared decision-making

Shared decision-making is today seen in countries worldwide as an important part of patient-centred cancer care (6, 99). A patient's right to be involved in the decision-making process regarding his or her medical treatment has also gained increased interest in Sweden. In 2015, a new law came into effect, which sought to more clearly assert that a patient has a right to receive adequate information regarding different treatment alternatives and to be involved in the decision-making process as much as possible, if this is what the patient wants (100). Two other opposing approaches have been described for the communication between physicians and patients, namely "doctor-directed" and "patient-directed" models. In the extremes of these models, either the doctor or the patient, respectively, is the dominant party and the decision-maker (101).

Studies have shown that SDM may have a positive impact on affective-cognitive outcomes (102), such as increased patient satisfaction (99, 103) and decreased decision regret (104). For patients with different medical conditions, SDM may have different implications and effects. For patients with chronic illnesses, such as asthma or diabetes, SDM is proposed to increase the patients' understanding of their condition and the potential positive effects of recommended treatment. It could thus increase patient compliance and lead to improved health. In acute care situations, such as in the emergency room, SDM is often not as relevant (103).

For cancer patients, the situation could be described as somewhere between chronic and acute. To receive a diagnosis of cancer is often very psychologically challenging for the patient (105). She may not be susceptible to information regarding different treatment options or may not be in a position to take an active role in the decision-making process regarding cancer treatment. In 2016, Swedish oncologists Glimelius and Cavalli-Björkman described in an editorial in Acta Oncologica how an ambition to involve the patient in difficult treatment options is especially sought in cancer care, since several oncological therapies are complex and may cause adverse effects to which the patient's individual response is difficult to foresee. It is thus important for the physician to acknowledge different patients' individual preferences and priorities. However, they noted that some patients need more time than is available to contemplate options and that some simply respond that the decision should be the doctor's (106). It is thus not always easy or even possible to achieve SDM.

In 2016, Frisell et. al. presented a Swedish national study in which the effects of different levels of patient participation were visible. The authors investigated regional differences regarding the frequency of breast reconstruction procedures performed immediately after breast cancer surgery. In their material, the differences between regions could not be explained by patient or tumour factors,

but were shown to be associated with levels of patient involvement in the decision-making process and with differences in information received by patients (107).

For the treatment of small tumour lesions, the BCT and mastectomy treatment options are considered equally safe from an oncological point of view (52). Knowledge of how Swedish women in this situation perceive the opportunity for SDM in the decision-making process regarding surgical treatment is limited.

Health-related quality of life

Health-related quality of life has gained increased interest in the research community and among medical practitioners as more medical treatments have evolved. When advanced treatments can prolong the lives of patients, it is important to evaluate the quality of this extra time (108). The definition of HRQoL is, according to the Centres for Disease Control and Prevention, U.S. Department of Health and Human Services, an individual's or a group's perceived physical and mental health over time (109).

Several factors affecting different aspects of HRQoL have been identified in women diagnosed and treated for breast cancer. Age is an important factor reported by several studies. Some studies indicate that younger women suffer from higher levels of anxiety and fear of recurrence (110), whereas other studies report better HRQoL ratings among younger women (111, 112). Time since treatment (112) and type of treatment have also been shown to be associated with HRQoL (113). Other factors that influence quality of life, not only for patients with breast cancer, are for example educational level, household income (112), occupation and marital status (114).

Health-related quality of life can be quantified with patient reported outcome measures (PROMs), i.e. standardised questionnaires intended to detect the impact of a surgical procedure on a patient's general well-being. A PROM should have adequate reliability and validity. Often, so-called generic instruments have been used, for example the Short Form-36 (115). Generic instruments may be validated and reliable, but are not designed to evaluate the impact of a specific type of intervention (116).

The Breast-Q™ questionnaire[1]

For the evaluation of HRQoL after breast surgery, Drs Pusic, Klassen, and Cano, in cooperation with Memorial Sloan-Kettering Cancer Centre and the University of British Colombia, developed the Breast-Q™. According to the literature, the Breast-Q™ was constructed by first creating a conceptual framework by interviewing patients who had undergone different types of breast surgery. Questionnaires (Breast-Q™ modules) were first developed for breast augmentation,

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Contact information and permission to use: MAPI Research Trust, Lyon, France. E-mail: PROinformation@mapi-trust.org – Internet: www.proqolid.org.

reduction and reconstruction. Six domains were created: “Satisfaction with breasts”, “Satisfaction with overall outcome”, “Psychosocial well-being”, “Sexual well-being”, “Physical well-being”, and “Satisfaction with care” (figure 3).

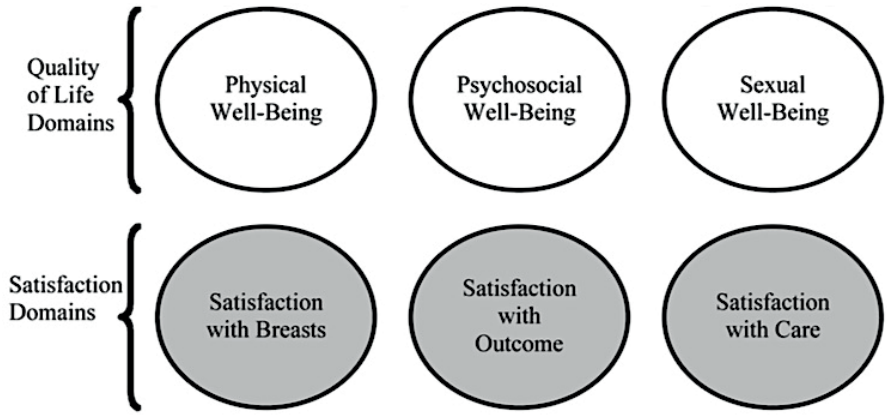


Figure 3. Breast-Q™ conceptual framework. From article by Pusic et al. (117) Printed with permission ©Wolters Kluwer Health, Inc.

The interviews were analysed in a qualitative manner to generate items (questions) for the different domains. Other issues that had been included in previous instruments and aspects deemed important by physicians, nurses, and psychologists were added. Drafts of the new questionnaire including all items were reviewed by focus groups of patients and also by experts. The modified drafts were checked for readability and comprehension of the questions by the patients was ensured. The questionnaire was then sent to more than 2000 women. Questionnaires that were answered and returned were analysed with traditional psychometric methods to ascertain acceptability, reliability and validity (117).

Traditional psychometric methods are based on Classical Test Theory. This theory is built on a series of assumptions, of which one is that for a specific question there is an “observed” score, a “true”, and an “error” score, and that the “true” score is the sum of the “observed” and the “error” score. A second assumption is that when a question is posed to a person several times, the “true” score is the mean of the “observed” scores. The theory is also based on the assumption that “error” scores are not correlated to each other or to the “true” score. The assumptions postulated in the Classical Test Theory cannot be verified, since it is not possible to measure either the “true”, or the “error” scales. In order to overcome these limitations, newer methods have been developed which are based on mathematical models that can be more thoroughly tested (118).

In the development of the Breast-Q™, the Rasch mathematical analysis was used (117). One aim when using the Rasch method is to produce linearity in the results, i.e. the units of measurement are the same across the continuum of the scale. Another aim is to make the outcome applicable to a larger population and not just to the sample from which it was constructed (118, 119).

A group of women were asked to complete the questionnaire twice, with a two-week interval, to investigate test-retest reliability. The final version was mailed to a group of patients, who were thereafter interviewed to ascertain their understanding of the questions, that the questions were acceptable to them, and to investigate the time required to complete the questionnaire (117). Further validation of the Breast-Q™ has since been published (120).

The Breast-Q™ module for BCT was later constructed and was translated into Swedish by Dr Jenny Heiman Ullmark (Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden). The translation process was performed according to the "Linguistic validation of a patient-reported outcomes measure" distributed by the MAPI Research Trust, a non-profit and independent organisation, which manages and distributes the Breast-Q™ questionnaires. Two professional linguists translated the original questionnaire, i.e. they performed "forward translation". These versions were merged to form *version 1*. A "backward translation" to form *version 2* in the source language was undertaken by a professional translator without access to the original questionnaire. The different versions were compared and adjusted to form *version 3*. An experienced nurse performed a face validation of the questionnaire. The postoperative BCT module was tested by five women (aged 52 to 68) who had previously undergone BCT (121). The final Swedish version was approved in 2015 by the MAPI Research Trust.

Aims

The development of breast cancer treatment was rapid during the last century. Surgical techniques have evolved towards more conservative approaches. Most women diagnosed with early breast cancer will survive the disease and live a long time after treatment, making aspects of HRQoL important outcome measures. Postoperative HRQoL is affected by the aesthetic result and efforts are made to optimise this outcome. However, there is still no gold standard method for evaluation of aesthetic results after breast cancer surgery. Shared decision-making has also gained increased interest in the medical community and among policy-makers, since it may lead to increased patient satisfaction and less decision regret.

The overall aims of the thesis were thus to study aesthetic result, SDM and HRQoL after BCS. The specific aims of the individual papers were to:

I. - Study patient satisfaction with the aesthetic result and skin sensitivity after conventional BCS and to identify factors associated with poor satisfaction.

II. - Investigate whether patients perceive a possibility to take part in the decision-making process concerning the surgical method and whether this is associated with patient satisfaction regarding the aesthetic result.

III. - Evaluate the aesthetic result with the BCCT.core software and analyse if the results are associated with long-term HRQoL using the Breast-Q™ questionnaire.

IV. - Evaluate the aesthetic result with a photo panel evaluation.

- Compare different evaluation modalities of the postoperative aesthetic result to each other and investigate which method best predicts HRQoL long-term.

Patients and methods

The OPB-pME Study

This thesis is based on a patient cohort originally included in a study named the "OPB (oncoplastic breast (surgery)) - pME (partial mastectomy)" study. It was initiated in Malmö, by breast and plastic surgeons, when the collaboration between the two surgical subspecialties was being strengthened through a joint clinic. The aim of the collaboration was to create a foundation for mutual exchange of expertise in order to facilitate development of better surgical techniques for patients with breast cancer. The aims of the OPB-pME study were thus to investigate the short and long-term results of BCS with conventional techniques versus more advanced OPBS techniques, and to identify patients suitable for OPBS.

Inadequate resources appearing during the time of inclusion led to there being fewer OPBS procedures than anticipated. This caused the focus to shift to the large group of patients treated with conventional BCS techniques.

Baseline

Study population

Between the 1st of February 2008 and the 31st of January 2012, women who were offered a BCS procedure for a breast mass suspected to be breast cancer were asked to participate in the study (see figure 4). A requirement for inclusion was comprehension of spoken and written Swedish. In all, 653 women were registered in the study database.

A total of 121 women were later excluded. Reasons for exclusion were: the patient had undergone a mastectomy (n=112), the surgical procedure was inhibited (n=6) or the consent form was not retrieved (n=3). Of the women who underwent a mastectomy, 24 did this as a primary procedure, whereas the majority did it after BCS because of either the histopathological findings (n=82), instead of re-excision for non-radical margins (n=4), or as part of a risk-reducing procedure for high-risk genes (n=2).

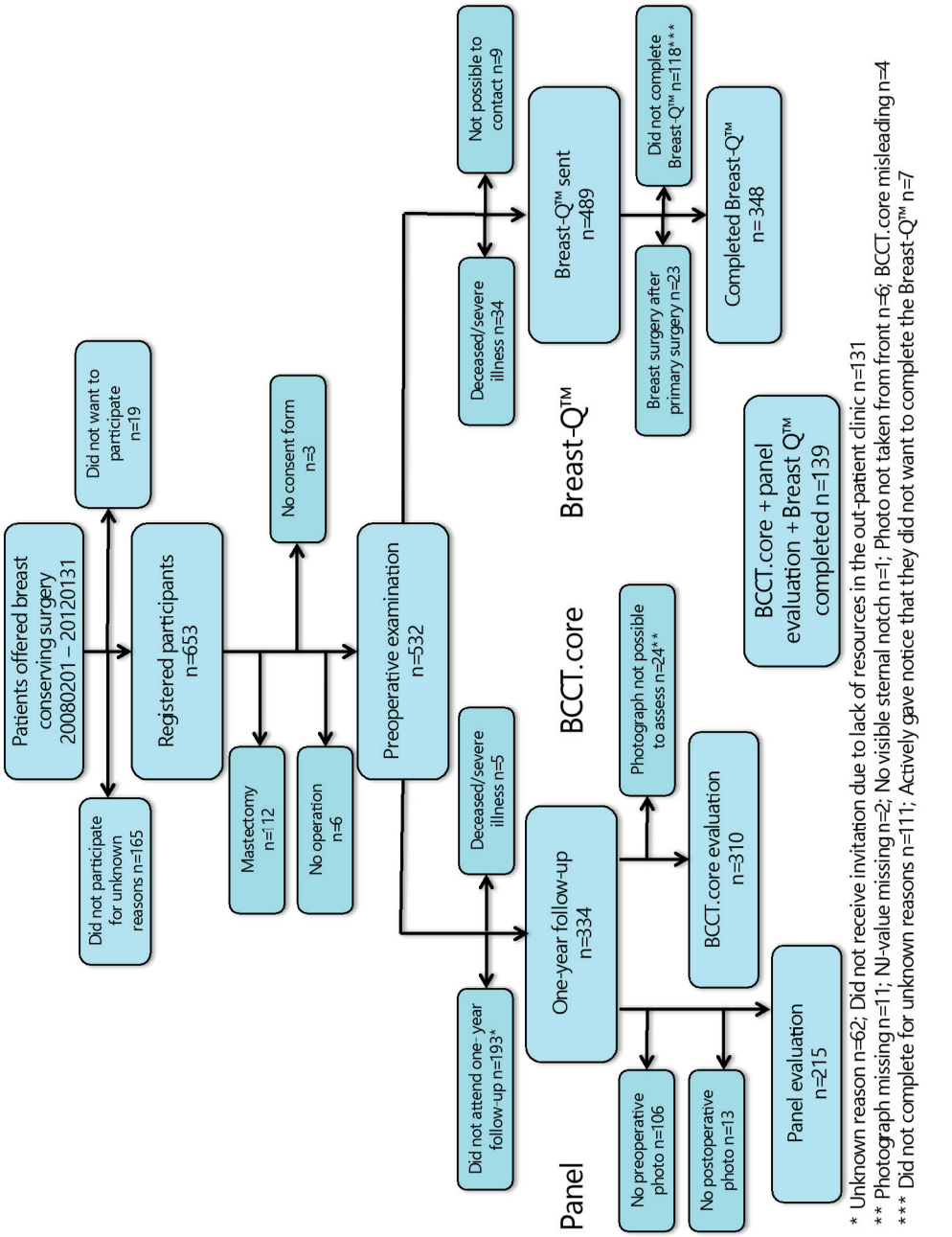


Figure 4. Study flow chart

Preoperative examination

The attending surgeon performed the preoperative examination. Patient weight was measured in kilograms to one decimal and height was registered in centimetres to the closest half centimetre. Breast volume was measured bilaterally in millilitres with plastic cups (figure 5) (122). Volume measurement using specially designed plastic cups is performed routinely in Malmö in the clinic and the method has been validated (123). It has been shown that measurements of breast volume made with plastic cups before a mastectomy correlate well to the volume of the mastectomy specimen (124).

Figure 5. Plastic cups for measurement of breast volume

The tumours were measured in millimetres. The size of palpable tumours was measured clinically and non-palpable tumours were measured with ultrasound or mammography. The position of the tumours was estimated to the nearest clock hour, and the distance from the NAC was measured in centimetres to the closest half centimetre. Tumours behind the NAC were registered as having a “central” position.

Nipple to jugular notch distances were measured in centimetres to the closest half centimetre.

The patients were photographed with a Nikon® Coolpix S200 camera (Nikon Europe, Amsterdam, the Netherlands) in a frontal projection with arms down.

Measurements and patient photos were entered into the study database (figure 6), which was constructed and designed specifically for the OPB-pME study, in FileMaker® Pro (FileMaker Inc, Santa Clara, CA, USA) software.

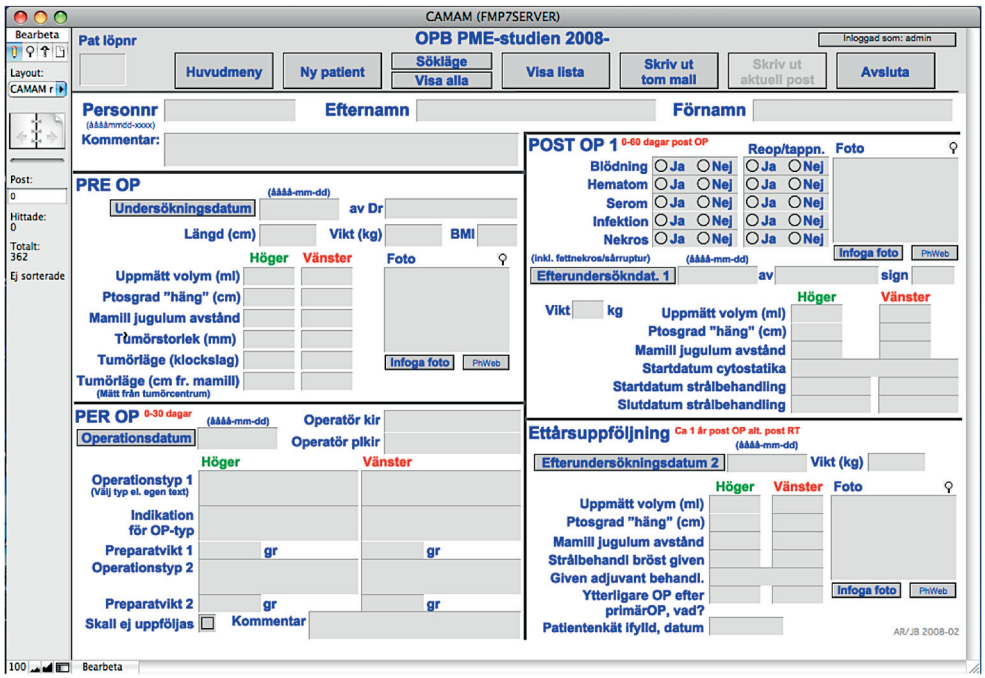


Figure 6. Layout of study database (in Swedish)

Analysis of BCS patients not included in the OPB-pME study

A comparison between the women registered in the study database and the Swedish Breast Cancer Registry was made to establish the proportion of eligible women included. The six Regional Cancer Centres in Sweden administer the register through the Information Network for Cancer Care (INCA). The inclusion rate in 2012 was reported to be 98.1% (125).

During the same time period as that in which the study patients were operated, 748 patients were registered in INCA as primarily operated with BCS at SUS Malmö. Only patients with verified malignancies are registered in this register. Since the study database also included 43 patients for whom the histopathological analysis showed non-malignant findings, such as atypical ductal hyperplasia or intraductal papilloma, these were left out of the comparison. Three of these patients were later excluded from further analysis since two withdrew their consent and for the third, the informed consent could not be verified.

As seen in the study flow chart (figure 4) there were patients registered in the study database who for different reasons were not operated (n=6) or underwent a primary mastectomy (n=24). These were also withdrawn from the calculation. Nineteen patients registered in the study database later declined to participate or withdrew their approval. There were 16 patients in the study database who were not registered in INCA. Comparable samples were thus: (653-43-6-24+19)/(748+16) = 0.78 (78%). The number of patients not registered in the study database for unknown reasons was 165.

To establish whether the study population was representative of the breast cancer population, a comparison was made of the baseline characteristics obtainable from the Swedish Breast Cancer Registry (age, menopausal status, T stage, histopathology) of the 165 non-participants and of the 583 patients registered in both the study database and in INCA. The non-participants were somewhat older, with a median age of 63 (range 29-97; IQR 52-70) compared to 60 (range 27-87; IQR 51-67). The other characteristics are shown in table 2. A larger proportion of the 165 patients not included in the study had no visible primary tumour (T0), or a tumour where the size could not be assessed (TX), a tumour fixed to the chest wall (T4a), or CIS (Tis). Invasive carcinoma was more common among the study participants.

Table 2. Comparison of patients not registered in study database to those registered

	Registered in study database and INCA n=583	Not registered in study database n=165
Menopausal status		
Premenopausal	132 (22.6%)	37 (22.4%)
6 months-5 years post menopause	59 (10.1%)	17 (10.3%)
>5 years post menopause	379 (65.0%)	106 (64.2%)
Unknown[a]	13 (2.2%)	5 (3.0%)
T stage[b]		
T0/X Cannot be assessed	14 (2.4%)	12 (7.2%)
T1 ≤ 20 mm	414 (71.0%)	90 (54.5%)
T2 > 20 ≤ 50 mm	105 (18.0%)	27 (16.4%)
T3 >50 mm	2 (0.3%)	0 (0%)
T4a Fixed against chest wall	0 (0%)	3 (1.8%)
Tis Cancer in situ	48 (8.2%)	33 (20.0%)
Invasive cancer[b]		
No invasive part	59 (10.1%)	37(22.4)
Cancer of NST[c]	393 (67.4%)	91 (55.1%)
Lobular cancer	67 (11.5%)	23 (13.9%)
Both NST and lobular	6 (1.0%)	0 (0%)
Medullar	13 (2.2%)	0 (0%)
Other	45 (7.7%)	14 (8.5%)
Cancer in situ		
No cancer in situ	117 (20.1%)	25 (15.2%)
DCIS	380 (65.2%)	112 (67.9%)
LCIS	59 (10.1%)	21 (12.7%)
DCIS and LCIS	24 (4.1%)	5 (3%)
Other	3 (0.5%)	2 (1.2%)

a.) for example after hysterectomy.

b.) p-value < 0.05.

c.) no special type (previously ductal cancer).

Surgery

Breast-conserving surgery was generally recommended in women with tumours smaller than four centimetres if the surgeon deemed it possible to obtain a good postoperative aesthetic result. Oncoplastic breast surgery was discussed with women in whom the tumours were large in relation to breast volume. At the time of the operation, the surgeon registered the surgical technique according to predetermined categories. Six surgeons operated on 99% of the patients. The majority of patients underwent conventional BCS (n=502). Five women had tumours in both breasts and were consequently operated bilaterally. In 30 patients, techniques of OPBS had been used, either with a partial mastectomy using the Grisotti technique (37) (n=2), by a cylindrical incision followed by purse-string sutures (n=11), by a therapeutic reduction mammaplasty with standard technique (n=6), or by use of a secondary (n=4) or an extended (n=7) pedicle (40). A breast reduction procedure on the opposite breast to achieve symmetry was performed in seven cases.

Non-palpable breast masses were preoperatively indicated by a radiologist with a hook-wire using ultrasound or stereotactic mammographic guidance. In order to examine the nodal status of the axilla using the sentinel node technique a radioactive isotope (99mTc-Nanocoll), in some cases together with blue dye, was preoperatively injected near the location of the tumour. Sentinel nodes located by gamma detector and/or by visualising the blue stain were surgically removed. Axillary clearance was undertaken if metastases were found.

In the operating room, a nurse weighed the excised breast tissue to the nearest gram. The estimated percentage of breast volume excised (EPBVE) was calculated by comparing this weight to the preoperative breast volume measurement in millilitres, assuming a one to one correlation between weight and volume. This is an approximation, which has been established and used in previous studies (126, 127).

Complications

According to the study protocol, complications that were to be registered at the first postoperative follow-up visit (within two months from surgery) were: bleeding, haematoma, seroma, infection, and fat necrosis. Infection was defined as administered antibiotics due to clinical symptoms, with or without a positive bacterial culture. Only those complications leading to active measures, such as reoperation for bleeding, evacuation of haematoma, aspiration of seroma, and revision of necrosis were analysed. An early postoperative photo was taken at the same visit.

Adjuvant therapy

A review of patient charts was undertaken to check which adjuvant treatment had been administered. Twenty-five women had been included in a simultaneous study, which investigated oncological outcome in women over 65 years of age who did not receive radiotherapy after BCS, and these women thus deviated from national guidelines (128). Patients undergoing radiotherapy were treated with 50 Gy per 25 fractions or 40 Gy per 16 fractions depending on age and tumour characteristics. A 16 Gy boost to the affected breast quadrant was administered to women younger than 40 years with an invasive breast cancer component.

Follow-up

One-year follow-up visit

The patients were again invited to a follow-up visit about a year after surgery and completed radiotherapy. The median time from operation to the follow-up examination was 16 months (IQR 15-18; range 11-23).

In all, 334 patients attended this follow-up examination. Of the 193 patients missing, 131 had not received the invitation as planned due to limited resources in the out-patient clinic during certain time periods (figure 4).

A nurse examined the patients at the one-year follow-up. Weight was again measured, as were nipple to jugular notch distances, and volumes of the breasts bilaterally. The patients were also photographed in the same way as preoperatively and were given a study-specific questionnaire (SSQ).

Study-specific questionnaire

At the one-year follow-up visit the patients were asked to complete an SSQ, which was constructed specifically for the OPB-pME study. The questionnaire was originally in Swedish. In the supplemental material to **paper I**, it is presented in a translated version (supplement Fig. 2). The reason for using an SSQ was that when the OPB-pME study was initiated, no appropriate validated questionnaire existed. Validated questionnaires at the time were mostly generic instruments that were not designed to evaluate the effect of a specific surgical procedure.

The chosen questions in the SSQ were influenced by questionnaires previously designed in the same institution and by some of the same authors (129, 130).

The first three questions in the SSQ referred to aspects of the preoperative consultation. The questions were chosen to find out the patients' opinions on the adequacy of the preoperative information and the possibility to participate in the decision-making process, since this was expected to be an important aspect of care (131).

Since one major end-point was to evaluate satisfaction with the aesthetic result after BCS with conventional versus OPBS techniques, several questions focused on aspects of the aesthetic result. To enable understanding of which aspect of the aesthetic result affected satisfaction most, apart from a question regarding the general appearance of the operated breast, also more detailed questions were posed regarding satisfaction with symmetry between the breasts, size and shape of the operated breast, location and appearance of the NAC, and appearance of the scars.

As skin sensitivity may be impaired by more extensive incisions, which are inherent to techniques of OPBS, the patients were asked about their satisfaction regarding this functional outcome.

A psychologist was consulted during the process of constructing the questionnaire. A four-point scale was actively chosen on her advice, to avoid a middle alternative. This also made it possible to dichotomise the results in future analyses.

Prior to usage, the readability and comprehension of the questionnaire was verified in a pilot test, which included five patients. To test the readability of patient questionnaires has been recommended to ensure that the language is such that persons outside the medical or academic field can understand the questions. Instruments that are difficult to comprehend could cause lower completion rates or misinterpretation of the questions, leading to inaccurate results (132).

BCCT.core

Photos from the one-year follow-up (n=310, figure 4) were analysed with the BCCT.core software by the author (CD). This was not planned at the start of the study. Hence, there were no calibration marks in the photos, as recommended by the user instructions (133). A marking was to be placed 25 cm vertically down from the jugular notch. Since the nipple to jugular notch distances had been measured in centimetres in a standardised way at the follow-up visit, these could be used to obtain the calibration point. The GIMP© software (GNU image manipulation program), an open source image editor, was used (by the author) to perform the calculation. The nipple to jugular notch distances in the photos were measured using the software and divided by the distances recorded at the follow-up visit. This value, which thus represented a centimetre in the photo, was then multiplied by 25. The resulting distance was used to place the calibration mark in the photo.

The photos were then analysed using the BCCT.core software. An example picture is shown below in figure 7.

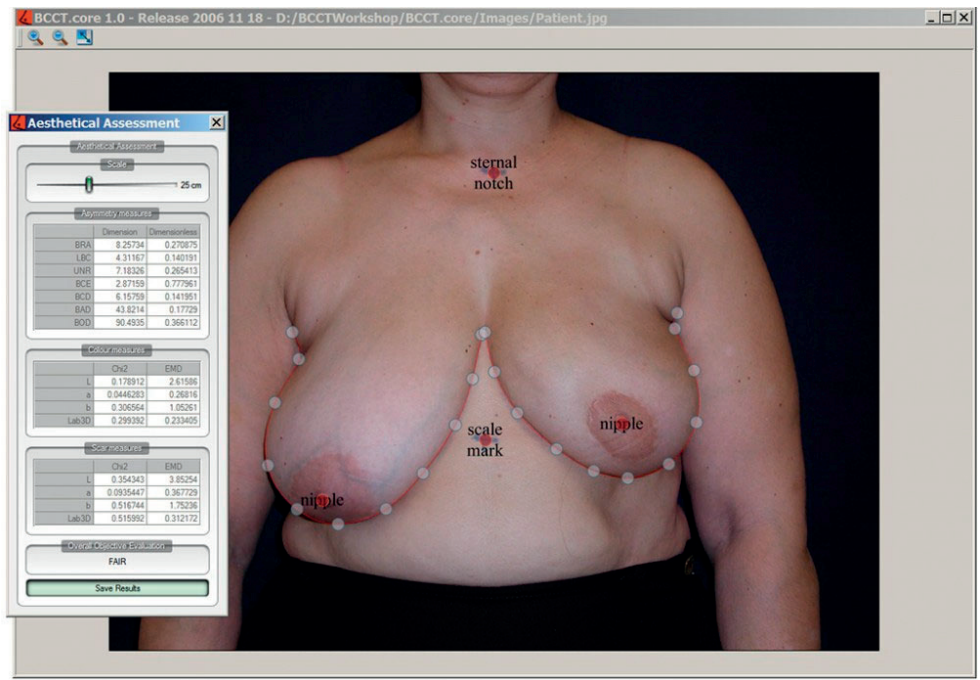


Figure 7. BCCT screenshot from http://medicalresearch.inescporto.pt/breastresearch/index.php/BCCT.core access date 2019-02-25. Printed with permission.

After each photo had been imported into the software, the contours of the breasts were marked out manually. The nipples, the jugular (sternal) notch and the scale mark were also indicated. Thereafter the software performed the analysis and produced a rating ("Excellent", "Good", "Fair", or "Poor") according to the specific algorithm (69).

Photo panel evaluation

A panel of three assessors performed the photo panel evaluation. The panel consisted of a registered nurse from the Department of Breast Surgery, a registered nurse from the Department of Plastic and Reconstructive surgery, and a plastic surgeon who is also specialised in general surgery. These assessors were chosen as they each had experience of patients undergoing breast surgery. It was an active choice not to include persons without prior experience of breast surgery, as it has been shown that agreement between non-experienced assessors is poor (68).

The panel evaluated the photos of 215 patients (figure 4), for whom both preoperative and postoperative photos were available. The assessors performed the evaluation individually, i.e. were blinded to each other. The Microsoft Power Point® software version 2013 for Windows® (Microsoft, Redmond, Washington, USA) was used to present the photos. The preoperative photo was shown first. An asterisk marked the affected breast. The postoperative photo was then shown next to the preoperative photo to enable comparison of the aesthetic outcome of the operated breast with the same breast preoperatively. The assessors had a time limit of one minute and 30 seconds per patient. The photos were shown in random order. The assessors were asked to rate the same aspects of aesthetic results as included in the SSQ, namely the general appearance, size, and shape of the operated breast and the general appearance and position of the NAC, compared to the same breast preoperatively. Also, the symmetry between the breasts preoperatively as well as postoperatively was evaluated, as was the appearance of the scar in the postoperative photo.

The same four-point scale as in the BCCT.core was used for the rating, i.e. "Excellent", "Good", "Fair", or "Poor". The assessors could also state: "Cannot be evaluated". In an attempt to standardise the method, example pictures were shown to the assessors before the evaluation sessions. These pictures were from a study by Wang et al. (86).

The assessors re-evaluated the photos after two weeks. The photos were then again shuffled, to obtain a different random order. External factors such as time of day and place of evaluation were very similar for assessors one and two. Patient-related matters, which had to be attended to immediately, interrupted the first

evaluation session by the third assessor (the surgeon). Hence, she evaluated the second half of the photos on the following day.

Breast-Q™

The postoperative part of the Breast-Q™ BCT module was sent in 2015 by mail to the study population (n=489, figure 4). Two reminder letters were sent and after this, 371 questionnaires were returned. A letter of information was sent with the Breast-Q™ questionnaire, together with an additional questionnaire concerning demographic characteristics. The patients were in this additional questionnaire asked which year they last underwent breast surgery. Of the responders, 23 women had undergone additional breast surgery after the one-year follow-up visit and were excluded. The median time from operation to completion of the questionnaires was 5.5 years (range 3.7-7.9).

The additional questionnaire comprised questions about marital status, home and work situation, level of education, smoking, and present body weight. Most of the questions had pre-set answer categories. Three questions concerning smoking were constructed to investigate smoking consumption. The design was based on the questionnaire completed by study participants in the Malmö Kost Cancer study (134).

The completed Breast-Q™ questionnaires were analysed according to the instructions provided by the MAPI Research Trust (see page 36). If a patient had neglected to answer more than half of the questions in one domain, this domain was excluded from further analysis. If less than half were missing, the mean number of the answered questions replaced those missing. The totals for each domain were converted to Q-scores between 0 and 100 according to a manual scoring table also provided by the MAPI Research Trust.

In **papers III** and **IV**, the domains “Satisfaction with breasts” and “Psychosocial well-being” were used for further analyses since these domains had acceptable response rates and were considered the most interesting for the study aims. These domains are displayed as figures 8 and 9.

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) VERSION 2.0
SATISFACTION WITH BREASTS

The following questions are about your breasts and your breast cancer treatment (by treatment, we mean lumpectomy with or without radiation). If you have had a lumpectomy and radiation of both breasts, answer these questions thinking of the breast you are least satisfied with.
With your breasts in mind, in the past week, how satisfied or dissatisfied have you been with:

		Very Dissatisfied	Somewhat Dissatisfied	Somewhat Satisfied	Very Satisfied
a.	How you look in the mirror clothed?	1	2	3	4
b.	The shape of your lumpectomy breast when you are wearing a bra?	1	2	3	4
c.	How normal you feel in your clothes?	1	2	3	4
d.	Being able to wear clothing that is more fitted?	1	2	3	4
e.	How your lumpectomy breast sits/hangs?	1	2	3	4
f.	How smoothly shaped your lumpectomy breast looks?	1	2	3	4
g.	The contour (outline) of your lumpectomy breast?	1	2	3	4
h.	How equal in size your breasts are to each other?	1	2	3	4
i.	How normal your lumpectomy breast looks?	1	2	3	4
j.	How much your breasts look the same?	1	2	3	4
k.	How you look in the mirror unclothed?	1	2	3	4

BREAST-Q® VERSION 2.0 © Memorial Sloan Kettering Cancer Center and The University of British Columbia, 2017, All rights reserved

Figure 8. Breast-Q™ domain "Satisfaction with breasts". Printed with permission.

BREAST-Q™ - BREAST CONSERVING THERAPY MODULE (POSTOPERATIVE) VERSION 2.0
PSYCHOSOCIAL WELL-BEING

With your breasts in mind, in the past week, how often have you felt:

	None of the time	A little of the time	Some of the time	Most of the time	All of the time
a. Confident in a social setting?	1	2	3	4	5
b. Emotionally able to do the things that you want to do?	1	2	3	4	5
c. Emotionally healthy?	1	2	3	4	5
d. Of equal worth to other women?	1	2	3	4	5
e. Self-confident?	1	2	3	4	5
f. Feminine in your clothes?	1	2	3	4	5
g. Accepting of your body?	1	2	3	4	5
h. Normal?	1	2	3	4	5
i. Like other women?	1	2	3	4	5
j. Attractive?	1	2	3	4	5

BREAST-Q® VERSION 2.0 © Memorial Sloan Kettering Cancer Center and The University of British Columbia, 2017, All rights reserved

Figure 9. Breast-Q™ domain "Psychosocial well-being". Printed with permission.

Statistical methods

The IBM Statistical Package for the Social Sciences (SPSS®) for Macintosh version 22.0 (IBM corp. Armonk, NY, USA) was used for the statistical analyses.

Paper I

To investigate potential determinants for patient satisfaction with the postoperative aesthetic result, logistic regression analysis was used. Logistic regression analysis was also undertaken to study potential determinants for patient satisfaction with skin sensitivity. To enable these analyses, the outcome variables, originally on a four-point scale, were dichotomised (1+2 versus 3+4). The analyses resulted in odds ratios (OR) together with confidence intervals (CI) for the different determinants in relation to not being satisfied. Continuous variables were categorised into subgroups in order to simplify the interpretation. Cut-off values were chosen either by often-used values (age and BMI) or by the median value. To decrease the number of subgroups regarding tumour location, the breast was divided into quadrants with 12 o'clock placed in the upper outer quadrant. Two additional models were created, one that adjusted for age and BMI, and one that also adjusted for variables that were statistically significant in either of the two previous models.

A sensitivity analysis was performed when analysing satisfaction regarding symmetry, excluding 16 patients who had undergone surgery of the opposite breast, in order to see how this affected the outcome.

Paper II

To investigate the association between potential determinants and perceived possibility to participate in the decision-making process according to the SSQ, a logistic regression analysis was performed. The dependant variable (rating) was dichotomised (1+2 versus 3+4) and continuous independent variables were categorised. The patient's perceived possibility to participate in the decision-making process was then analysed as a potential determinant for whether she considered her expectations to have been met and whether she was satisfied with the aesthetic outcome and symmetry. The analyses were age-adjusted.

In a sensitivity analysis, 25 patients with benign histopathological findings were excluded to investigate whether this changed the results.

Paper III

Cross-tables were used to visualise the associations between BCCT.core scores and various patient and treatment factors. Statistically significant differences (*p*-values less than 0.05) were identified with a chi-2 test.

The Breast-Q™ Q-scores of each of the domains "Satisfaction with breast" and "Psychosocial well-being" were grouped into quartiles and compared separately to the BCCT.core scores in a cross-table. The association between BCCT.core scores and Q-scores below the median value was then studied in a logistic regression analysis. Apart from the crude analysis, an age-adjusted model was constructed, as well as one that adjusted for variables that had been shown to have a statistically significant association with the BCCT.core scores.

Paper IV

Kappa statistics were used to investigate inter-observer agreement between the three assessors in the photo panel evaluation.

Kappa statistics were first introduced by Cohen in 1960, and as such, are often referred to as Cohen's kappa (135). In 1968, he described a method, now known as weighted kappa, to use for ordinal data. This method takes into consideration that the discrepancy between for example poor versus excellent is larger than between poor versus fair (136).

As the outcome in the current study was ordinal, weighted kappa analysis was used. The weighted kappa values of the agreement between the assessors' two different individual evaluation sessions were calculated to obtain intra-observer agreement. The third assessor's first half and second half from the first evaluation session were calculated separately.

Assumptions that need to be met when using kappa statistics are that the scale on which the observers rate is nominal, with an equal number of categories, which do not overlap. The observations must be paired, i.e. two raters assess the same thing. The raters must be the same throughout the assessment and must be blinded to each other (137, 138).

If there is no correlation other than that caused by chance between two observations, the kappa value is 0. Complete agreement gives a value of 1. Negative kappa values are possible and represent disagreement between raters. In 1977, Landis and Koch proposed criteria that are often used today for the interpretation of kappa values (139). According to these criteria, kappa values up

to 0.2 show slight agreement, 0.21-0.4 fair, 0.41-0.6 moderate, 0.61-0.8 substantial, and 0.81-1.0 almost perfect agreement.

To enable comparisons with patient satisfaction measured with the SSQ and the BCCT.core scores, the mean of the three assessors' first evaluation sessions was calculated and rounded off to the nearest integer. The correlations between the different evaluation modalities were analysed using Spearman's rho (r_s) as the correlation coefficient. A p-value below 0.05 was considered statistically significant.

In order to study which of the three evaluation modalities best predicted aspects of HRQoL, receiver operating characteristics (ROC) curves were used (140). Outcome variables were the Q-scores of the chosen Breast-Q™ domains and quartiles of the separate Q-scores were used as cut-offs. Area under the curve (AUC) values were obtained, together with *p*-values.

A sensitivity analysis was performed for the prediction of Q-scores, excluding patients who had undergone chemotherapy, since the baseline comparison between the patients who had been evaluated with the different evaluation modalities showed a discrepancy in frequency of administered chemotherapy.

Additional analyses

As neither the final results of the evaluations with different methods, nor complete information concerning demographic characteristics, were available when the first manuscripts were completed, some additional analyses of interest were performed during the process of writing this thesis.

With the aim of determining which patients are at risk of a poor postoperative aesthetic result after conventional BCS, the association between different potential risk factors and results of the different evaluation methods was analysed. As previously, the four-point scales were dichotomised (1+2 versus 3+4) to enable logistic regression analyses. In addition to the previous variables that were considered potential determinants, smoking was added as a potential risk factor for poor results.

The continuous variables were categorised. Categorisation of continuous variables reduces the information potentially available in the material. However, it makes the results more easily interpretable for use in clinical practice. How to choose cut-off values can be discussed. In **paper I**, cut-off values were based on often-used values or the median values. For this additional analysis, the cut-off values of age were adjusted to 55 and 60, as these distribute the study cohort into three more equally sized groups.

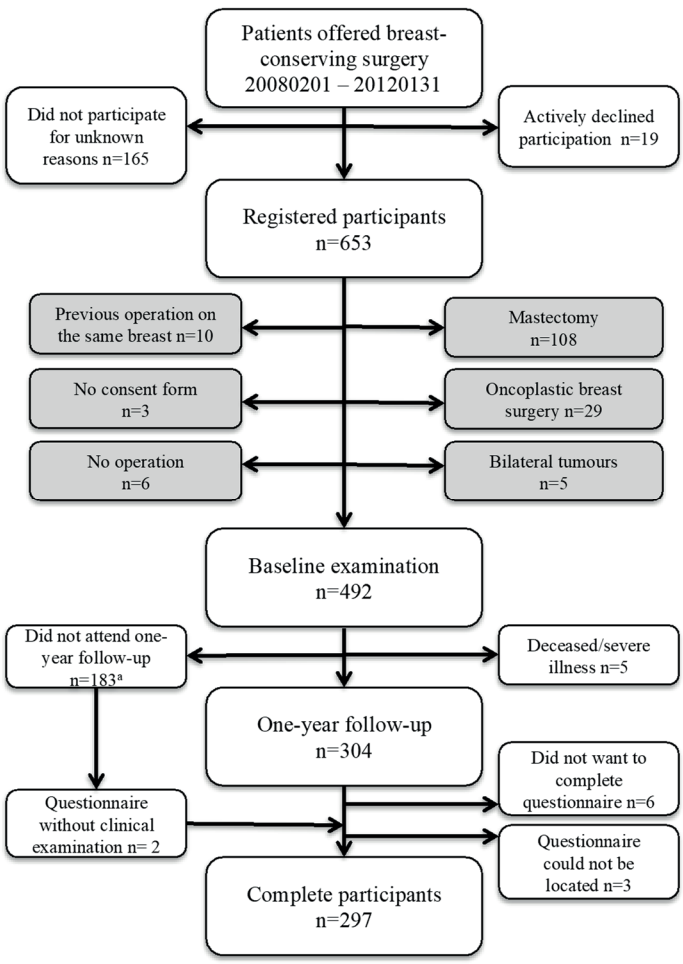
Ethics

The study was conducted in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments. It was approved by the regional ethics committee of Lund University (Dnr 488/2007 and 230/2015). All patients gave informed written consent.

Results

Paper I

The study cohort of **paper I** included 297 patients who had undergone conventional BCS (figure 10).



a. Patient did not attend: Unknown reason (n=60); Invitation was not sent (n=123)

Figure 10. Flow chart paper I

The median age of the study population was 62 years. The characteristics of the study population were compared to the patients lost in follow-up in table 3.

Table 3. Characteristics of participants and non-participants.

	Study population[a] n=297	Not complete[b] n=67	Not invited[c] n=123
Age (years)	62 (54-68; 34-85)[d]	55 (48-62)[e]	59 (49-67)[e]
BMI (kg/m^2)	25 (23-29; 18-51)[d]	25.5 (22-30)[e]	26 (23-29)[e]
Tumour size (mm)	15 (10-20; 0,5-60)[d]	13.5 (9-20)[e]	15 (10-20)[e]
Breast size (ml)	500 (375-737.5; 160-1800)[d]	475 (360-790)[e]	510 (350-800)[e]
EPBVE[f] (%)	12.4 (9.2-17.1; 1,3-73,8)[d]	11.3 (8.0-14.1)[e]	12.5 (9.4-16.4)[e]

a. Complete participants.
b. Patients who did not attend follow-up or complete questionnaire or questionnaire missing.
c. Patients who did not receive invitation to follow-up (administrative reasons).
d. Median (interquartile range; range).
e. Median (interquartile range).
f. Estimated percentage of Breast Volume Excised.

Of the patients who had completed the SSQ, 84% were satisfied or very satisfied with the aesthetic result of the operated breast, 68% with the symmetry between the breasts and 67% with the skin sensitivity of the operated breast (table 4).

Table 4. Results of the study-specific questionnaire

	Very satisfied n (%)	Satisfied n (%)	Not entirely satisfied n (%)	Dissatisfied n (%)	Missing n (%)
Aesthetic outcome	123 (41.4)	126 (42.4)	28 (9.4)	5 (1.7)	15 (5)
Symmetry	74 (24.9)	128 (43.1)	47 (15.8)	14 (4.7)	34 (11.4)
Skin sensitivity	82 (27.6)	117 (39.4)	65 (21.9)	8 (2.7)	25 (8.4)
Shape of op. breast	98 (33.0)	139 (46.8)	30 (10.1)	4 (1.3)	26 (8.8)
Size of op. breast	94 (31.6)	142 (47.8)	36 (12.1)	2 (0.7)	23 (7.7)
Appearance of scar	122 (41.1)	118 (40.0)	27 (9.0)	6 (2.0)	24 (8.1)

Factors associated with not being entirely satisfied or being dissatisfied with the aesthetic result were an EPBVE ≥20%, axillary clearance, re-excision, and postoperative infection (table 5). In the multivariable analysis, only axillary clearance remained statistically significant.

Regarding symmetry, patients with a BMI ≥30 kg/m^2, a specimen weight over median value, re-excision, and postoperative infection were less satisfied (table 5). Re-excision was the only factor remaining statistically significant in the multivariable analysis.

Poor satisfaction with skin sensitivity was associated with BMI ≥25-<30 kg/m^2, tumour size over median value, EPBVE ≥20%, axillary clearance, re-excision, radiotherapy, and postoperative infection (table 5). In the multivariable analysis, BMI, tumour size, re-excision, and infection remained statistically significant.

Odds ratios with 95% CI for the factors associated with satisfaction regarding aesthetic result, symmetry, or skin sensitivity, with statistical significance in either the crude or the adjusted analyses, are presented in table 5.

Table 5. Factors associated with less satisfaction regarding aesthetic result, symmetry and skin sensitivity. (Crude analysis)

		Aesthetic result OR (95% CI)	Symmetry OR (95% CI)	Skin sensitivity OR (95% CI)
BMI (kg/m^2)	< 25		1	1
	≥ 25 - 30		1.66 (0.84-3.26)	1.79 (0.97-3.30)
	≥ 30		2.14 (1.02-4.46)	1.33 (0.65-2.73)
Tumour size (mm)	< 15			1
	≥ 15			2.64 (1.49-4.68)
Specimen weight (g)	< 63		1	
	≥ 63		2.32 (1.28-4.22)	
EPBVE (%)	< 10	1		1
	≥ 10 - 20	1.30 (0.51-3.30)		1.47 (0.77-2.81)
	≥ 20	3.71 (1.30-10.65)		2.57 (1.11-5.96)
Axillary clearance	No	1		1
	Yes	2.94 (1.32-6.59)		2.19 (1.13-4.23)
Re-excision	No	1	1	1
	Yes	2.79 (0.94-8.25)	3.32 (1.28-8.60)	3.80 (1.43-10.02)
Postoperative infection	No	1	1	1
	Yes	3.0 (1.0-8.95)	2.90 (1.09-7.71)	3.35 (1.30-8.62)
Radiotherapy	No			1
	Yes			3.31 (1.13-9.70)

Paper II

The study cohort of **paper II** consisted of 324 patients (figure 11).

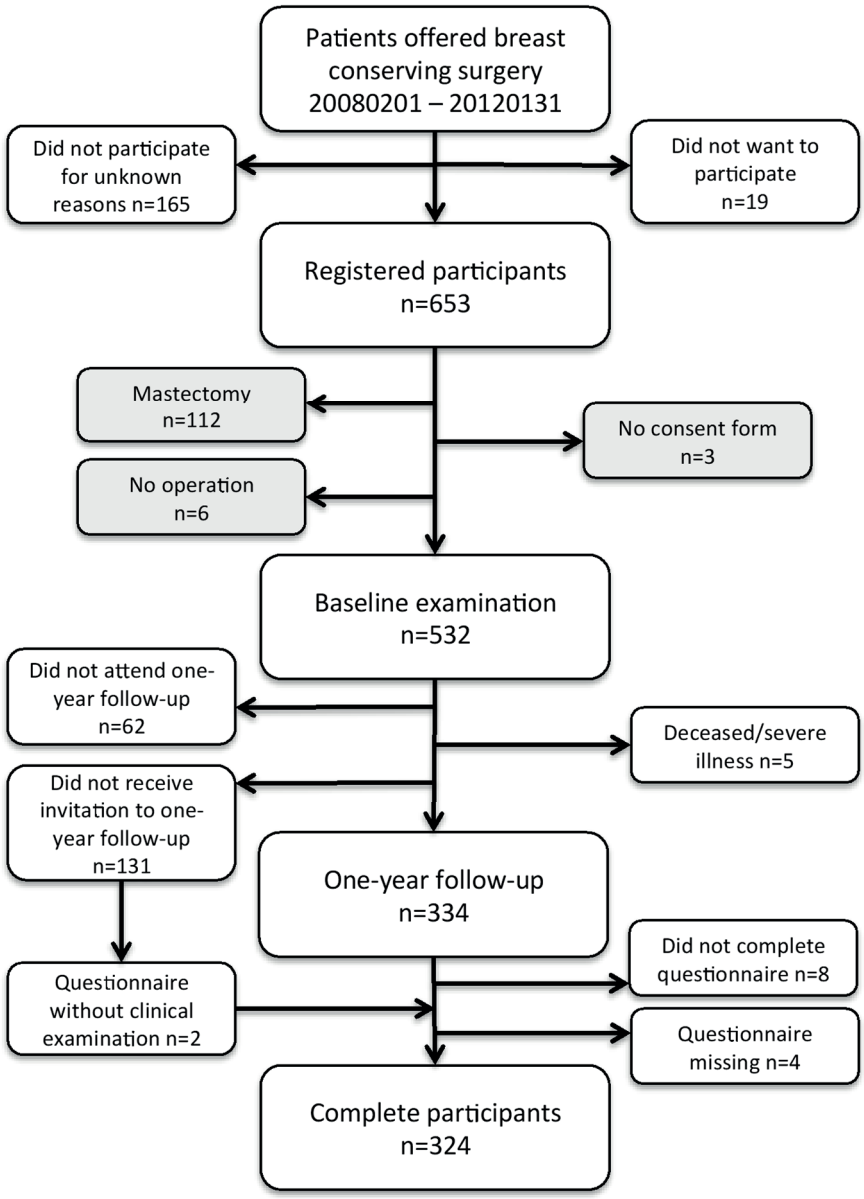


Figure 11. Flow chart paper II

In all, 173 women (53,4%) stated at the one-year follow-up visit that they had not or only partly perceived a possibility to participate in the decision-making process regarding surgical method (table 6).

Table 6. Results of the study-specific questionnaire (SSQ)

	Not at all n (%)	Partly n (%)	Almost entirely n (%)	Entirely n (%)	Missing n (%)
Did you feel that you could take part in deciding which operation should be performed?	119 (36.7)	54 (16.7)	40 (12.3)	94 (29.0)	17 (5.2)
Did you receive enough information regarding the expected aesthetic result?	24 (7.4)	54 (16.7)	77 (23.8)	162 (50.0)	7 (2.2)
Has the operation met your expectations regarding the aesthetic result?	9 (2.8)	24 (7.4)	90 (27.8)	194 (59.9)	7 (2.2)

The results were almost identical in the sensitivity analysis excluding patients with benign histopathology.

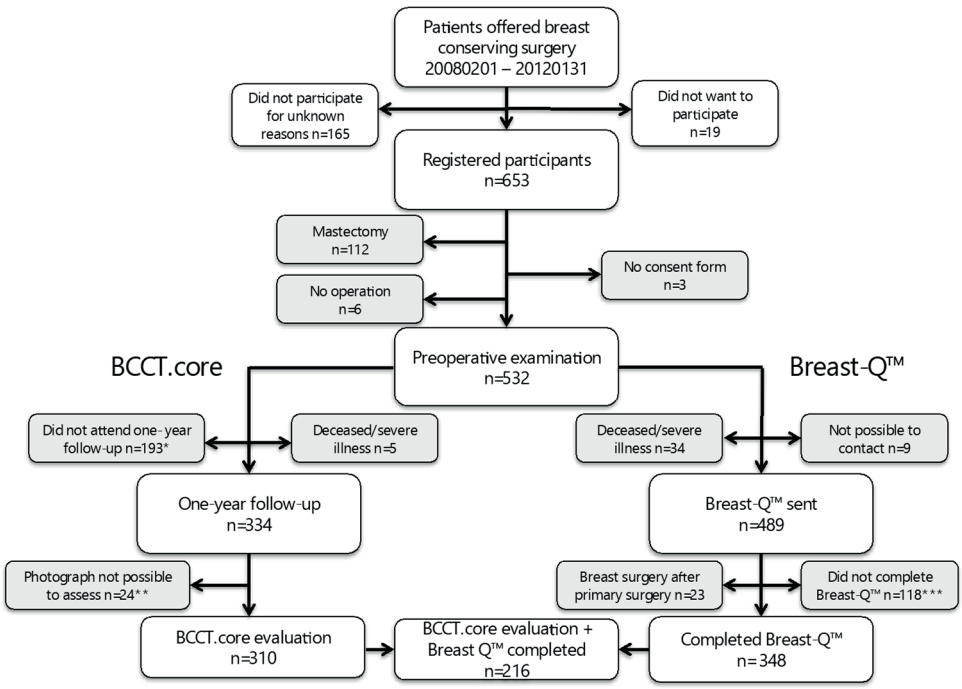
When investigating different potential determinants for not having perceived a possibility to participate in the decision-making process, the only factor that showed a statistically significant association was how the patient had reported preoperative information regarding the expected postoperative aesthetic result. The patients who stated that they had “not at all” or “partly” received enough preoperative information had less often perceived a possibility to decide on treatment (OR 5.4; CI 2.8-10.4).

The women who had perceived a possibility to participate in the decision-making process were more often satisfied or very satisfied with the aesthetic result (OR 2.7; CI 1.2-6.3). They had also to a higher degree had their expectations of the aesthetic result fulfilled (OR 5.9; CI 2.0-17.4).

According to the SSQ, seven women stated that they had preferred a mastectomy instead of BCS. Six of these had replied “not at all” or “partly” to the question regarding whether they perceived it possible to participate in the decision-making process.

Paper III

The number of patients who had both undergone BCCT.core evaluation and completed the Breast-Q questionnaire was 216 (figure 12).



* Unknown reason n=62; Did not receive invitation due to lack of resources in the out-patient clinic n=131
** Photograph missing n=11; NJ-value missing n=2; No visible sternal notch n=1; Photo not taken from front n=6; BCCT.core missguiding n=4
*** Did not complete for unknown reasons n=111; Actively gave notice that they did not want to complete the Breast-Q™ n=7

Figure 12. Flow chart paper III

The aesthetic result according to the BCCT.core evaluation was excellent in 15.8% (n=49), good in 57.4% (n=178), fair in 23.5% (n=73), and poor in 3.2% (n=10).

Low BMI (<25) and small breasts preoperatively (<450 ml) had statistically significant associations with higher BCCT.core scores (p=0.002 and p=0.012 respectively) whereas radiotherapy was associated with lower scores (p<0.001).

The median Q-score for the Breast-Q™ domain "Satisfaction with breasts" was 66, and for "Psychosocial well-being" it was 82.

A cross-table investigating BCCT.core result in relation to Breast-Q™ quartiles is shown in table 7.

Table 7. Distribution of BCCT.core results in the different Breast-Q™ quartiles™.

	Breast-Q™ Satisfaction with breasts			
	≤ 57 n (%)	58-66 n (%)	67-80 n (%)	>80 n (%)
BCCT.core result				
Good/Excellent	33 (33.7)	34 (44.2)	52 (55.3)	44 (57.9)
Fair/Poor	23 (23.5)	13 (16.9)	10 (10.6)	5 (6.6)
Missing	42 (42.9)	30 (39.0)	32 (34.0)	27 (35.5)
BCCT.core result				
Excellent	3 (5.4)	4 (8.5)	12 (19.4)	12 (24.5)
Good	30 (53.6)	30 (63.8)	40 (64.5)	32 (65.3)
Fair	19 (33.9)	13 (27.7)	9 (14.5)	4 (8.2)
Poor	4 (7.1)	0 (0)	1 (1.6)	1 (2.0)

	Breast-Q™ Psychosocial well-being			
	≤ 59 n (%)	60-82 n (%)	83-99 n (%)	100 n (%)
BCCT.core result				
Good/Excellent	27 (33.3)	45 (48.4)	18 (46.2)	71 (55.5)
Fair/Poor	16 (19.8)	16 (17.2)	6 (15.4)	12 (9.4)
Missing	38 (46.9)	32 (34.4)	15 (38.5)	45 (35.2)
BCCT.core result				
Excellent	3 (7.0)	8 (13.1)	3 (12.5)	17 (20.5)
Good	24 (55.8)	37 (60.7)	15 (62.5)	54 (65.1)
Fair	13 (30.2)	16 (26.2)	4 (16.7)	11 (13.3)
Poor	3 (7.0)	0 (0)	2 (8.3)	1 (1.2)

The patients who had good or excellent aesthetic results according to the BCCT.core more often had Q-scores above median (OR 3.4; CI 1.7-6.8 regarding "Satisfaction with breasts" and OR 2.2; CI 1.1-4.2 regarding "Psychosocial well-being"). The statistical significance of the results remained in the adjusted models.

Paper IV

Patient and tumour characteristics of the study cohort (figure 4), as well as information regarding treatment, are shown in table 8. Since not all patients were examined with all evaluation modalities, the characteristics of the different groups are presented separately. It can be noted that most of the characteristics are very similar between the groups. However, there are differences in the frequencies of administered adjuvant treatment, such as chemotherapy.

Table 8. Characteristics of the study population and also of patients evaluated with different evaluation modalities presented separately.

	Patients included n=532	BCCT.core evaluated n=310	Photo panel evaluation n=215	Breast-Q™ completed n=348
Age (years)[a]	60 (51-67)	62 (54-68)	62 (57-69)	60 (51-67)
BMI (kg/m^2) [a]	26 (23-29)	25 (23-29)	26 (23-29)	26 (23-30)
Breast size (ml) [a]	500 (375-800)	500 (375-790)	500 (400-765)	500 (375-825)
Tumour size (mm) [a]	15 (10-20)	15 (10-20)	15 (10-20)	15 (10-20)
Re-excision rate (n)	38 (7.1%)	20 (6.5%)	15 (7.4%)	23 (6.6%)
Axillar clearance (n)	95 (17.9%)	54 (17.4%)	32 (14.9%)	66 (19.0%)
Invasive cancer[b] (n)				
- of no special type (NST[c])	335 (63 %)	188 (60.6%)	133 (61.9%)	235 (67.5%)
- lobular	42 (7.9%)	26 (8.4%)	15 (7.0%)	26 (7.5%)
- both NST and lobular	2 (0.4%)	2 (0.6%)	1 (0.5%)	1 (0.3%)
- medullary	12 (2.3%)	5 (1.6%)	3 (1.4%)	9 (2.6%)
- other invasive cancer	38 (7.1%)	31 (10%)	17 (7.9%)	25 (7.2%)
Cancer in situ (CIS) [b] (n)				
- DCIS (ductal CIS)	320 (60.2%)	187 (60.3%)	129 (60.0%)	221 (63.5%)
- LCIS (lobular CIS)	33 (6.2%)	20 (6.5%)	11 (5.1%)	21 (6.0%)
- both DCIS and LCIS	19 (3.6%)	13 (4.2%)	7 (3.3%)	12 (3.4%)
- other CIS	3 (0.6%)	3 (1.0%)	1 (0.5%)	2 (0.6%)
T classification[b] (n)				
- Tis (cancer in situ)	41 (7.7%)	21 (6.8%)	20 (9.3%)	23 (6.6%)
- T1 (≤20 mm)	354 (66.5%)	204 (65.8%)	132 (61.4%)	248 (71.3%)
- T2 (>20≤50 mm)	70 (13.2%)	46 (14.8%)	33 (15.3%)	45 (12.9%)
- T3 (>50 mm)	2 (0.4%)	1 (0.3%)	1 (0.5%)	1 (0.3%)
- TX (primary tumour could not be assessed)	10 (1.9%)	5 (1.6%)	4 (1.9%)	6 (1.7%)
Radiotherapy (n)	445 (83.6%)	261 (84.2%)	176 (81.9%)	310 (89.1%)
Chemotherapy [d] (n)	94 (17.7%)	39 (12.6%)	19 (8.8%)	65 (18.7%)
Hormonal therapy (n)	289 (54.3%)	180 (58.1%)	119 (55.3%)	199 (57.2%)

a.) Presented with the median value and interquartile range

b.) Data extracted from the Swedish breast cancer registry (55 patients not registered, whereof 40 patients had non-malignant histopathology).

c.) Previously ductal

d.) Statistically significant difference measured with chi-2 test (p = 0.003)

When the different evaluation modalities were compared to one another using Spearman's correlation coefficient, the correlation between the photo panel evaluation and the SSQ was r_s: 0.29 ($p<0.001$) regarding the aesthetic result of the operated breast and r_s: 0.35 ($p<0.001$) regarding symmetry. Regarding the correlation coefficients when comparing BCCT.core to the symmetry ratings of the photo panel evaluation and SSQ, the correlations were r_s: 0.59 ($p<0.001$) and r_s: 0.25 ($p<0.001$), respectively.

The inter-observer agreement between the three different assessors in the panel, measured with weighted kappa, ranged from 0.43 to 0.48 in the evaluation of aesthetic result of the operated breast and from 0.49 to 0.60 in the evaluation of symmetry. The results were statistically significant.

The intra-observer agreement between the assessors' first and second sessions ranged from 0.53 to 0.66, except for the weighted kappa of one assessor, evaluating symmetry, who had an agreement of 0.14.

The merged photo panel evaluation results regarding the aesthetic result of the operated breast compared to preoperatively were: 41% excellent, 45% good, 10% fair, and 4% poor. The results of postoperative symmetry were: 31% nearly identical breasts, 49% slight asymmetry, 20% notable asymmetry, 1% considerable asymmetry.

The SSQ was shown to predict the results of HRQoL best. When studying the Breast-Q™ domain "Satisfaction with breasts" the AUC-values ranged from 0.61 to 0.80 with a Q-score cut-off of 57. Patient satisfaction with aesthetic result according to the SSQ had the highest AUC-value, i.e. predicted a Q-score above 57 best (figure 13). All p-values were below 0.05 except the photo panel evaluation of general appearance of the operated breast compared to the same breast preoperatively ($p=0.071$).

When analysing "Psychosocial well-being" the AUC-values ranged from 0.52 to 0.73 with a Q-score cut-off of 59.5. Patient satisfaction with symmetry according to the SSQ predicted the results of this domain best (figure 14). The AUC-values of the BCCT.core and the photo panel evaluation of general appearance of the operated breast were not statistically significant (p-values 0.13 and 0.79 respectively). The results from the SSQ and from the panel evaluation regarding symmetry had p-values below 0.05.

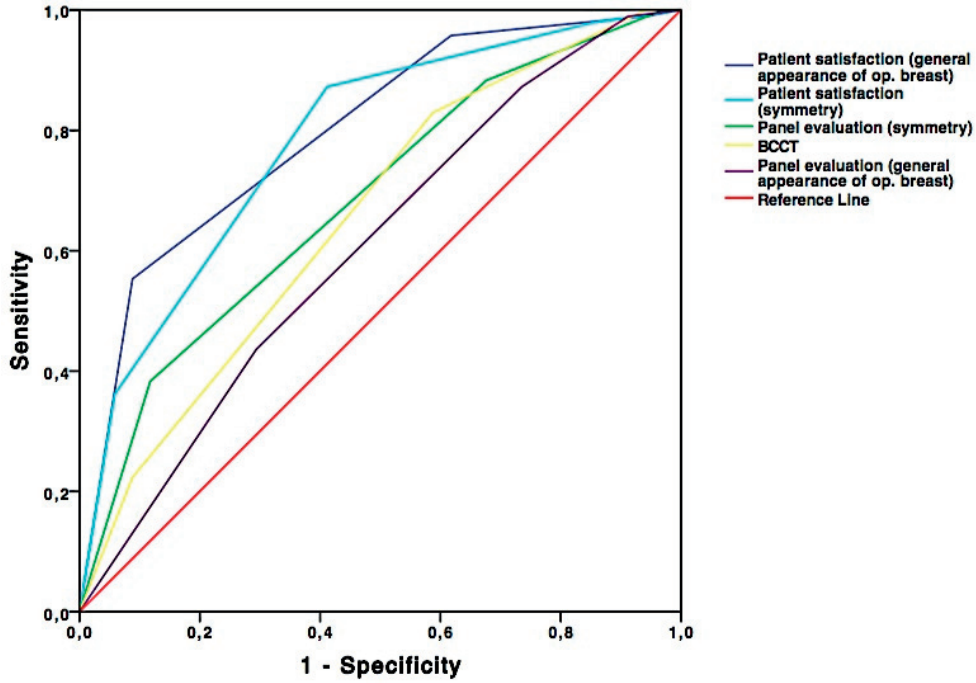


Figure 13. ROC-curve "Satisfaction with breasts". Q-score cut-off 57

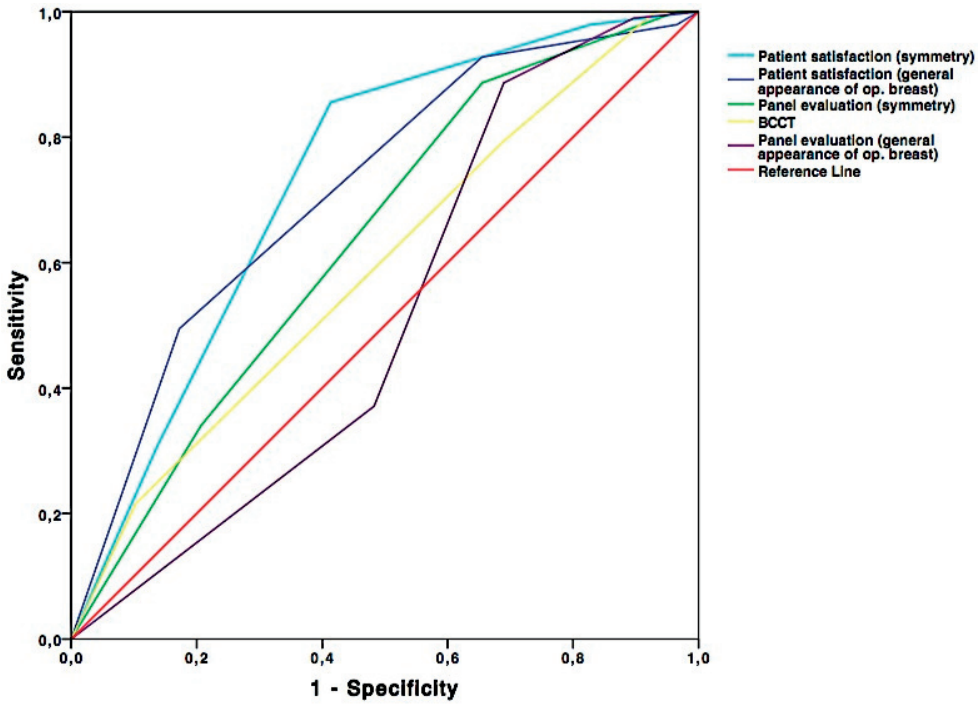


Figure 14. ROC-curve "Psychosocial well-being". Q-score cut-off 59.5.

Additional results

The analysis of potential risk factors for a poor aesthetic result evaluated by patient satisfaction according to the SSQ, the photo panel evaluation and the software BCCT.core is shown in table 9.

It can be observed that the results differed somewhat depending on the evaluation method and also depending on whether the aesthetic result of the operated breast or symmetry was evaluated.

A high BMI was associated with poor results regarding symmetry according to the SSQ and the photo panel evaluation. Also the results of BCCT.core, which were largely based on symmetry measures, were associated with BMI. An EPBVE exceeding 20% was associated with poor results regarding the postoperative aesthetic results of the operated breast according to the SSQ and the photo panel evaluation. The BCCT.core also showed this association. Axillary clearance was associated with poor results according to the SSQ. Re-excision impaired outcome as evaluated by the SSQ and the photo panel. No statistically significant association was shown between poor BCCT.core result and axillary clearance, re-excision, or radiotherapy.

Age did not seem to influence the aesthetic result or symmetry according to any evaluation method, and nor did smoking, chemotherapy, or hormonal therapy.

When comparing the evaluation of postoperative aesthetic result by the SSQ to the photo panel evaluation, tumour location also seemed to have an influence on the outcome according to the photo panel, but not according to the SSQ. A tumour in the upper outer quadrant resulted in a higher photo panel evaluation score, but it can be observed that the confidence intervals are very wide, indicating few patients in some of the groups.

Regarding symmetry, tumour location did not seem to impair the result according to either the SSQ or the panel evaluation. Radiotherapy was associated with poor outcome according to the photo panel evaluation, but not according to the SSQ. It can be observed that no value is presented in the table for photo panel evaluation of the aesthetic result. Of the patients who had not undergone radiotherapy, only one had a poor result according to the photo panel evaluation.

Table 9. Analysis of potential determinants of aesthetic result and symmetry after conventional BCS, evaluated by different methods. Odds ratios are presented with CI in brackets for poor/fair results.

		SSQ aesthetic result	SSQ symmetry	Photo panel aesthetic result	Photo panel symmetry	BCCT.core
Age (years)	<55	1	1	1	1	1
	55-65	1.3 (0.5-3.3)	1.2 (0.6-2.5)	0.7 (0.2-2.3)	0.9 (0.3-2.6)	1.0 (0.5-1.9)
	≥65	0.8 (0.3-2.0)	1.0 (0.5-2.0)	0.9 (0.3-2.6)	1.5 (0.6-3.8)	1.6 (0.8-3.0)
BMI (kg/m^2)	<25	1	1	1	1	1
	25-30	1.4 (0.6-3.3)	1.7 (0.8-3.3)	1.2 (0.5-2.9)	3.7 (1.5-9.1)	1.5 (0.8-2.7)
	≥30	1.3 (0.5-3.5)	2.1 (1.0-4.5)	0.5 (0.1-1.7)	3.8 (1.4-10.1)	2.7 (1.4-5.3)
Smoking	Never	1	1	1	1	1
	Former	1.2 (0.4-3.2)	1.2 (0.6-2.5)	1.3 (0.5-3.6)	0.7 (0.3-1.6)	0.7 (0.3-1.4)
	Current	1.5 (0.4-5.4)	1.8 (0.7-4.7)	2.0 (0.5-7.6)	1.3 (0.4-4.4)	1.0 (0.4-2.7)
EPBVE (%)	<10	1	1	1	1	1
	10-20	1.3 (0.5-3.3)	1.3 (0.7-2.5)	3.0 (0.8-10.8)	2.2 (0.8-6.1)	1.1 (0.6-2.0)
	≥20	3.7 (1.3-10.7)	1.8 (0.7-4.4)	4.0 (1.0-17.0)	4.2 (1.3-13.6)	2.7 (1.2-6.2)
Quadrant	UOQ	1	1	1	1	1
	LOQ	0.5 (0.2-1.6)	0.7 (0.3-1.6)	4.4 (1.3-14.8)	1.4 (0.6-3.5)	0.9 (0.5-1.9)
	LIQ	1.3 (0.4-4.1)	1.0 (0.4-2.8)	13.9 (3.8-50.8)	2.0 (0.7-6.1)	1.4 (0.6-3.3)
	UIQ	0.6 (0.2-1.8)	0.6 (0.3-1.4)	3.2 (1.0-10.7)	0.7 (0.3-1.9)	0.4 (0.4-1.7)
	Central	---	---	---	---	1.3 (0.1-14.6)
Axillary clearance	No	1	1	1	1	1
	Yes	2.9 (1.3-6.6)	1.3 (0.6-2.7)	2.5 (0.9-6.7)	1.8 (0.7-4.6)	1.4 (0.7-2.8)
Re-excision	No	1	1	1	1	1
	Yes	2.8 (0.9-8.2)	3.3 (1.3-8.6)	6.1 (2.0-18.0)	1.8 (0.6-5.6)	1.1 (0.4-3.1)
Radio-therapy	No	1	1	1	1	1
	Yes	1.7 (0.5-6.0)	1.8 (0.7-4.9)	---	11.3 (1.5-85.5)	1.9 (0.8-4.2)
Chemo-therapy	No	1	1	1	1	1
	Yes	1.0 (0.3-3.2)	1.0 (0.4-2.4)	2.7 (0.8-9.3)	1.1 (0.3-4.4)	0.7 (0.3-1.6)
Hormonal therapy	No	1	1	1	1	1
	Yes	1.3 (0.6-2.6)	1.7 (0.9-3.1)	1.1 (0.5-2.5)	1.2 (0.6-2.5)	1.2 (0.7-2.0)

UOQ:upper outer quadrant; LOQ: lower outer quadrant; LIQ: lower inner quadrant; UIQ upper inner quadrant.

Discussion

Breast cancer is a common disease with a large number of long-term survivors.

To improve treatment of breast cancer it is important to establish the best possible methods for follow-up of treated patients. Concerning BCS, the results of our studies indicate that the BCCT.core software may be a valuable addition to PROMs, such as the Breast-Q™. Based on our results, photo panel evaluation is not recommended, due to its low reproducibility and high time consumption.

The patients treated with conventional BCS in this study cohort reported high levels of satisfaction concerning the postoperative aesthetic result. An EPBVE exceeding 20% was associated with poor aesthetic result according to the SSQ on patient satisfaction, the photo panel, and BCCT.core evaluation. Hence, if the surgeon preoperatively estimates that more than a fifth of the breast volume needs to be excised to obtain oncologically safe margins, surgical techniques other than conventional BCS should be considered, such as the use of oncoplastic techniques and/or a contralateral procedure to improve symmetry.

To further increase patient satisfaction, ways to improve the communication to the patients of the possibility of SDM may be tried. Many women in the study cohort had not perceived an opportunity to take part in the decision-making process and this was associated with lower satisfaction rates. Adequate and sufficient preoperative information is important to enable patient involvement.

Is the study sample representative?

The results presented in this thesis are based on a study population originally included in the OPB-pME study. A number of eligible patients (n=165) were not included in the study for unknown reasons. Comparison of these patients to the study population revealed a difference in age and tumour stage. The non-participants were somewhat older with a mean age of 63 compared to 60. It is possible that older patients, perhaps with multiple illnesses, are less likely to be interested in participating in a study such as this. Tumour stages such as T0, TX, T4, and Tis were more frequent among the non-participants. Uncertainty concerning the size and location of the tumour, whether BCS would be feasible, might have contributed to these patients not being included in the study. The observed differences should be taken into account when drawing conclusions from

the material. However, the difference in mean age was slight and the study population may be considered to be representative of the population intended to study.

Patients were also lost in follow-up for different reasons after inclusion in the OPB-pME study. In each of the papers, comparisons were made between the patients lost in follow-up to the resulting study sample. The characteristics were similar, with minor differences presented in the separate papers. The loss in follow-up is unlikely to have had a significant impact on the results.

Aesthetic result after BCS

Patient self-evaluation

Patient satisfaction with the aesthetic result after conventional BCS in this study population, according to the SSQ, is in line with the results from other studies (81, 83). Of those treated, 84% reported that they were satisfied or very satisfied with the aesthetic result of the operated breast. Satisfaction concerning symmetry was somewhat lower with 68% being satisfied or very satisfied.

In the evaluation of patient satisfaction, formally developed and tested PROMs are highly preferable to use in scientific research. Study-specific questionnaires, sometimes called *ad hoc* questionnaires, may include logical and rational questions, but without formal development and testing, the reproducibility and validity of the instrument is uncertain (116). The Breast-Q™ questionnaire, which has undergone a meticulous construction process to ensure reproducibility and validity, is preferable to use in future studies aiming to evaluate patient satisfaction. However, this questionnaire was not available when the OPB-pME study was initiated. Generic instruments available at the time, such as the Short Form-36 (115), were deemed less suitable to sufficiently answer the questions posed in the study. Another issue with generic questionnaires is their responsiveness, i.e. their ability to measure changes in HRQoL after a medical procedure (116). In light of this, construction and use of an SSQ in this study was chosen and steps were taken to increase its usefulness. It was based on similarly constructed questionnaires used in previous research in our institution (129, 130) and a psychologist was involved in the construction process. A pilot test was performed prior to the start of the study.

The patients received the SSQ at the time of the follow-up examination and as such, the majority completed it on site. A few patients brought it home and subsequently sent it by mail. Questionnaires that are completed in the presence of

a health care official have the advantage of an increased response rate and thereby, decreased risk of non-response bias. However, the responders might avoid expressing their dissatisfaction to the same extent that they would have at home. In addition to this, positively skewed answers are known to be an inherent issue in research using questionnaires in the evaluation of patient satisfaction with healthcare. Efforts need to be made in the construction process of the questionnaire to reduce the effect of this (59).

Photo panel evaluation

The assessment of the postoperative aesthetic result using a photo panel evaluation of 215 patients showed poor intra- and inter-observer agreement, as reported in **paper IV**. This evaluation modality was also highly resource-consuming. Much time was needed for both the preparation and arrangement of the photos to be presented and for the evaluation sessions, each lasting approximately four hours.

There are no established guidelines for how a panel evaluation should be performed. There are differing recommendations as to how many assessors should take part (58, 67). It is possible that a larger number of participants in a panel could potentially reach a higher level of "accuracy", i.e. closer to a consensus of how an aesthetic result should be assessed. However, to have more than three participants in a panel evaluation, in which each session takes several hours, does not seem reasonable in terms of resource use.

A panel evaluation, or a single physician's opinion, of aesthetic result has been traditionally much used as an addition to the patient's evaluation. However, poor agreement between different assessors (141) and for the same assessor at different evaluation sessions (66) has been reported in other studies. As it is a subjective type of evaluation, the results will differ depending on which individuals are chosen for the panel.

Most previous studies have been based solely on the postoperative result, without the possibility of taking the preoperative situation into account (58). As preoperative photos were also available in this material, the evaluation of the postoperative aesthetic result could be assessed in relation to the same breast preoperatively, and to the contralateral breast. This could potentially make the evaluation more just, since many women have asymmetrical breasts. However, as the agreement between the different evaluation sessions was low, it is difficult to draw conclusions.

Computerised assessment of patient photos - the BCCT.core

A more objective method of evaluation than patient self-evaluation and panel evaluation is desirable. A computerised assessment could hopefully enable reliable results, more comparable over time and between populations of different cultures and demographics. For the studies presented in this thesis, the BCCT.core software was chosen. The reasons for this were that it was freely accessible for research purposes and compatible with the material. The BCCT.core has been increasingly used worldwide, and is included in the study protocol of new trials (142, 143), which has further strengthened its use.

The BCCT.core results of the study cohort presented in this thesis (Excellent 16%; Good 57%; Fair 26%; Poor 3%) were very similar to comparable samples of other studies (65, 75). Methodological considerations of using the software on the current study population include that it was not planned in the OPB-pME study protocol and as such, no calibration marks were placed prior to photography. Since the calibration marks could be placed with acceptable accuracy using available data variables, this limitation should not have affected the results. Another consideration is that photo quality was not ensured with standardised lighting, but no such requirements were presented by the user instructions of the BCCT.core software. The same photographer took all the photos from the one-year follow-up. The background setting was the same (white) and all patients were photographed in the same frontal position with arms down. The photos are thus considered to be of sufficient quality to be analysed with this method.

A software-based evaluation method such as the BCCT.core, which only analyses one photo of the patient photographed from a single projection, will surely be a blunt instrument and perhaps not suitable for an aesthetic evaluation of a single patient. It will be dependent on the way the photograph has been taken and it cannot assess the firmness of the breast tissue. However, these limitations are also inherent in a photo panel evaluation and in contrast, the BCCT.core is resource-efficient and easy to use. The time consumption for the semi-automated assessment, when the calibration marks were in place, was limited to about one minute per patient. It may be suitable to use such an instrument for routine quality control and for comparisons between centres.

Factors affecting the aesthetic outcome after conventional BCS

Several patient, tumour and treatment factors can potentially influence the postoperative aesthetic result after BCS, as discussed previously. In this study cohort, an EPBVE exceeding 20% was associated with less satisfaction regarding the aesthetic result according to the SSQ. The effect of EPBVE on aesthetic result

was also seen in the photo panel evaluation and in the BCCT.core scores. The results correlate well with other studies with information regarding preoperative breast size available (126, 144), and strengthen the current recommendations to use alternative surgical techniques, such as OPBS, when a large portion of the preoperative breast volume needs to be excised (1, 42). An upper limit of 20% is proposed by Clough, who has developed a classification system with "level I and level II" OPBS. Level I OPBS is described as a conventional partial mastectomy with incision around, and potential repositioning of the NAC. When more than one fifth of the breast tissue needs to be removed, level II OPBS, i.e. methods based on reduction mammaplasty techniques, are recommended (145). This classification system was recently recommended by an expert panel of breast surgeons from Holland, Austria, and Switzerland, with the aim of forming consensus for the use of OPBS in clinical planning (42).

Axillary clearance correlated to an inferior aesthetic result according to the SSQ and the photo panel evaluation, but not according to the BCCT.core. How an axillary clearance might impair the aesthetic result of the breast is not clear. It could be caused by oedema in the breast, which has been shown in a previous study to appear after axillary clearance (77). It could also potentially occur if the scar causes traction of the breast and causes it to deviate towards the axilla. Axillary clearance has also been shown to be associated with poor aesthetic result according to the BCCT.core evaluation in another recent study (146).

Obesity (BMI ≥ 30) seemed to increase the risk of breast asymmetry according to the SSQ, the photo panel evaluation and the BCCT.core software. This is in accordance with other studies (85). Reasons for this could include a more negative effect of radiotherapy on large, pendulous breasts, due to a higher risk of dose inhomogeneity and perhaps the need for a higher dose to penetrate the whole breast (147). Obese patients have a higher frequency of complications (148) and even though complication rates were low in this study cohort, surgeons' knowledge of an increased risk for these patients could decrease the incentive for extensive mobilisation of breast tissue, OPBS and reduction mammaplasty of the opposite breast.

Methodological considerations – confounding and statistical power

When analysing potential determinants for satisfaction with the aesthetic result, we chose to present an age- and BMI-adjusted model, as well as a multivariable model adjusted for the factors shown to be associated with patient satisfaction according to the previous analyses. These adjusted models were used to manage the risk of confounding, which is an inherent issue in epidemiological research. A confounder is a factor associated with both exposure and the outcome, but it cannot be an intermediate and lie on the causal pathway (61). It is important to identify potential confounders since these may indicate an association that does

not exist. Confounding can be managed by adjusting for the potential confounder in a multivariable analysis. Age is a common confounder. In this material age could potentially affect both adjuvant therapy and patient satisfaction. In the process of identifying potential confounders in the current material, consideration was given to the risk of concealing an existing association by including two co-varying factors in a multivariable analysis. Several factors could possibly co-vary to a large degree, such as BMI, breast size and EPBVE.

The study cohort was relatively large and the risk of type II error, i.e. not finding an existing difference, is considered low for most analysed factors. However concerning tumour location, since there were five different locations in the breast, and very few patients had tumours in the central position, there was a risk of not identifying an existing impact. Type II error is directly related to statistical power, which can be defined as the probability of rejecting a null hypothesis that is false. Type II error is also known as beta (β) and power is mathematically 1- β. Sample size is an important aspect in power calculations, as is estimated effect size of the studied intervention and also chosen significance level. The size of β is often set at 0.2 and a power level of 0.8 is often seen as minimum (61).

Skin sensitivity in the operated breast

Skin sensitivity of the operated breast was evaluated by patient satisfaction as reported in the SSQ completed at the one-year follow-up visit. According to this, 67% were very satisfied or satisfied.

It was not possible to verify whether the patients' subjective level of satisfaction with skin sensitivity correlated to the actual sensory state of the breast, as no further techniques for a more objective measurement of skin sensitivity, such as those presented in the introduction, were used in the study. The correlation between subjective and objective evaluation methods of skin sensitivity has been investigated in other research fields, such as after surgery to the mandibula, causing sensory changes due to damage to the lingual and inferior alveolar nerve (149). Pepersack and Chausse presented a study in 1978 in which the authors had tested skin sensitivity long-term (≥ 5 years) following correctional surgery for mandibular prognathism. Patient self-evaluation using an SSQ was correlated to clinical testing of skin sensitivity. It was found that 26 of 28 patients who had reported some sort of disturbance actually had a clinically detectable impairment in skin sensitivity, whereas 15 patients who had no complaints were found to have impaired skin sensitivity in clinical testing (150). It was proposed by Jacks et. al. that patient-reported alterations in skin sensitivity following surgery may be over-

estimated initially but may, due to patients becoming accustomed to impaired skin sensitivity, be underestimated long-term (151).

Thus, it is likely that the women, who were dissatisfied at the one-year follow-up visit according to the SSQ, did have impaired skin sensitivity that would have been clinically detectable. However, if clinical evaluation of skin sensitivity had been performed in our study, it is probable that a group of patients who were satisfied with skin sensitivity would have had some sort of clinically detectable sensory loss. It can be debated what is most important, the patient's perception or the results of a clinical investigation. As such, even though an objective clinical evaluation of skin sensitivity in addition to the patient self-evaluation would be preferable, the results from the SSQ by itself may still be of interest.

A number of factors were associated with less satisfaction with skin sensitivity of the breast, including BMI, large tumour size, EPBVE ≥ 20, axillary clearance, re-excision, radiotherapy and infection.

More extensive nerve damage, caused by larger excisions, could be the reason for the observed association between less satisfaction regarding skin sensitivity and large tumour size, EPBVE ≥ 20, axillary clearance, and re-excision.

Nerve regeneration with axonal regrowth after a peripheral nerve injury is complex, involving a multitude of interrelated factors. After an injury, the distal part of the axon degenerate (known as "Wallerian degeneration") and leaves a microenvironment stimulating axonal regrowth. Molecular and cellular changes also occur in the neuronal body (152). Postoperative infection may interrupt this sophisticated process of nerve regeneration.

An interesting finding was that women with a BMI between 25 and 30 had the lowest satisfaction rates. Women with obesity (BMI ≥ 30) may have had decreased skin sensitivity before surgery, as described in previous studies on patients with macromastia (91). Impaired skin sensitivity at baseline could have potentially reduced the patient's perception of further sensory loss.

Possible pathophysiological mechanisms by which radiotherapy may impair skin sensitivity have been proposed to be nerve compression by surrounding radiation-induced fibrosis and/or cell damage of nerves and surrounding blood vessels (153).

Shared decision-making

In this study cohort, 41% of the patients reported that they had perceived an opportunity to take part in the decision-making process regarding surgical method. Many (53%) stated that they had "not at all" or "partly" perceived such an opportunity, while 5% gave no answer.

The women who had perceived a possibility of SDM were more often satisfied with the postoperative aesthetic result (OR 2.7; CI 1.2-6.3). It could be interpreted as that a possibility of SDM increased satisfaction. However, as the patients responded to both questions simultaneously, there is a risk of "reverse causality" (61). The patients who were satisfied with the aesthetic result could have been more inclined to remember an opportunity to participate in the decision-making process regarding the surgical approach. With a cross-sectional study design, it is difficult to establish causality. Causality is often tricky to determine and it has been argued that the only true criterion to establish causality is temporality, namely that the exposure takes place prior to the outcome (154). Despite difficulties in determining causality, the correlation between increased satisfaction and the perceived possibility of SDM is still interesting, indicating that if physicians can communicate an opportunity of SDM, the patients may be more satisfied with the results.

The patients who reported inadequate preoperative information concerning the postoperative aesthetic result were less likely to have perceived it possible to participate in the decision-making process. This indicates that sufficient preoperative information is important in order to enable SDM.

The other factors analysed as potential determinants for having perceived a possibility of SDM showed no statistically significant associations. Some previous studies have indicated that educational level is associated with patients' preferences regarding decisional involvement (155, 156). When the analyses for **paper II** were performed, no information concerning the patients' level of education was available. This information has since been retrieved through the additional SSQ collected together with the Breast-Q™. Subsequent analysis of women with versus without a university degree showed no statistically significant association (OR 1.35; CI 0.76-2.39).

It can be noted that the patients were not asked whether they had in fact taken part in the decision-making process, nor were they asked if they had any desire to do so. Three patients wrote as an extra note in the questionnaire that they would not have wanted to decide on treatment.

Shared decision-making is a complicated matter. In a situation in which a patient has recently been diagnosed with breast cancer, she might not be receptive of

information regarding different treatment alternatives. There is also a danger in leaving the decision solely to the patient, since previous studies have shown that if patients who have recently been diagnosed with breast cancer are left to make the decision on surgical treatment, many will choose the most radical surgical alternative despite information on equal mortality rates (157, 158). Receiving information about a malignancy in the breast is a threatening situation to the individual and the first impulse may be a wish to remove as much as possible of the breast to more safely remove the cancer.

Previous studies have shown that patients are most satisfied if the level of participation in the decision-making process matches her individual preference to take part (159). Since only the question of perceived opportunity was raised, this aspect could not be analysed. Mismatch between the patient's preferred level of SDM and the perceived level could occur if the patient experiences either too much or too little involvement (155, 160). Previous studies have shown that a patient's desire to decide on treatment decreases in cases of a more severe disease (161, 162).

The current study was undertaken before the publication of studies showing an increased survival rate with BCT compared to mastectomy (163-165). Questions have since been raised, following these reports, concerning whether patients should in fact be given a choice between mastectomy and BCT (166). This discussion is of particular interest in countries where increased mastectomy rates have been noticed for the treatment of small tumours (167). During the time period of inclusion in the OPB-pME study, the two surgical treatments were still considered equal concerning survival.

The evaluation of the patients' perception of an opportunity to be involved in the decision-making process was performed with an SSQ. As previously discussed, the reliability and validity of this questionnaire has not been established. Did the patients perceive the single question concerning this issue as intended? The same aspect applies to the question regarding the adequacy of preoperative information. In regard to this issue, it is possible to make a blunt comparison between the responses to the question posed in the SSQ to the Breast-Q™ domain "Satisfaction with information from breast surgeon". The Breast-Q™ domain is a multi-item domain dedicated to the subject, with specific questions concerning how the surgeon presented information about different aspects of the different treatment alternatives. In figure 15, the distribution of responses on the SSQ in relation to the Q-score is graphically displayed.

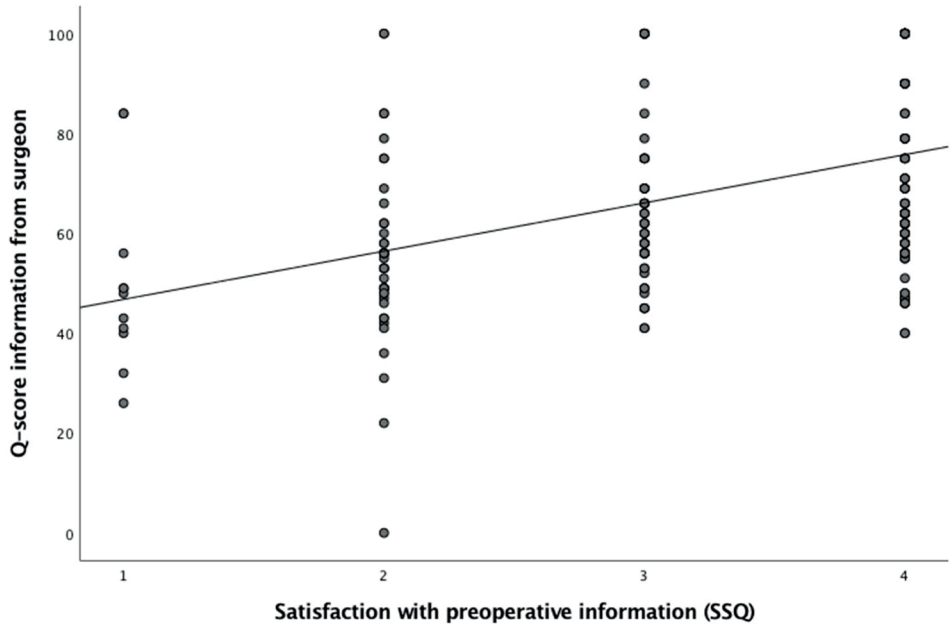


Figure 15. Correlation between satisfaction with information according to the SSQ (1 not at all, 2 partly, 3 almost entirely, 4 entirely) and the Breast-Q™ domain "Satisfaction with information from breast surgeon"

The Spearman correlation coefficient (r_s) was 0.44. It must be noted that the single question posed in the SSQ is not completely comparable to the multi-item domain of the Breast-Q™ and the time at which the patients completed the questionnaires differed. However, one would assume that the answers would co-vary to some extent.

Since the Breast-Q™ has been subjected to more rigorous validation and has a multi-item structure, it is likely that the results of this questionnaire come closer to the truth. While it is recommendable to use a more validated questionnaire, the BCT module of the Breast-Q™ was not available at the time of the study.

Decisional aids

To achieve SDM, it has been proposed to use decisional aids in the decision-making process. Decisional aids are tools to help patients comprehend pros and cons concerning different treatment options and lead them in the decision-making process. They can be printed material, web-based tools or videos that are used in addition to the physician's information and advice (6). In a randomised trial presented by Whelan et al. in 2004, the effect of a decisional aid was studied in Canadian patients eligible for BCT, with mastectomy as an equally safe alternative. It was shown that patients who met a physician equipped with a

decisional aid on knowledge and treatment were more likely to choose BCT. They scored higher when tested on knowledge concerning treatment options and were more satisfied with the decision process (168).

Much research has been published on decisional aids and there have been several Cochrane reviews concerning this topic. In the latest of these reviews, published in 2017, the authors concluded that patients can benefit from decisional aids through the enhanced knowledge they provide of different treatment alternatives and because they decrease decisional conflict (169). The effect on these aspects of patient care are dependent on the quality of the decisional aid and how they are used in daily practice (6).

Health-related quality of life

The women of the study cohort, on whom this thesis is based, completed the Breast-Q™ questionnaire median 5.5 years after undergoing BCS. The median score for the domain "Satisfaction with breasts" was 66 (IQR 57-80), for "Psychosocial well-being" it was 82 (IQR 61-100), and for "Sexual well-being" it was 60 (IQR 48-79). Very few of the women had experienced adverse effects of radiotherapy: Q-score 100 (IQR 89-100). For physical well-being, some women remarked that their problems had nothing to do with the breast surgery, making the results difficult to interpret. The median Q-score for the domain "Physical well-being" was 81 (IQR 69-92).

A reliable reference score to compare the results with is still lacking, since the Breast-Q™ BCT module is still relatively new. An initiative to construct a "normative score" was taken by Mundy et al. in 2017. Data were published on 1200 women completing the Breast-Q™ questionnaire, with or without a history of breast cancer and recruited through an online community, raising awareness around breast cancer research (170). The mean scores (±standard deviation) were 58(±18) for "Satisfaction with Breasts", 71(±18) for "Psychosocial Well-being", and 56(±18) for "Sexual Well-being". However, these values were based on a population including women treated with all kinds of interventions, as well as women with no history of breast cancer. Another effort to produce a reference scale was made by Lagendijk et al. in 2018 (171). Also the data of this publication was based on an online resource, namely a patient advocate society. For the women treated with BCS, mean values (±standard deviations") were for "Satisfaction with breasts" 62(±22), 67 (±19) for "Psychosocial well-being" and 53(±17) for "Sexual well-being". The Q-scores of the current study population are more readily comparable to the latter publication, since the patients treated with BCS were reported separately in this study. However, since the study populations

in these studies were recruited from online communities of women with a specific interest in breast cancer treatment and research, the results may be biased. Even taking this into account, it can be observed that the median Q-scores of the current study population are not inferior to the "normative scores" proposed in the above-mentioned publications.

There is also a possibility of bias that needs to be taken into account in the interpretation of the results of the current study population. The Breast-Q™ questionnaires were sent out and collected by mail. When compared to interview-based collection of data, self-administered questionnaires have the advantage of having less risk of interviewer bias. The limitations of the method include a possibility of non-response bias and no way to control the circumstances in which the questionnaires are completed (59).

There was a statistically significant association between a better BCCT.core score and higher Q-scores of the domains "Satisfaction with breasts" and "Psychosocial well-being". This indicates that the software may be valuable in the follow-up of patients treated with BCT. In contrast, Volders et al. presented a study in 2016 in which no statistically significant association was seen between aspects of quality of life and BCCT.core scores (3). In this study, quality of life was measured with EORTC QLQ-C30, which was originally developed for lung cancer patients receiving chemotherapy (172) and the breast-specific QLQ-Br23 module, which was developed in the 1990s (173), prior to the implementation of routines such as the sentinel node technique for staging the axilla, and OPBS techniques. The use of diverging instruments for the measurement of quality of life could to some extent explain the observed difference.

Patient satisfaction according to the SSQ in our study predicted aspects of HRQoL best: the domain "Satisfaction with breasts" by satisfaction with the aesthetic result and the domain "Psychosocial well-being" by satisfaction with symmetry. These results indicate that PROMs are important in the follow-up of breast cancer surgery. The non-validated SSQ predicted HRQoL long-term best when compared to the software BCCT.core and the photo panel evaluation. This SSQ may be used in the clinic for internal quality control and to find patients who are dissatisfied. However, for a more standardised practice, well-validated instruments are highly preferable. The Breast-Q™ is increasingly used worldwide (143, 174), which further strengthens its use, as it is possible to compare the results of ones own department to those of other surgical centres.

Conclusion

Most patients treated with conventional breast-conserving surgery in this study were satisfied with the postoperative aesthetic result according to a study-specific questionnaire. The patients who had had more than a fifth of the preoperative breast volume excised were less satisfied. A high percentage of breast volume excised was also associated with poor aesthetic outcome according to a photo panel evaluation and the BCCT.core software. Hence, if the surgeon estimates that a large proportion of the breast needs to be removed for oncological safety, other surgical approaches such as oncoplastic breast surgery or mastectomy with or without reconstruction could be discussed.

An association between patient satisfaction and perceived possibility to influence the decision regarding the surgical method was observed. To better communicate to the patient that she has an opportunity to participate in the decision-making process may increase satisfaction rates. Sufficient preoperative information is important in order to enable shared decision-making.

BCCT.core scores for the aesthetic result after breast-conserving surgery were associated with long-term health-related quality of life. The software was user-friendly and resource-efficient. It may be of value as a tool for quality control and, as a more objective instrument, suitable for comparisons of outcomes between populations.

The photo panel evaluation showed poor agreement between the different assessors as well as for the same assessor between evaluation sessions. As it is a subjective assessment, dependant on the experiences and expectations of the individuals in the panel, highly time-consuming, and not superior to the other methods of evaluation, it seems unsuitable to use this evaluation modality in the follow-up after breast cancer surgery.

Long-term health-related quality of life was best predicted by the patients' level of satisfaction according to the study-specific questionnaire. The results indicate that for the individual patient, evaluation of patient-reported outcome measures in the follow-up of breast cancer surgery is most important. When choosing which to use, well-validated instruments are recommended to ascertain the validity and reliability of the results and to allow comparisons with other patient populations.

Svensk sammanfattning

Bröstcancer är en allvarlig och potentiellt dödlig sjukdom. Ungefär var tionde kvinna i Sverige kommer att drabbas under sin livstid. Framstegen i behandlingen av bröstcancer har dock varit stora och femårsöverlevnaden är idag över 95% om man upptäcker tumören i tidigt stadium. Vid behandling av en liten brösttumör (under cirka 3-4 cm) har flera stora studier med lång uppföljningstid visat att risken att dö i bröstcancer inte är högre om man genomgår en bröstbevarande operation med efterföljande strålbehandling jämfört med om man tar bort hela bröstet. Nya studier har till och med visat bättre överlevnadsresultat för kvinnor som genomgått bröstbevarande kirurgi.

Eftersom så många kvinnor drabbas och lever länge med resultaten av sin behandling är det viktigt att kontinuerligt utvärdera resultaten och försöka förbättra behandlingsmetoderna för att öka patienternas livskvalitet även på lång sikt.

Den vanligaste metoden för bröstbevarande kirurgi (kallas här konventionell teknik) innebär att tumören med intilliggande vävnad skärs ut och vävnaden sys ihop. Nya metoder är under utveckling, s.k. onkoplastikkirurgi, där operatören tillämpar plastikkirurgiska tekniker, som att omfördela eller ersätta bröstvävnad vid canceroperationen för att kunna ta bort större tumörer med bevarad estetik och mindre känselbortfall än när hela bröstet tas bort.

I denna avhandling har kvinnor, som behandlats med bröstbevarande kirurgi under fyra år (2008-2012) vid Skånes Universitetssjukhus, Malmö, studerats, med syfte att utvärdera estetiskt resultat och livskvalitet.

*Vilka faktorer påverkar patientens nöjdhet med estetiskt resultat och känsel efter konventionell bröstbevarande operation? (**I**)*

De flesta av patienterna var nöjda eller mycket nöjda med utseendet av det opererade bröstet vid en ettårsuppföljning efter bröstbevarande kirurgi med konventionell operationsteknik. Många var också nöjda eller mycket nöjda avseende symmetrin (likheten) mellan brösten och med känseln i det opererade bröstet. Flera faktorer tycktes påverka patientnöjdheten. En viktig faktor var hur mycket bröstvävnad man tagit bort vid operationen i förhållande till hur stort bröst man hade innan operationen. De patienter där man tagit bort mer än en femtedel av bröstet var mindre nöjda med resultatet.

Våra slutsatser är att de allra flesta patienter kan opereras med vanlig operationsteknik. Om operatören räknar med att behöva ta bort mer än en femtedel av bröstet så bör andra operativa metoder övervägas, såsom att använda onkoplastikkirurgiska tekniker, alternativt ta bort hela bröstet (med eller utan återskapande av ett nytt bröst).

*Upplever patienterna möjlighet att delta i beslut om behandling? **(II)***

Vid ettårsuppföljningen rapporterade många av patienterna att de inte eller endast delvis upplevt en möjlighet att vara med och bestämma kring vilken operation som skulle göras. De som inte tyckte att de fått denna möjlighet var i lägre utsträckning nöjda med det estetiska resultatet. De patienter som angett att de fått tillräcklig information kring förväntat resultat hade i högre utsträckning upplevt att de deltagit i beslutet kring operativ metod.

Patientdeltagande är idag en viktig fråga och 2015 kom en ny patientlag som ytterligare stärkte patienternas rätt. Att kommunicera till patienterna att de kan vara med och besluta om behandling när det finns flera alternativ kan öka patientnöjdheten. En förutsättning för möjlighet att delta i beslutsfattande är adekvat och tillräcklig information.

*Hur utvärderar man bäst estetiskt resultat? Vilken metod förutspår livskvalitet på längre sikt bäst?**(III-IV)***

Patienternas utvärdering med ett studiespecifikt frågeformulär vid ettårsbesöket jämfördes med bedömningar gjorda av foton som tagits vid samma besök, dels i en panelbedömning och dels i ett datorprogram, BCCT.core. Detta datorprogram är utvecklat i syfte att på ett mera objektivt och automatiserat sätt utvärdera det estetiska resultatet efter bröstkirurgi genom att jämföra det opererade bröstet med det icke-opererade.

För utvärdering av livskvalitet användes ett frågeformulär som är utarbetat specifikt för bröstcancerpatienter opererade med bröstbevarande kirurgi och används i många länder (Breast-Q™). Detta frågeformulär samlades in per post flera år efter behandlingen (år 2015).

Ett sämre estetiskt resultat enligt BCCT.core var kopplat till lägre livskvalitet vad gällde nöjdhet med bröst och psykosocialt välbefinnande enligt Breast-Q™. Det som förutsade livskvalitet bäst var dock patientnöjdhet enligt det studiespecifika frågeformuläret vid ettårsbesöket. I panelbedömningen var överensstämmelsen låg både mellan samma bedömares skattning vid olika tidpunkter och mellan de olika bedömarna.

Det är svårt att på ett objektivt och korrekt sätt utvärdera estetiskt resultat. Panelbedömning, som är en subjektiv bedömningsmetod, var tidskrävande och resultaten svåra att tolka med tanke på den låga överensstämmelsen mellan

bedömningarna. BCCT.core var tidseffektivt, fritt tillgängligt och användarvänligt, vilket kan möjliggöra rutinmässig användning. Det kan vara av värde till exempel när man vill jämföra resultaten mellan olika sjukhus eller för intern kvalitetskontroll. Vad gäller den enskilda patienten är det viktigast att fånga upp de patienter som är missnöjda vid ettårsuppföljningen, eftersom dessa riskerar sämre livskvalitet på längre sikt.

Det studiespecifika frågeformulär som använts i de studier som presenterats i denna avhandling tycks fungera väl för att fånga upp patienter som har risk för lägre nöjdhet med bröst och sämre psykosocialt välbefinnande på längre sikt och kan troligen fungera som ett instrument för kvalitetskontroll vid den enskilda kliniken. För att kunna jämföra resultat mellan olika sjukhus och länder bör man dock använda frågeformulär som har framställts enligt specifika metoder och genomgått kvalitetstestning som säkerställer att instrumentet mäter det som det är avsett att mäta. Breast-Q™ har genomgått denna framställnings- och kontrollprocess och har en version som är specifikt utarbetad för bröstcancerpatienter som genomgått bröstbevarande kirurgi. Det skulle kunna vara lämpligt att använda detta frågeformulär i uppföljningen av denna patientgrupp framöver.

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