Aspects of breast-conserving surgery

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KIM GULIS is a senior consultant in surgery, working at the Breast Cancer Centre in Kristianstad Central Hospital, Department of surgery.

In this thesis, different aspects of breast-conserving surgery were studied, specifically cosmetic outcomes, health-related quality of life, risk factors for positive margins, and breast conserving surgery after neoadjuvant treatment.

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Aspects of breast-conserving surgery

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Kim Gulis M.D

DOCTORAL DISSERTATION

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Abstract:
With improved survival among patients with breast cancer, patients will also live longer with the surgical and cosmetic outcomes and their potential impact on health-related quality of life (HRQoL). However, larger cohort and prospective studies in this field are lacking. The overall aim of this thesis was to study the different aspects of breast-conserving surgery (BCS), specifically cosmetic outcomes, health-related quality of life, risk factors for positive margins, and BCS after neoadjuvant treatment.

Study I was a retrospective analysis involving 146 patients, aimed at investigating cosmetic outcomes and breast symmetry in patients undergoing bilateral therapeutic mammoplasty. Cosmetic outcome scores were collected from the patients, surgeons, and BCCT.core (computer software). The results showed that 89% of patients had good or excellent cosmetic outcomes, as evaluated using the software. Both patients and surgeons reported high average scores (9/10 vs. 8/10).

Study II was a retrospective analysis involving 432 patients in the primary cohort, aimed at developing a predictive model for positive margins after BCS based on preoperative data. This study presented a nomogram for risk evaluation that included seven variables. In the development cohort, the prediction model achieved an area under the receiver operating characteristic curve of 0.8. The model was validated in two cohorts, demonstrating its efficacy in predicting patients at high risk of positive margins.

Study III was a prospective study involving 226 patients, aimed at monitoring surgical planning in patients before and after neoadjuvant surgery in relation to the final procedure. The secondary aim was to identify the variables associated with the application of BCS after neoadjuvant treatment. This study revealed that the rate of BCS after neoadjuvant treatment increased from 37% to 52% during the study period. Factors associated with BCS included smaller tumour size, benign axillary status, and low mammographic density.

Study IV was a prospective study involving 340 patients, aimed at analysing HRQoL at diagnosis and at the 1-year follow-up in four separate surgical groups. Patients who underwent partial or oncoplastic partial mastectomy were more satisfied with their breasts, had a better body image, and had higher sexual functioning scores than those who underwent mastectomy with or without reconstruction. The mastectomy group had the least number of symptoms in the chest area.

In conclusion, these studies indicate that many patients have good outcomes in terms of both HRQoL and cosmetic outcomes after breast cancer surgery. The rate of BCS can still be improved, especially after neoadjuvant treatment. The nomogram can help identify patients at a high risk of positive margins and guide surgical planning to minimize the need for a second surgery.

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Till pappa – ingen hade varit stoltare än du

Table of Contents

Abstract

Background

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”Allt stort som skedde i världen skedde först i någon människas fantasi."

- Astrid Lindgren

Populärvetenskaplig sammanfattning

Bröstcancer drabbar tusentals kvinnor varje år och är den vanligaste cancertypen hos kvinnor i Sverige, där över 9000 svenska kvinnor årligen drabbas av bröstcancer. Antalet bröstcancerfall ökar i världen men med moderna behandlingsmetoder har prognos och överlevnad förbättrats. Bröstcancer kan kirurgiskt behandlas med bröstbevarande kirurgi, där patienten får behålla större delen av sitt bröst och tumören opereras bort, eller med mastektomi där hela bröstet opereras bort. Flera studier har visat att patienter som behandlas med bröstbevarande kirurgi och efterföljande strålbehandling har samma överlevnad som patienter som behandlas med mastektomi. Nyare studier har även visat en tendens till bättre överlevnad hos patienter som genomgått bröstbevarande kirurgi.

Det övergripande målet för denna avhandling är att studera olika aspekter av bröstbevarande kirurgi. Samtliga projekt i avhandlingen baseras på uppgifter inhämtade från bröstcancerpatienter och deras behandling. Fokus är livskvalitet, kosmetik, operationsteknik och risk för omoperationer.

I takt med att överlevnaden förbättrats för bröstcancerpatienter, har fokus inom bröstkirurgin skiftat från att primärt handla om risk för återfall i bröstet eller att dö av sjukdomen till att även inkludera hälsorelaterad livskvalitet och kosmetiskt utfall. Patienterna själva involveras i allt högre grad i besluten gällande sin behandling. Det här är en utveckling som detta avhandlingsarbete vill bidra till.

En andra operation efter bröstbevarande kirurgi är nödvändig när tumören ej är radikalt borttagen, det vill säga om kanten av den borttagna vävnadsbiten innehåller kvarvarande tumörceller. Enligt internationella studier är andelen av patienter med kvarvarande tumörceller efter bröstbevarande kirurgi mellan 10–30%.

Onkoplastikkirurgi innebär att kombinera cancerkirurgin med plastikkirurgiska tekniker för att optimera det kosmetiska resultatet. En fördel med onkoplastik-kirurgiska tekniker är möjligheten att operera bort större vävnadsbitar ur bröstet med samma eller bättre kosmetiska utfall, vilket minskar risken för att första operationen ej blir radikal. Studier har även visat att patienterna är mer nöjda med det kosmetiska utfallet efter onkoplastikkirurgi. Onkoplastikkirurgin har blivit alltmer vanligt förekommande i Sverige det senaste decenniet och det pågår en snabb utveckling inom genren, men det finns enbart ett begränsat antal studier som sammanställt hur rutinmässig användning av onkoplastikkirurgi påverkar livskvalitet, kosmetiskt utfall, samt även andelen omoperationer på grund av ej radikal operation.

För att utvärdera användningen av nyare kirurgiska tekniker behövs studier som kan bidra med bevis för metodens inverkan på onkologiska, kirurgiska,

livskvalitets-mässiga och kosmetiska faktorer och det finns få studier inom området som insamlar data framåt i tiden (prospektivt).

Användandet av patientrapporterade utfallsmått är allt viktigare att inkludera i planering av vård och behandling. Enkätundersökningar som patienten själv fyller i anonymt eller med kodade uppgifter ger möjlighet att få patientens egen uppfattning om behandling och resultat. Detta kan bidra med värdefull information, i fall där vi tidigare främst undersökt onkologiska och kirurgiska utfall.

Det har utförts och pågår än i dag omfattande forskning inom bröstcancer. Den största delen av forskningen som utvärderar bröstbevarande kirurgi är baserad på data insamlade i efterhand (retrospektivt) och med den snabba utveckling som skett inom onkologi och bröstcancerkirurgi blir resultatet av retrospektiv forskning snabbt föråldrade.

Samtliga frågeställningar och målsättningar i studierna har som fokus att kunna bidra med kliniskt relevant information för bröstcancerpatienters framtida kliniska vård, gällande livskvalitet, kosmetik och val av operationsteknik. Resultatet av studierna kommer potentiellt kunna vara av stor nytta för framtida patienter med bröstcancer och för kirurger inför val av operationsmetod. Med bättre kännedom om det kosmetiska utfallet samt effekten på livskvalitet kommer kirurgen kunna ge patienten val utifrån individens personliga förutsättningar och önskemål samt optimera handläggningen av patienter med bröstcancer. Den onkologiska säkerheten kommer alltid komma i första hand, men patientens livskvalitet samt det kosmetiska utfallet har betydelse för patientens framtida liv.

Studie I

Första studien i avhandlingen handlar om kosmetiken efter bröstförminskning i samband med bröstcanceroperationen. Vid denna operation tas tumören bort och samtidigt minskas volymen på brösten, ofta görs även andra sidan samtidigt för att uppnå symmetri mellan brösten. I denna studie opererades samtliga patienter i båda brösten vid första operationen.

Studien undersökte hur patienten, kirurgen samt ett datorprogram kallat BCCT.core bedömde kosmetik och symmetri ett år efter operationen. 146 patienter inkluderades i studien. Slutsatsen var att en majoritet av patienterna hade ett bra eller perfekt kosmetiskt utfall enligt datorprogrammet (89%). Patienterna var mer nöjda med det kosmetiska resultatet än kirurgen. Patienternas medelpoäng var 9 på en 10-gradig skala medan kirurgens medelscore var 8 av 10.

Studie II

Syftet med studien var att utveckla ett så kallat nomogram, som är ett beslutsstöd inför operation utifrån uppgifter som är tillgängliga före operationen. Nomogrammet bedömer risken för att patienten ska behöva bli opererad en andra

gång på grund av icke radikal operation. Detta sker genom att fylla i individuella patient- och tumördata för den enskilda patienten i nomogrammet. Utifrån det så kan man utläsa en poäng som motsvarar en uppskattad procentuell risk för att behöva en andra operation på grund av att första ej blev radikal. Med hjälp av det utvecklade nomogrammet kan kvinnor som är aktuella för bröstbevarande kirurgi i framtiden potentiellt erbjudas en individuell riskbedömning för risken för omoperation i just deras specifika fall. Patienten kan då involveras mer i rekommendationer och beslut gällande sin behandling. Kirurgen kommer även få en indikation om risken för icke radikal operation och om man behöver överväga mer generösa marginaler eller annan operationsteknik som onkoplastikkirurgi.

Nomogrammet testades i en annan grupp av patienter från ett annat sjukhus, och hade då god förmåga att förutspå vilka patienter som skulle drabbas av icke radikal operation.

Studie III

Studiens syfte var att följa patienter som gavs neoadjuvant cellgiftsbehandling och var planerade för bröstbevarande operation och sedan se vad operationsutfallet blev; bröstbevarande kirurgi eller mastektomi. Det andra syftet var att hitta faktorer som påverkade möjligheten för bröstbevarande kirurgi.

Studien inkluderade 226 patienter under flera år och andelen bröstbevarande kirurgi ökade under åren, från 37% till 52%. Primära faktorer som påverkade möjligheten för bröstbevarande kirurgi var tumörstorlek, sjukdom i körtlarna i armhålan och brösttätheten på mammografi. I takt med förbättrad behandling ska även andelen bröstbevarande kirurgi kunna öka. Faktorerna som identifierades i denna studie kan ge stöd i beslutet hur bröstbevarande kirurgi används på bästa sätt inom denna patientgrupp.

Studie IV

Studiens syfte var att undersöka livskvalitet före och efter bröstcanceroperation och studera eventuella skillnader i livskvalitet och patientnöjdhet mellan olika operationsmetoder. Totalt inkluderades 351 patienter som fyllde i livskvalitetsenkäter vid diagnos samt vid 1-årsuppföljningen. Studien visade att onkoplastikkirurgi och traditionell bröstbevarande kirurgi hade bäst resultat avseende kroppsbild, sexuell hälsa och nöjdhet med brösten jämfört med mastektomerade patienter och även patienter som rekonstruerades med protes. Mastektomerade patienter hade minst symptom från operationsområdet.

Denna studie betonar hur viktigt det är att bevara bröstet när det är möjligt och understryker att en bröstrekonstruktion inte är likvärdigt med en bröstbevarande operation.

List of included papers

The studies are referred to in the text by their Roman numerals.

Paper I

Cosmetic Outcomes and Symmetry Comparison in Patients Undergoing Bilateral Therapeutic Mammoplasty for Breast Cancer.
Gulis K, Rydén L, Bendahl PO, Svensjö T.
World J Surg. 2021 May;45(5):1433-1441.

Paper II

Validated prediction model for positive resection margins in breast-conserving surgery based exclusively on preoperative data.
Ellbrant J, **Gulis K**, Plasgård E, Svensjö T, Bendahl PO, Rydén L.
BJS Open. 2021 Sep 6;5(5):zrab092

Paper III

A prospective cohort study identifying radiologic and tumor related factors of importance for breast-conserving surgery after neoadjuvant chemotherapy.
Gulis K, Ellbrant J, Svensjö T, Skarping I, Vallon-Christersson J, Loman N, Bendahl PO, Rydén L.
Eur J Surg Oncol. 2023 Jul;49(7):1189-1195.

Paper IV

A prospective longitudinal cohort study of health-related quality of life by type of breast surgery in women with primary breast cancer.
Gulis K, Ellbrant J, Bendahl PO, Svensjö T, Rydén L.
Submitted manuscript

Authors' contributions to papers

Paper I

Study concept, study design, data acquisition, quality control of data, data analysis and interpretation, statistical analysis, manuscript preparation.

Paper II

Data acquisition, quality control of data, data analysis and interpretation, statistical analysis, manuscript preparation

Paper III

Data acquisition, quality control of data, data analysis and interpretation, statistical analysis, manuscript preparation

Paper IV

Study concept, study design, data acquisition, quality control of data, data analysis and interpretation, statistical analysis, manuscript preparation.

“Everything is hard before it is easy”

- Goethe

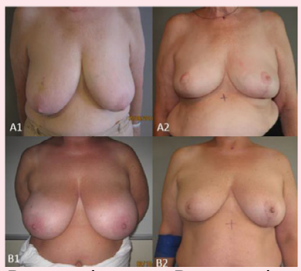
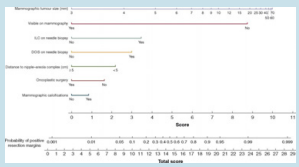
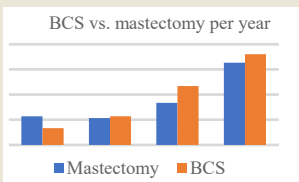
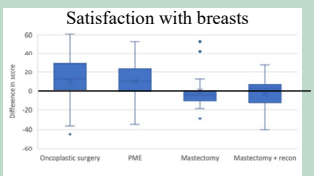
Abbreviations

ALND	Axillary lymph node dissection
ANOVA	Analysis of variance
ANCOVA	Analysis of covariance
AUC	Area under the curve
BCCT.core	Breast cancer conservative treatment. Cosmetic results
BCS	Breast-conserving surgery
BMI	Body mass index
CI	Confidence interval
DCIS	Ductal carcinoma in situ
EBSQ	European Board of Surgery Qualifications
EORTC	European Organisation for Research and Treatment of Cancer
EPBVE	Estimated percentage of breast volume excised
ER	Oestrogen receptor
ESMO	The International European Society for Medical Oncology
HER-2	Human epidermal growth factor receptor 2
HRQoL	Health related quality of life
ISRCTN	International Standard Randomised Controlled Trial Number
NAC	Neoadjuvant chemotherapy
NHG	The Nottingham histological grade
MRI	Magnetic resonance imaging
OPBS	Oncoplastic breast surgery
OR	Odds ratio
PGR	Progesterone receptor
PCR	Pathological complete response
PROM	Patient-reported outcome measure
ROC	Receiver operating characteristics
TAD	Targeted axillary dissection
WHO	World Health Organisation

A disease known is half cured

- Thomas Fuller

Thesis at a glance

Study	Aims	Methods	Results
I  Preoperative Postoperative	To investigate cosmetic outcomes and breast symmetry in breast cancer patients undergoing bilateral therapeutic mammoplasty.	Retrospective study involving 146 patients. Scores from patients, surgeons, and BCCT.core were collected. Correlations between scores were compared using Wilcoxon's matched-pairs signed-rank sum test and Spearman's rank correlation coefficient.	The majority (89%) of the patients had good or excellent cosmetic outcomes based on BCCT.core scores. The patients were more satisfied with the cosmetic outcomes than the surgeons.
II Nomogram for predicting positive resection margins 	To develop a prediction model for positive margins after BCS based exclusively on predictors that are easily available before surgery.	Retrospective study using multivariable logistic regression to develop a prediction model for positive margins including variables with discriminatory capacity identified in a univariable model. Two validation cohorts were used.	Seven variables were included in the final prediction model, which had an area under the curve of 0.80. The prediction model showed good ability to predict positive margins after BCS also in the validation cohorts.
III 	To monitor patients before the start of NAC in relation to the final surgical procedure and to identify variables of clinical significance associated with the application of BCS after NAC.	Prospective study involving 226 patients using univariable and multivariable logistic regression models including covariates of known clinical relevance and those associated with the outcome.	The BCS rate after NAC increased from 37% to 52% during the study years. Factors associated with BCS included tumour size, axillary status, and mammographic density.
IV 	To analyse HRQoL in patients with breast cancer undergoing surgery at baseline and 1-year follow-up and to evaluate if the surgical groups had different outcomes.	Prospective study involving 340 patients using ANOVA and the Kruskal–Wallis test to analyse differences in HRQoL between four surgical groups. The results were adjusted for confounders using ANCOVA.	Oncoplastic surgery and partial mastectomy were associated with the best outcome in body image and breast satisfaction. Patients undergoing mastectomy had the least symptoms in the chest area.

“To cure sometimes, to relieve often, and to comfort always.”

- 15th century folk saying

Introduction to the thesis

Breast cancer is currently the most prevalent cancer among women. In Sweden, approximately 9000 patients are diagnosed with breast cancer annually. Surgery remains the primary treatment for most patients with breast cancer. According to the National Quality Register for Breast Cancer in Sweden, the rate of breast-conserving surgery (BCS) in 2010 was 57%; 10 years later, in 2022, the rate had increased to 73%. Substantial differences persist among Sweden's hospitals, with rates ranging from 56% to 90% [1]. Survival rates have followed a similar trend, increasing from a relative 5-year survival rate of 74% in the 1980s to 93% by 2020 [2].

The overall aim of this thesis was to explore different aspects of BCS. More specifically, the four studies within this thesis explored cosmetic outcomes, health-related quality of life (HRQoL), risk factors for positive margins, and BCS after neoadjuvant treatment.

With overall survival steadily increasing following breast cancer treatment, many women are expected to live for a long time with the cosmetic results of their surgery. Therefore, improving HRQoL and cosmetic outcomes should be among the main aims in breast cancer surgery. Both cosmetic and functional outcomes contribute to patient satisfaction and quality of life. Personalised oncoplastic surgery, which integrates oncoplastic surgery into BCS, allows wider excision and expands the limits of breast conservation. This approach helps prevent cosmetic deformities and reduces both re-excision and mastectomy rates.

Breast cancer is a heterogeneous disease, and no two patients have identical breast sizes, shapes, and other personal attributes. Additionally, the composition of the tumour and prognosis vary. The size of the tumour in relation to the size of the breast is the single most important predictor of potential cosmetic results after BCS. A higher likelihood of a poor cosmetic outcome exists when a large proportion of the tumour volume is excised without incorporating an oncoplastic approach. Systematic schedules have been developed to facilitate decisions regarding the surgical method (Figure 1). The location of the tumour within the breast also influences cosmetic outcomes, with the central, medial, and inferior parts of the breast being more challenging locations.

Effective surgical management is the cornerstone of breast cancer treatment. This is a rapidly evolving field in medical and surgical practice, and personalised, tailored treatment is a priority in the modern era. Oncoplastic surgery combines

oncological principles with plastic surgery techniques, but it is much more than a mere combination of the two disciplines. It is a toolbox and philosophy on how to best choose and perform surgery for each individual patient with breast cancer. The concept of oncoplastic surgery not only refers to a surgical procedure but also defines an approach and mindset for decision-making and execution of breast surgery. Oncoplastic breast surgeons make a commitment to consider the cosmetic results of all breast cancer surgeries and not only for larger resections. Therefore, all patients can be considered for an oncoplastic approach because the integration of cosmetic results into oncological and surgical decision-making applies to all patients undergoing breast cancer surgery. Regardless of whether a specialised technique is indicated, the approach and planning ought to be oncoplastic in nature.

Many patients present with a small tumour, detected within the screening program, and a favourable tumour-to-breast size ratio. They could be candidates for conventional forms of BCS with a simple lumpectomy and a scar over the tumour location. On the other end of the scale are patients who, for oncological reasons, need a mastectomy or have a genetic mutation and are recommended a risk-reducing mastectomy. The oncoplastic approach permeates right down to a cosmetically optimised simple mastectomy. The area between the two extremes of simple lumpectomy and mastectomy is the main field for the oncoplastic toolbox. Obtaining the experience needed to understand where, when, and which tool is best used for each individual patient requires training and hands-on supervision. To optimally choose the best surgical technique, continuous and systematic evaluations of outcomes, including HRQoL and cosmesis, should be conducted to establish evidence-based guidelines. Finally, patients' wishes and opinions on the preferred treatment should always be considered. Breast cancer is a complex, multifactorial disease, and effective treatments are continually evolving through research, clinical trials, and multidisciplinary collaborative efforts.

As breast surgeons, we have the responsibility to guide our patients in decision-making, as well as to continue development and training to further promote the goal of an optimal outcome for each patient. Considering the advances in breast cancer surgery over the last 20 years and the oncological advances leading to longer survival for breast cancer patients, the skills required by breast cancer surgeons have increased alongside the development of a favourable prognosis.

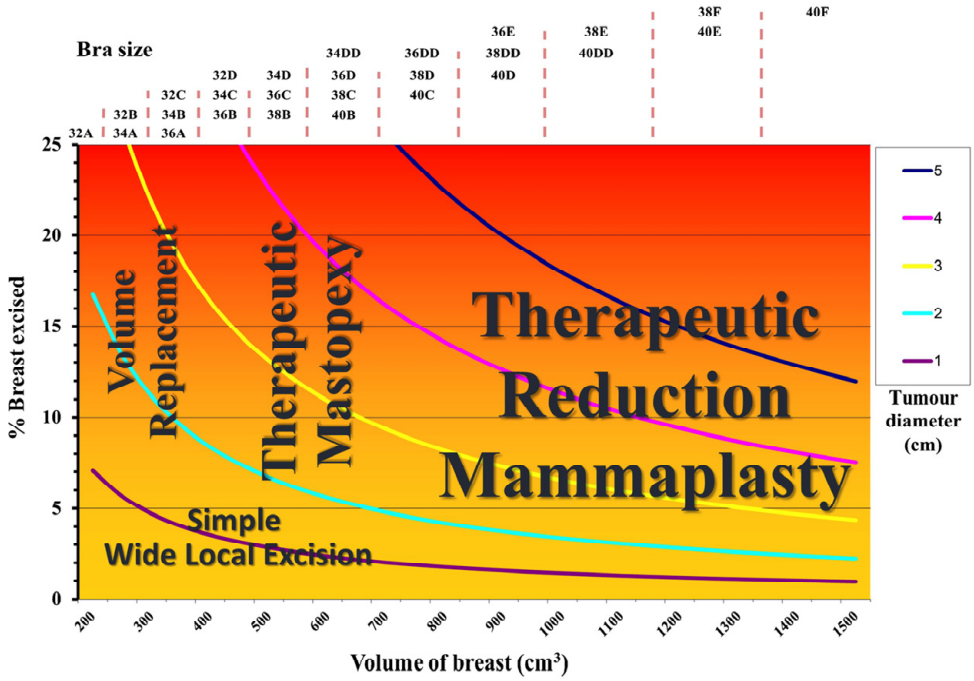


Figure 1. Schematic representation of oncoplastic surgery (*Adapted from Open Access* [3])

“We are what we repeatedly do.
Excellence, then, is not an act, but a habit.”

- Will Durant

Background

Epidemiology and risk factors

In 2022, 9429 new cases of breast cancer were diagnosed in Swedish women, according to the annual National Swedish Quality Registry report. The 5-year observed survival rate was reported to be 84%, and the average 10-year survival rate was 72% [1]. When including patients from all Nordic countries, the number is close to 210000 new cases per year, and 4000 women die annually from breast cancer. In 2020, over 328000 women were living with breast cancer in Nordic countries [4].

The incidence of breast cancer has increased since the 1980s (Figure 2), and breast cancer mortality has decreased during this period (Figure 3) [4]. This means that the number of women living with breast cancer is increasing annually, but cancer is still the most common cause of death in women below the age of 80 years.

The most important risk factor for the development of breast cancer is female sex. Other risk factors include older age; family history; reproductive factors; oestrogen supplements; dense breasts; and lifestyle factors, such as alcohol consumption and obesity [5]. Several genetic risk factors for breast cancer also exist, the most common being BRCA1 and BRCA2, found in 2–3% of all women diagnosed with breast cancer. During the screening of patients with a family history of breast cancer, seven other genes have been analysed (*ATM*, *BARD1*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D* and *TP53*) [6].

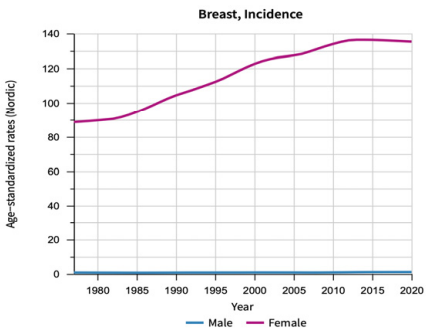


Figure 2. Breast cancer incidence [4]

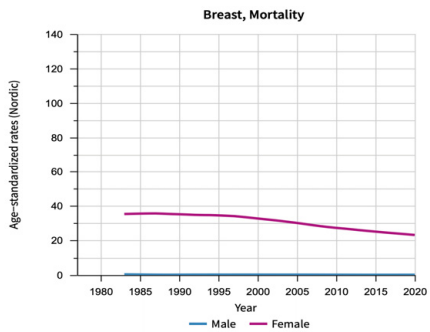


Figure 3. Breast cancer mortality [4]

Treatment of breast cancer

Diagnostics

The National Board of Health and Welfare in Sweden has recommended mammographic screening for all women since 1985, and currently, all women aged 40–74 are invited to undergo screening every 18–24 months [7]. Every year, over one million women are invited to undergo screening mammography, and approximately 60% of all breast cancers are detected through screening [8].

The gold standard for assessing a suspected lesion, whether detected through screening or symptoms, is triple diagnostics. This includes radiological assessment using both mammography and ultrasound of the breast and axilla, along with a biopsy. Triple diagnostics have high sensitivity, and in previous studies, their accuracy reached over 95% [9, 10]. Today, many Swedish hospitals have established breast cancer centres where teams work multidisciplinary, both in diagnostics and treatment planning for patients with breast cancer. This involves multidisciplinary conferences and assistance from contact nurses and other healthcare personnel.

Classification of breast tumours

The histological classification of malignant breast tumours is depicted in Figure 4 [11]. The WHO classification of breast tumours states that the most common type of breast cancer is "no special type," previously referred to as invasive ductal cancer, accounting for approximately 70% of all cases [6]. The second most common type is invasive lobular cancer, which accounts for approximately 5–15% of cases.

The molecular classification of breast tumours is stratified into five groups: luminal A, luminal B, HER-2 positive luminal, HER-2 positive non-luminal, and basal/triple negative. This is based on immunohistochemical subtyping, complemented by *in situ* hybridisation according to the St. Gallen International Consensus [12]. The classification is mainly determined by the oestrogen receptor (ER) status, progesterone receptor (PGR) status, HER-2 status, and proliferation assessed using Ki67 (Figure 5).

Recently, gene expression analysis using RNA expression levels has been introduced as a new molecular classification method. These genomic tests provide information about the molecular type of breast cancer. They also offer prognostic predictions using a risk score to help determine the best adjuvant treatment for each patient. In Sweden, gene expression analysis is recommended for postmenopausal women with luminal tumours and an ambiguous risk of recurrence (Figure 5). This allows tailoring of adjuvant treatment according to the

risk of recurrence [6]. A variety of tests, including Oncotype DX™, Mammaprint®, and Prosigna®, are available. In Region Skåne, a single-sample predictor developed from the Scan-B initiative is utilised [13].

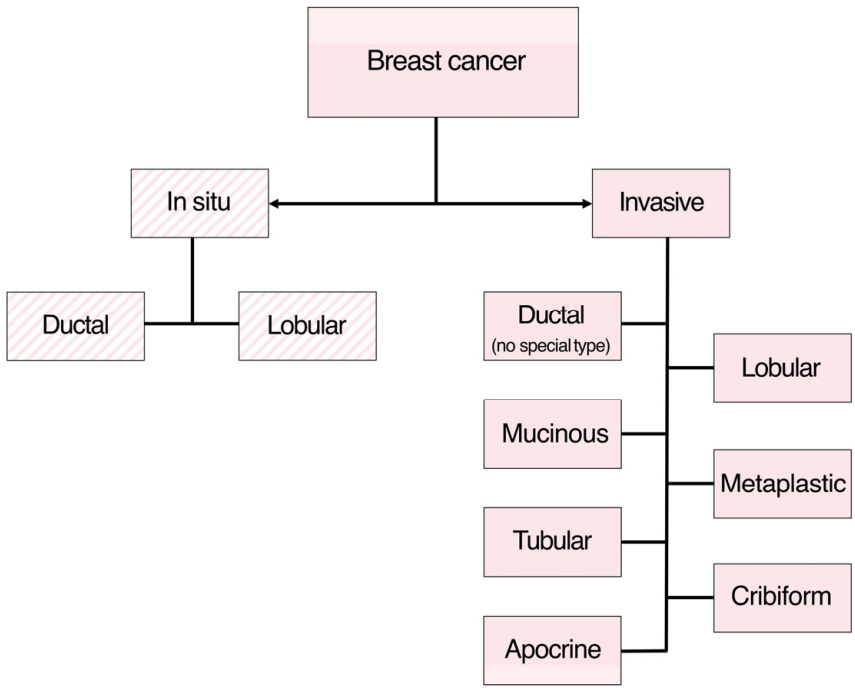


Figure 4. Histological classifications of breast cancer (Made by K. Gulis)

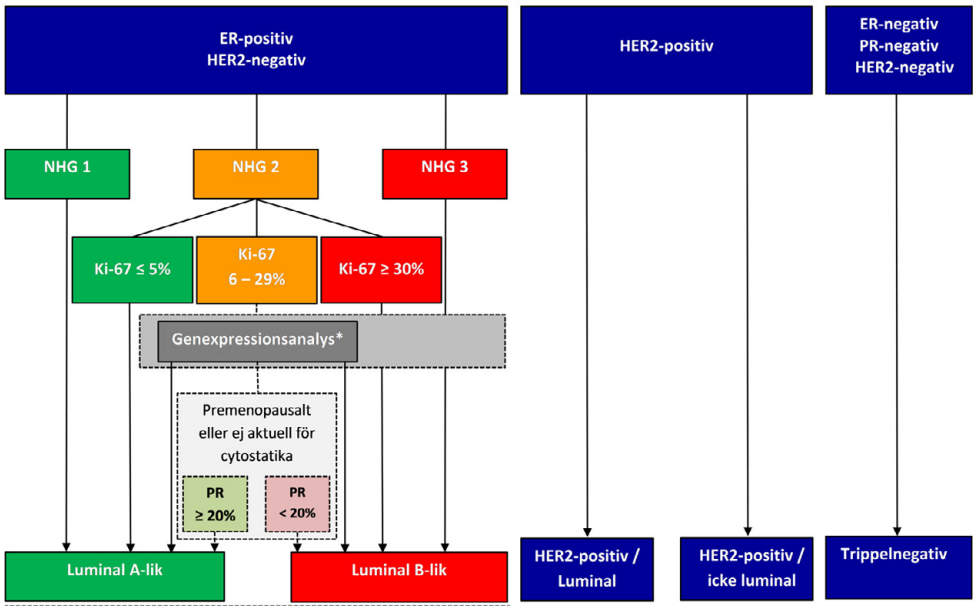


Figure 5. Molecular classification of breast cancer [6]

Surgery

Mastectomy

Mastectomy traditionally involves the removal of all breast tissue, breast skin, and the nipple-areola complex. Radical mastectomy was introduced in the late 19th century and involved a large incision and removal of the whole breast, both pectoral muscles, and the entire axillary lymphatic tissue, ad modum Halsted (Figure 6) [14]. The modern version, in which only the breast and axillary nodes are removed, called modified radical mastectomy, has been the standard surgical procedure for more than 50 years in Sweden and was developed by Patey [15]. According to the current international consensus guidelines, mastectomy should only be performed when BCS is not feasible or ontologically safe [16]. This is based on numerous studies showing no difference in survival when comparing mastectomy to BCS with radiation therapy [17-19]. Additionally, studies have demonstrated improved HRQoL for women who have undergone BCS compared with those who have undergone mastectomy [20]. A recent study conducted in Sweden even showed a slight improvement in the survival of women who underwent BCS over mastectomy [21].

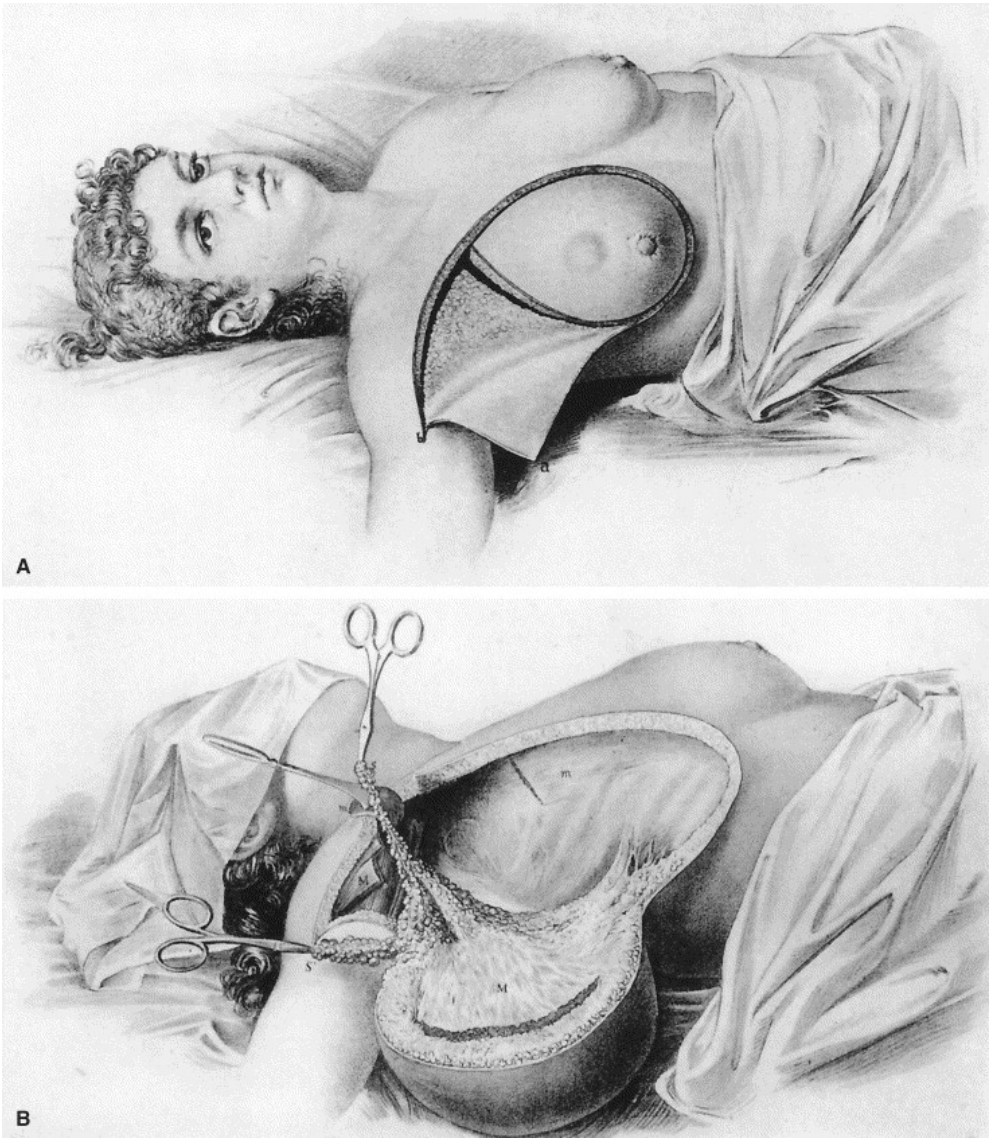


Figure 6. Halsted's radical mastectomy (*Reprinted with permission from Elsevier* [22])

The last decade has also seen some advances in the surgical approach for patients with indications for mastectomy, such as those with a large tumour size or those diagnosed with a hereditary predisposition. These improvements include skin- and nipple-sparing mastectomies. In nipple-sparing mastectomy, both the skin of the breast and the nipple-areola complex are spared, making it an acceptable

alternative to standard mastectomy [23-25]. This enables surgeons to perform the surgical incision for example through the inframammary fold, keeping the mound of the breast without scarring and preserving the best cosmesis when performing breast reconstruction. Several other incisions are possible for nipple-sparing mastectomy (Figure 7). Studies have shown a similar risk of local recurrence, with no difference in survival [23-25].

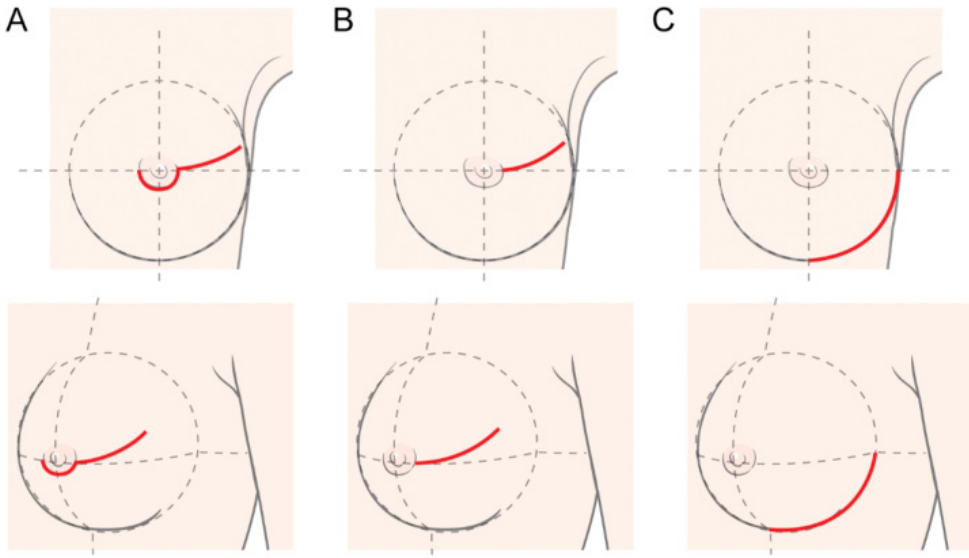


Figure 7. Incisions in nipple-sparing mastectomy (A: periareolar, B: radial, C: inframammary fold) *(Reprinted from Open Access [26])*

Breast reconstruction can be performed with either a breast implant or autologous tissue, enabling breast reconstruction using the patient's own tissue. It can also be performed as an immediate or delayed procedure, either in conjunction with the primary cancer surgery or one to several years later [27-29].

The decision on immediate or delayed reconstruction varies based on factors ranging from the patient's preference to technical aspects, such as the necessity of postoperative radiotherapy. No differences in oncological outcomes have been reported based on the timing of breast reconstruction [30]. Both immediate and delayed reconstructions have been shown to improve the quality of life of patients compared with those who underwent mastectomy only [31, 32].

Breast-conserving surgery

As early as 1954, a Finnish radiation oncologist reported that 127 patients who were treated with only tumour extirpation, followed by radiotherapy, had oncological outcomes similar to those of patients treated with radical mastectomy [33]. The first large studies on the safety of BCS in combination with radiotherapy compared with mastectomy were published in the 70s by Fisher and Veronesi. The traditional breast-conserving surgical techniques described by Fisher (lumpectomy) and Veronesi (quadrantectomy) essentially involve an incision over the tumour, removing the tumour and a piece of healthy breast tissue around the tumour. The current practice is to combine radiotherapy for the remaining breast tissue to reduce the risk of local recurrence [34].

In 2002, follow-ups in both the Fisher and Veronesi trials showed no survival benefit for mastectomy compared with BCS followed by radiotherapy, even after 20 years [17, 18] (Figure 8).

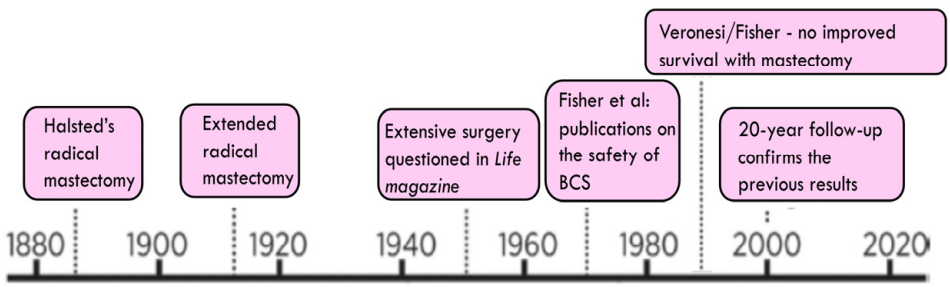


Figure 8. Timeline of the development of BCS (Made by K. Gulis)

Oncoplastic breast surgery (OPBS)

In the 90s, the introduction of oncoplastic surgery, which combines standard BCS with plastic surgery, further advanced the surgical field for patients with breast cancer [35, 36]. If less than 15% of the breast is removed, standard BCS often results in good cosmetic outcomes [37]. If larger excisions need to be made, oncoplastic surgery helps facilitate a better cosmetic outcome [38-41] and also offers the possibility of avoiding mastectomy in patients with larger tumours [42, 43]. A meta-analysis showed superior or at least equivalent outcomes in the included studies when comparing OPBS with BCS [44]. The benefits of OPBS include the possibility of resecting larger tumours, wider surgical margins, and better aesthetic results [44].

Many different classifications have been suggested for oncoplastic surgery, with one of the most widely used being the Clough bi-level classification. In this classification, the amount of tissue removed determines whether the surgery is classified into level 1 (up to 20%) or level 2 (over 20%). This classification was recommended in clinical practice at the 2017 International Consensus conference [45].

The same consensus conference also recommended using Hoffman's classification system for surgical reports. This classification includes six different levels and is further divided into 12 main categories, 13 subcategories, and 39 subcategories [46]. This demonstrates the complexity of oncoplastic surgery, and the description of techniques can be made very complicated.

For simplicity, oncoplastic can be divided into three main principal techniques: volume displacement, volume replacement, and reduction techniques [36, 47, 48].

Volume displacement is essentially the reorganisation of the existing tissue to fill the cavity after a tumour is removed, whereas volume replacement involves moving the tissue from outside the breast mound into the breast to fill the same cavity (Figure 9). Breast reduction techniques involve reducing the volume of the breast and moving the nipple position to make the breasts smaller while removing the tumour and maintaining an optimal breast shape. Typically, this involves performing the same surgery on the contralateral side [49].

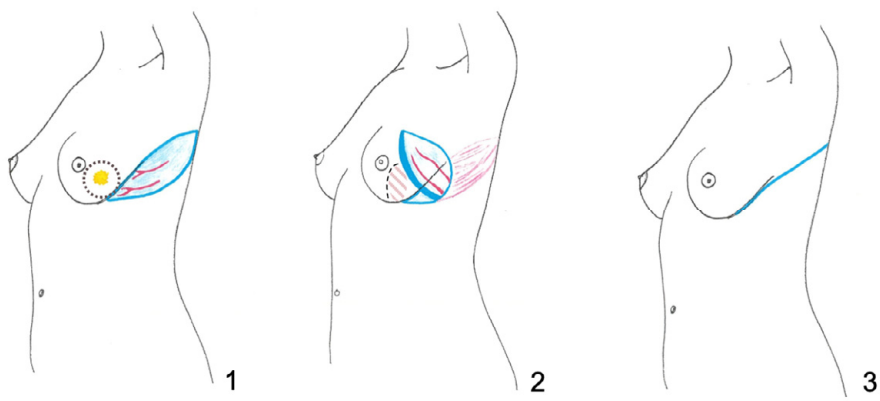


Figure 9. Volume replacement technique—lateral intercostal perforator flap (LICAP)
(Original artwork by Dr. Höskuldsdottir).

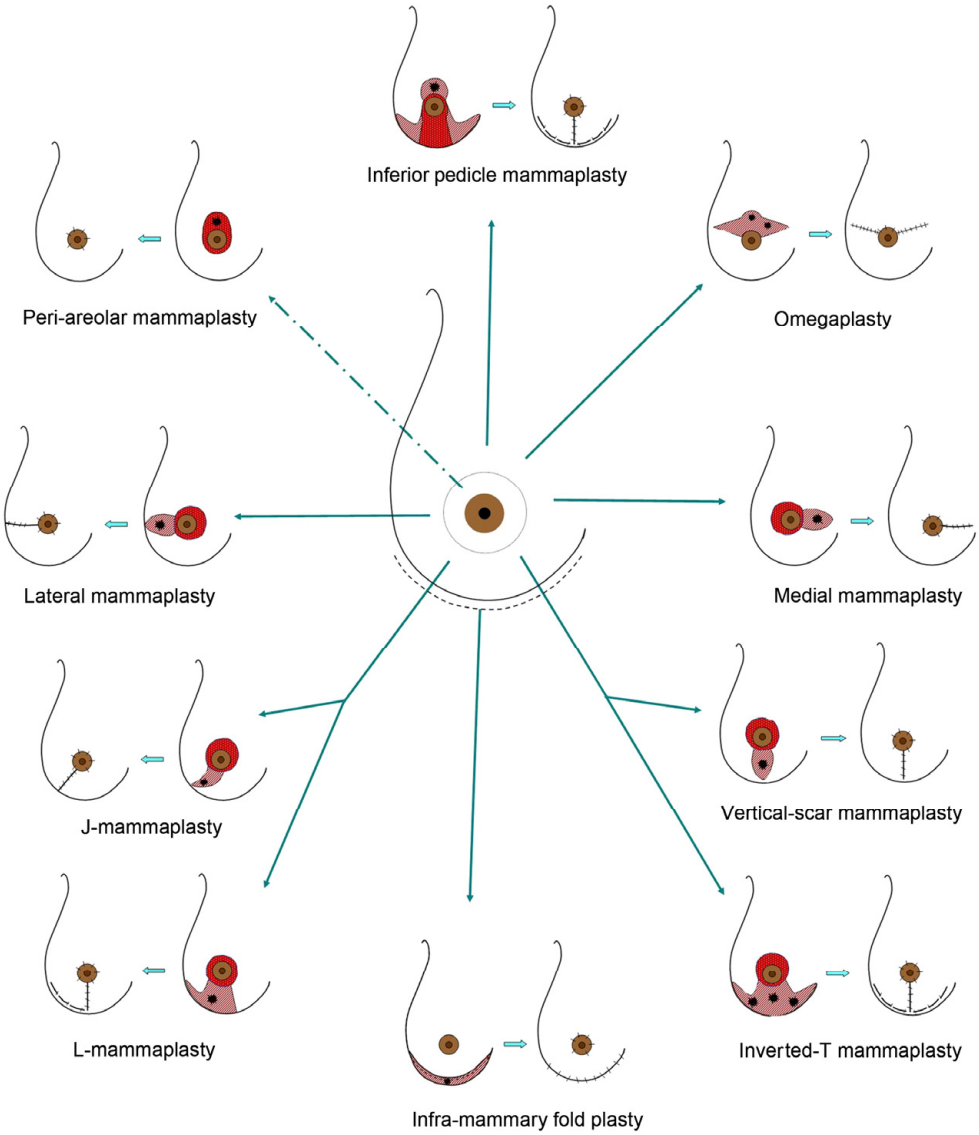


Figure 10. Oncoplastic surgical techniques. (*Reprinted with permission from* Elsevier [50])

Figure 10 shows some common volume displacement techniques, as well as the most common reduction technique (inverted-T mammoplasty).

Regardless of the classification used, mastering these surgical skills requires training in plastic surgery techniques in addition to standard breast surgery. Plastic and general surgeries are two distinct surgical specialties in Sweden. Therefore, training for a breast surgeon often needs to involve plastic surgery, either by

working at a breast cancer centre with a plastic surgeon on the team or by visiting a centre that has a plastic surgeon on site. Sweden has no specific examination for breast or oncoplastic surgery. However, the European Board of Surgery Qualifications (EBSQ) offers examinations in Breast Surgery. Successful candidates are granted the title of Fellow of the European Board of Surgery in Breast Surgery. Additionally, one can apply for certification in "additional education in oncoplastic surgery" from the Swedish Association of Breast Surgery. No official program is available for this educational pathway, but specific skills are recommended for applying for certification.

Axillary surgery

Axillary surgery has undergone similar developments as breast surgery. In Halstead's time, all patients underwent a full axillary lymph node dissection (ALND). ALND involves the removal of tissue between three anatomic landmarks: the axillary vein superiorly, the thoracodorsal bundle laterally, and the chest wall with the long thoracic nerve medially. Between 10 and 30 lymph nodes are usually removed en bloc [51].

ALND is extensive and carries the risk of complications, such as lymphoedema, neuropathic pain, and limitations in shoulder motion [52, 53]. In the early 90s, sentinel node biopsy was first described [54]. Subsequently, evidence arose that sentinel node biopsy was equivalent to ALND as a staging procedure, as long as the sentinel nodes were benign [55].

During the last few decades, several studies have proven the safety of omitting ALND with micrometastatic nodes alone or fewer than three macrometastatic nodes. These guidelines have now been implemented in Sweden [56]. The most recent research suggests that axillary surgery can be omitted completely in certain patient categories without affecting oncological outcomes [57].

Adjuvant therapy

Endocrine therapy

Endocrine therapy with tamoxifen or aromatase inhibitors is a cornerstone in adjuvant treatment for all patients with hormone receptor-positive disease, which applies to close to 80% of all patients. Endocrine therapy substantially reduces both local recurrence and mortality rates [58].

Tamoxifen is an anti-oestrogen drug, which is a competitive inhibitor of oestradiol, blocking its effects on target organs [59]. Tamoxifen was first developed in the 70s but continues to be one of the primary adjuvant treatments for breast cancer.

Aromatase inhibitors are drugs that inhibit the enzyme aromatase, resulting in a decrease in oestrogen synthesis in tissues containing aromatase [60]. Serum levels of oestradiol are reduced by 70–80% in healthy postmenopausal women [61].

The recommendation is 5 years of adjuvant endocrine therapy for node-negative patients and up to 10 years for node-positive patients. For premenopausal women, tamoxifen or aromatase inhibitor in combination with ovarian suppression are recommended. For postmenopausal women, aromatase inhibitors are the preferred initial therapy but can be switched to tamoxifen if needed, for example, if the side effects are poorly tolerated [6, 62, 63].

Radiation therapy

Current guidelines recommend that all patients with breast cancer undergoing BCS receive postoperative radiotherapy [6]. Radiotherapy reduces the risk of local recurrence and improves survival [34, 64, 65].

In node-negative patients, radiotherapy is localised only to the breast, whereas node-positive patients receive locoregional radiotherapy, including both the breast and regional lymph nodes. In patients who have undergone mastectomy, local radiotherapy is recommended only if the tumour is larger than 5 cm or there is overgrowth to the chest wall and/or the skin of the breast. Finally, patients with inflammatory breast cancer are candidates for radiotherapy, even when mastectomy is performed.

In a small subgroup of patients with low-risk cancer and those aged > 65 years, radiotherapy can be omitted. However, this approach entails a higher risk of local recurrence (up to 9% in 10 years) but has no negative effect on survival [66, 67].

Initially, all patients received 50 Gray in 25 fractions. This dose was de-escalated to 40 Gray in 15 fractions, with studies showing no difference in the outcomes [68]. Recently updated guidelines now reduce the fractions to 26 Gray in 5 fractions for patients aged >50 years, with no difference in outcomes [69].

Chemotherapy

Chemotherapy is usually administered postoperatively, and approximately 30% of all patients with breast cancer receive some form of chemotherapy [1]. The most common treatment involves a combination of anthracyclines and taxanes. These cytotoxic drugs kill rapidly growing cells, including cancer, hair, skin, and gastrointestinal tract cells. Studies have shown improved survival and recurrence rates with adjuvant chemotherapy [70, 71], and the first meta-analysis was published as early as 1988 [72].

The choice of systemic therapy, including chemotherapy after surgery, is based on tumour biology, tumour stage, and individual factors, such as age. Endocrine therapy and radiotherapy are sufficient for favourable tumour subtypes (node-

negative, low-grade, and hormone-positive). Triple-negative, HER-2 positive, and inflammatory cancers are more aggressive subtypes. However, they are also chemotherapy-sensitive, and most patients with these subtypes receive either neoadjuvant or adjuvant chemotherapy if they can tolerate it.

Neoadjuvant therapy

Neoadjuvant chemotherapy (NAC) is defined as chemotherapy administered preoperatively. Trials with NAC started in the 70s, involving patients with inoperable breast cancer [73], and showed improved survival compared with radiotherapy alone. Subsequent studies have shown that NAC in patients with operable breast cancer yields similar survival rates [74]. However, one study showed a slightly higher risk of local recurrence [75]. A Cochrane review conducted in 2007 showed that NAC was safe and could be used to evaluate chemosensitivity, downstage tumours, and subsequent surgical requirements [76]. Total pathological response, defined as the absence of invasive tumour cells in the surgical specimen after NAC, significantly improves the prognosis and survival of the patient [77, 78]. ER negativity and high Ki-67 levels are two of the most important predictive markers for a better response to NAC [79]. Additionally, HER-2 positivity is also an important predictive marker [80]. In a recent meta-analysis, invasive lobular cancer was shown to have a lesser marked response to NAC than ductal invasive cancer [81].

Two independent meta-analyses concluded that undergoing chemotherapy before surgery instead of after does not result in a survival disadvantage [82, 83]. More recent research has indicated improved surgical outcomes for the patients through BCS and de-escalation of axillary surgery [84]. A third meta-analysis showed no difference in the number of surgical complications between patients treated with NAC and a control group of patients not receiving NAC [85].

BCS should be performed after NAC if feasible and if no contraindications exist (for example mutation carriers or inflammatory cancer). A study involving over 1000 patients showed that the rate of BCS remained constant over a 10-year period, even though treatment improved, and the response rates were much higher. The reason for mastectomy was a personal choice in 53% of the patients, suggesting that surgical decisions are often driven by factors beyond the disease and treatment response [86].

Previously, all patients who underwent NAC were considered candidates for ALND after NAC. Studies have shown that if the axillary nodes are healthy before NAC the sentinel node procedure is sufficient [87]. When one to three axillary nodes are metastatic before NAC, one of the nodes is clipped. If the nodes show no signs of disease after NAC (evaluated by ultrasound), then targeted axillary dissection (TAD) can be performed instead of ALND, without affecting survival

or recurrence rates [88, 89]. TAD involves the removal of the clipped node, and simultaneously a standard sentinel node procedure is performed.

Ongoing studies are investigating the prospect of omitting surgery in exceptional responders who are assumed to achieve a pathological complete response (PCR) after NAC. One prospective study involving 50 patients with triple-negative tumours performed vacuum-assisted biopsies after NAC. If PCR was confirmed in the obtained samples, no further surgery was performed. Early results have not revealed any recurrences thus far [90].

Currently, approximately 13% of all patients with breast cancer in Sweden receive NAC as the primary therapy [1]. The main target groups are patients with triple-negative, HER-2 positive, and inflammatory breast cancers. However, locally advanced cancers of other subtypes can be candidates for NAC. Figure 11 shows an example of NAC response on mammogram images before and after NAC.

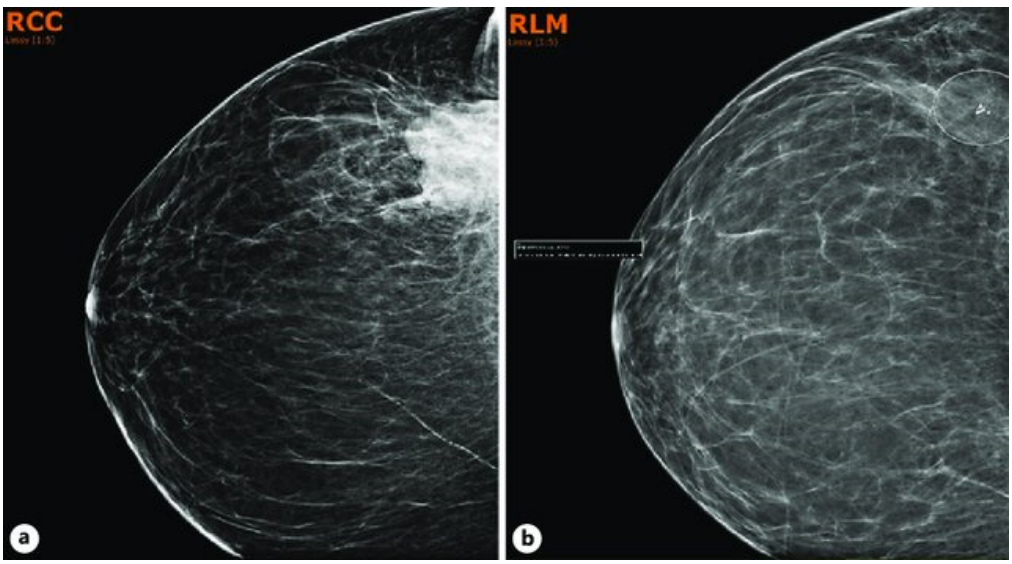


Figure 11. Mammogram images of breast cancer before (a) and after (b) NAC. (Reprinted from Open Access [91])

Margin assessment in breast surgery

BCS has the disadvantage of a risk of positive margins, necessitating a second surgery for the patient. The incidence of positive margins in BCS ranges from below 10% to 30% [92, 93]; thus, one to three of every ten patients will require more than one surgical procedure for their breast cancer. Secondary surgery has multiple potential negative implications, such as an impact on cosmetic outcomes, quality of life, delay in adjuvant therapy, and healthcare costs [94-97]. The optimal resection margin for BCS remains a topic of ongoing debate and has been a field of research for more than 20 years. The finding that a positive margin is a risk factor for local recurrence was established early [98-100], but the optimal size of the free margin is still being investigated.

The current Swedish guidelines state that a radical surgery requires "no tumour on ink," meaning no tumour cells on the margin of the specimen. For ductal carcinoma in situ (DCIS), the guidelines currently recommend a 2 mm margin [6]. The guidelines in Europe and America are similar [16, 101] and are all primarily based on the American guidelines published in 2016 [102].

One area of research in the field of positive margins has been to identify possible predictors to better guide surgeons in the choice of surgery. The early studies primarily evaluated postoperative variables associated with positive margins, revealing that large tumour size, lobular cancer subtype, DCIS, and multifocality are important factors [100, 103-105]. Follow-up studies have developed various nomograms for assessing the risk of positive margins, mainly using postoperative variables, with the goal of facilitating decision-making by surgeons [106, 107]. Recent studies have used preoperative variables, arguing that to make decisions ahead of planning surgery, only preoperative variables can be included, rather than postoperative information. The more recent nomograms developed involved similar risk factors associated with positive margins as those based on postoperative findings [108-111].

The trend in the last decade has been to move towards smaller resection margins needed for oncological safety. However, last year, a study was published proposing that a 1 mm margin should be recommended over the "no tumour on ink" guideline that has been applied the last decade [112]. The recommendation was based on the finding that a survival benefit was found with wider margins of at least 1 mm.

Recent studies have also revealed new modern assessment possibilities, such as MRI of intraoperative specimens or fluorescent stain pairs, for evaluating clear margins and further reducing the number of positive margins, consequently decreasing the need for a second surgery [113, 114].

Health-related quality of life in cancer patients

With improved survival in patients with breast cancer, the focus on patient-reported outcome measures (PROMs) has increased. PROMs quantify aspects of the health-related quality of life (HRQoL) from the patient's perspective. PROMs complement traditional oncological outcomes and offer important information regarding the patients' views on the impact and outcomes of their surgery and treatment. Given the ongoing development of surgical techniques to preserve the breast, evaluating HRQoL using PROMs is important.

The first studies on HRQoL in patients with breast cancer were published in the 1980s. Meyerowitz examined the psychosocial correlates of breast cancer, and Spiegel et al. studied the psychosocial support needs of women with metastatic breast cancer [115, 116].

The development of a new PROMs is a long and time-consuming process that involves structured steps and strict norms. Therefore, finding and using a pre-existing validated PROMs is of value if there is a suitable PROMs for the intended study. If no suitable PROMs exists, the previously made PROMs can be a stepping stone to creating a new one.

The development usually starts with either a concept or idea and then a conceptual framework is created. An example of how this can be visualized was presented already in 1984, shown in figure 12 [117].

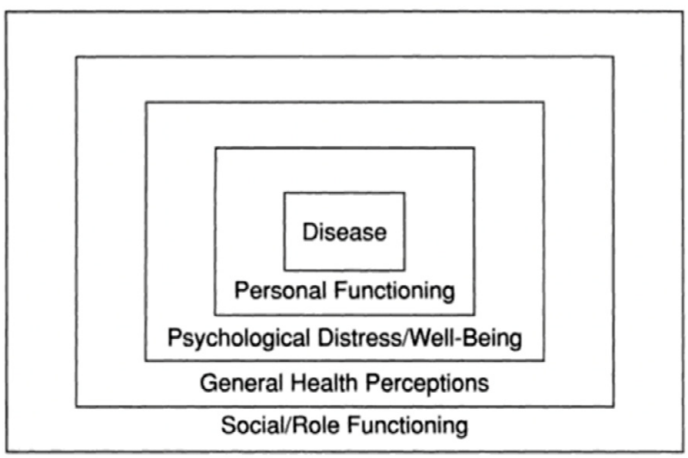


Figure 12. Evaluating the impact of disease. *(Reprinted with permission from John Wiley and Sons [117])*

Thereafter interviews can be conducted and analysed qualitatively to generate questions for each domain, and there can also be further questions added that are deemed important by health-care professionals (for example physicians, nurses, and psychologists). Test questionnaires can then be developed and sent out for a first verification of the questionnaires. The returned questionnaires can then be analysed using psychometric methods for validity, reliability, and acceptability. The updated questionnaires can then be sent out for a second verification [118].

One important aspect of evaluating HRQoL is capturing longitudinal data, showing changes in HRQoL over time. Many studies on patients with breast cancer have been performed on captured postoperative data, disregarding the level of patients' HRQoL before surgery. Longer follow-up is also important because postoperative satisfaction can change over an extended period.

The most common PROMs used in breast cancer is the Breast-Q. In 2016, a study was published in which 200 women were included postoperatively after BCS. The authors concluded that the domain "Satisfaction with breasts" had a significant correlation with the other domains, suggesting that satisfaction with the postoperative result is a good proxy for the other domains [119].

One domain frequently used is physical well-being, and a Cochrane review conducted in 2006 showed that exercise is an effective intervention to improve the quality of life, cardiorespiratory fitness, physical functioning, and fatigue in patients with breast cancer and survivors [120].

Other domains include social issues and financial concerns. A systematic review and meta-analysis evaluated the effect of financial toxicity in patients with breast cancer, and showed a substantial impact on patients worldwide [121]. Financial toxicity is the negative impact of the cost of care on financial well-being. The study showed that low- and middle-income countries experience much higher toxicity than high-income countries. The other PROMs used in this thesis, the EORTC-QLQ, covers both the social and financial domains.

Cosmetic outcomes in breast cancer

Cosmetic outcomes are studied in different ways in patients with breast cancer: by a panel of surgeons, by the patients themselves, and by different objective instruments for evaluating cosmesis. These are described further in the Methods section.

Most evaluation methods are subjective, but this does not negate the importance of evaluating cosmetic outcomes in patients with breast cancer. In 2003, a Cochrane review showed that cosmesis and satisfaction after BCS correlated with the percentage of breast volume excised (EPBVE) [37]. The findings revealed that when the EPBVE was below 10%, over 80% of patients were very satisfied with their appearance, and only 3% were not satisfied. In contrast, when the EPBVE exceeded 10%, the satisfaction rates dropped to 37%, and dissatisfaction increased to 17%. In addition, medial tumour location was associated with worse cosmetic outcomes, indicating that tumour location has an impact [37].

A systematic review conducted in 2013 showed that OPBS led to good cosmetic outcomes in over 80% of patients. However, the conclusion was that most studies were poorly designed and underpowered [122].

A Cochrane review conducted in 2021 stated that oncoplastic surgery gave similar or more favourable cosmetic results, but well-conducted studies evaluating the efficacy, safety, and PROMs of OPBS were lacking [123]. Thus, prospective research on the cosmetic outcomes of OPBS in breast cancer surgery is necessary.

“The best way to predict the future is to create it”

– Abraham Lincoln

Methods

Instruments for assessing health-related quality of life

Breast-Q

The Breast-Q was developed in 2009, through the steps previously described for a validated PROM [124, 125].

The Breast-Q evaluates preoperative and postoperative HRQoL, and the domains include satisfaction with the breasts, overall outcome, process of care, and psychosocial, physical, and sexual well-being (Figure 13). The scale of each domain is independent. The Breast-Q contains modules for different surgical groups, including mastectomy, BCS, and reconstructive surgery. Its main objective is to evaluate the impact and effectiveness of breast cancer surgery from the patient's perspective. The Breast-Q also includes separate questionnaires on augmentation and reduction surgeries performed for cosmetic reasons.

A systematic review was made in 2021, on the Breast-Q model for breast reconstruction after mastectomy, and it concluded that BREAST-Q can effectively and reliably measure satisfaction and wellbeing of breast cancer patients after reconstruction [126].

The first Swedish translation of the breast cancer domains was completed in 2015, eliminating language barriers for use in the Swedish population. In Study IV of this thesis, the Breast-Q was employed for longitudinal measurements of HRQoL in the cohort.

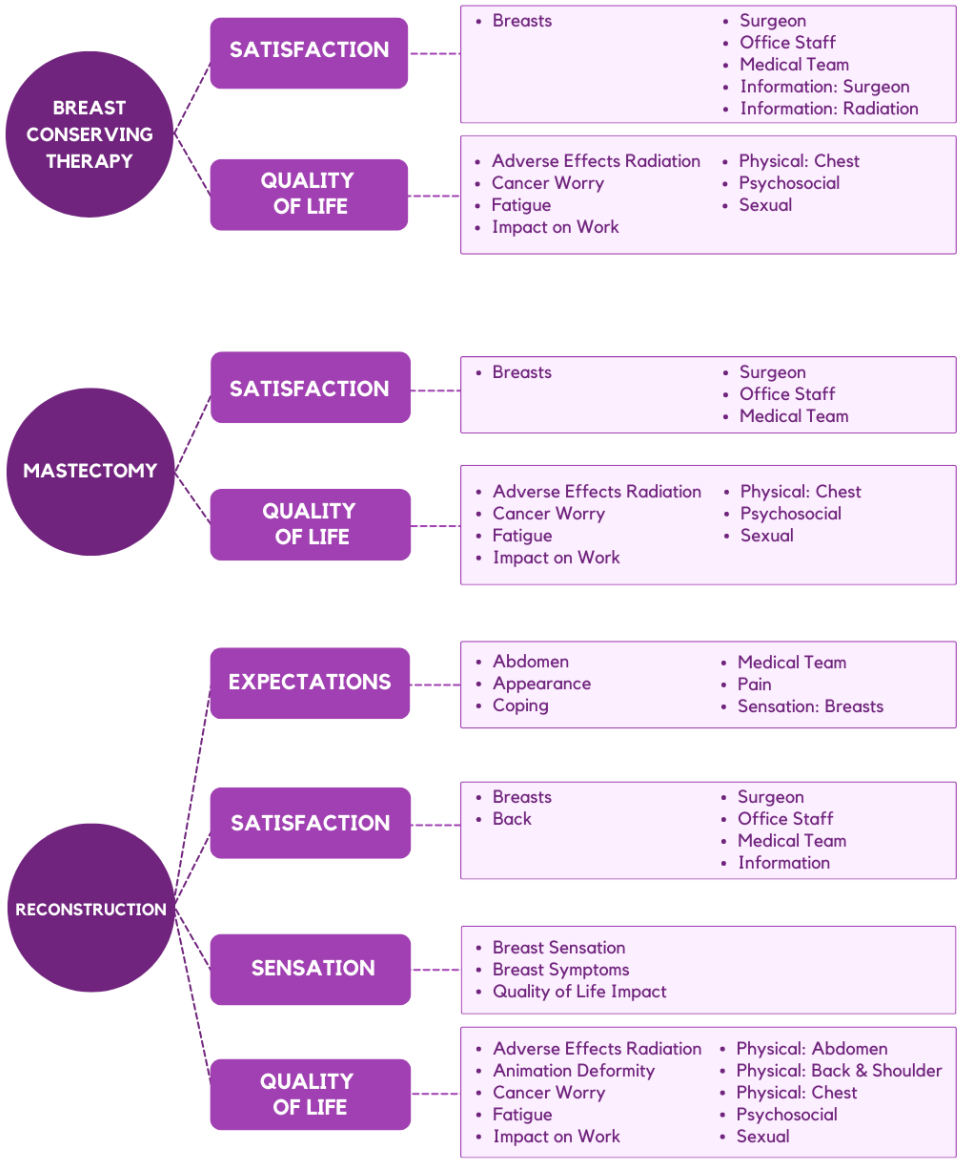


Figure 13. Breast-Q domains and modules *(Reprinted with permission from Memorial Sloan-Kettering Cancer Center)*

EORTC QLQ

The European Organisation for Research and Treatment of Cancer (EORTC) has been active for over 60 years and has presented 75 questionnaires on the quality of life of patients with cancer, available in over 120 languages [127]. The EORTC QLQ Core Questionnaire (EORTC QLQ-C30) is a 30-item instrument designed to measure quality of life in all patients with cancer (Figure 14). This questionnaire was used in this thesis together with the breast cancer-specific EORTC QLQ-BR23.

The EORTC QLQ-BR23 was developed in 1996 to measure the quality of life in patients with breast cancer. A review done in 2015 concluded that QLQ-BR23 is reliable and valid for assessing HRQoL in breast cancer patients [128]. Both questionnaires have Swedish translations. Both questionnaires were utilised in Study IV of this thesis to measure the postoperative HRQoL of the patients.

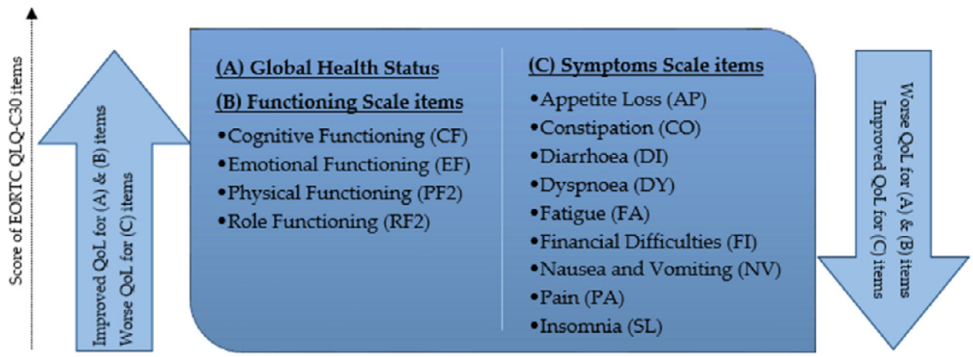


Figure 14. EORTC QLQ-C30 scales *(Reprinted from Open Access* [129]*)*

Instruments for assessing cosmetic outcomes

BCCT.core

The "breast cancer conservative treatment and cosmetic results" (BCCT.core) software digitally evaluates breast cosmesis after BCS. First published in 2007, BCCT.core has been utilized in nearly 100 published studies. The software performs automated analysis of postoperative images after BCS. The postoperative image is uploaded into the software, and the following landmarks are digitally marked: nipples, suprasternal notch, and the most medial and lateral points of the breasts. The software automatically adjusts the outline of the breast contour and

generates the final cosmetic result, classified as one of four categories: excellent, good, fair, or poor. The evaluation is based on asymmetry, colour, and scar visibility features and then further analysed by a pattern classifier performing the categorisation (Figure 15 and 16). The advantage is that it is an objective assessment of postoperative cosmetic results. The software results are comparable to those of a panel of experts, according to previous studies [130, 131]. One systematic review showed fair to moderate agreement between BCCT.core and subjective measurements [132]. This free software is available upon request from the original author. BCCT.core was utilized in Study I of this thesis to evaluate the postoperative results of bilateral therapeutic mammaplasty.

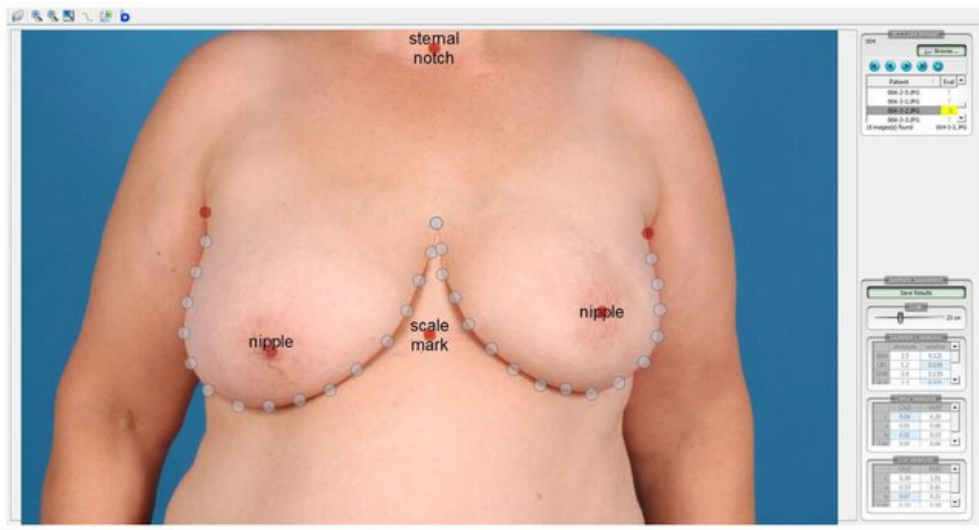


Figure 15. BCCT.core software (*Reprinted from Open Access* [133]*)*

Other attempts have been made to subjectively measure postoperative cosmetic results. One such attempt was the "breast retraction assessment," published in 1988. Breast retraction assessment measures the level of deformity in the operated breast compared with that in the untreated breast [134]. A PubMed search revealed that this approach has not been used in any larger studies since then. This could be attributed to the manual measurement of retraction using a clear acrylic sheet on the patient's torso, and then using vector geometry to calculate the retraction in centimetres.

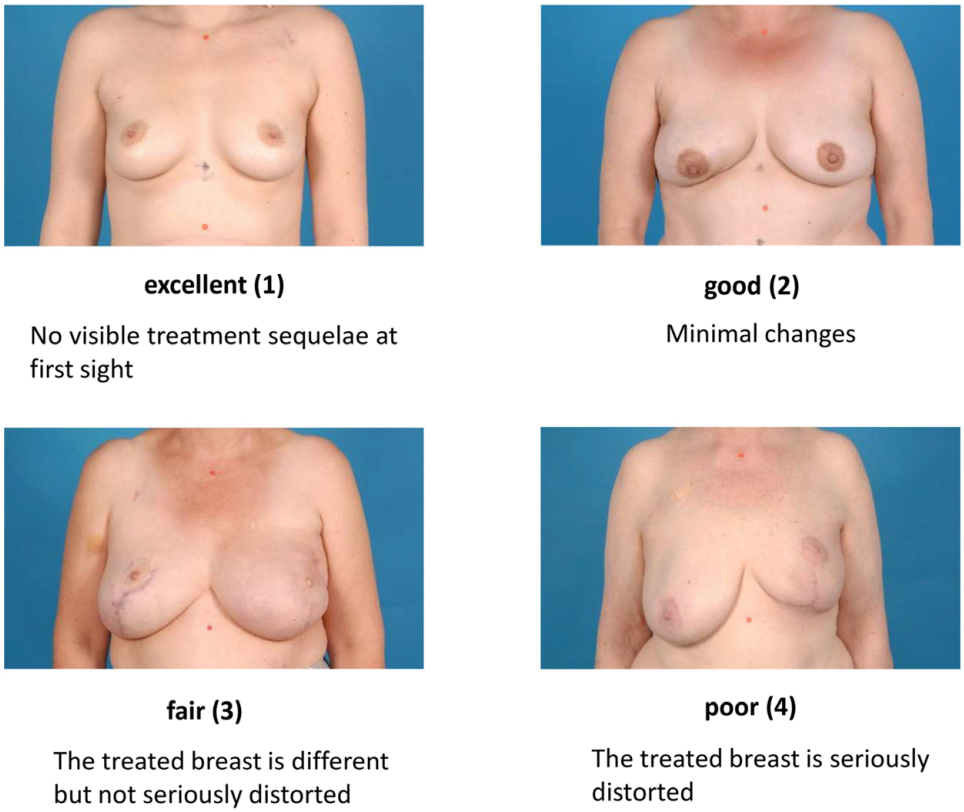


Figure 16. BCCT.core classification *(Reprinted from Open Access [133])*

Subjective measurements

Several methods are available for subjectively evaluating cosmesis, with the most common being panel or physician evaluations and patient self-evaluations [135, 136].

The rating can be performed by either a single examiner or a panel of examiners, preferably trained in the field. It can be performed by physical examination, but the rating is usually obtained by photographic evaluation. The most commonly used criteria is a 4 grade scale suggested by Harris et al. [137]:

- Excellent: the treated breast is almost identical to the untreated one.
- Good: the treated breast is slightly different from the untreated one.
- Fair: obvious difference between the two sides without major distortion
- Poor: the treated breast is seriously distorted.

Other reports have suggested a 10-grade scale: Excellent (9 and 10), good (7 and 8), fair (5 and 6), and poor (4 and below) [138, 139].

Statistical methods

Statistical methods are described in part from the book "Essential Medical Statistics" by Kirkwood and Sterne [140].

Spearman rank correlation coefficient

The Spearman rank correlation coefficient, a nonparametric method based on ranks, measures the strength of the association between two variables.

In Study I of this thesis, the Spearman rank correlation coefficient was utilised to measure pairwise correlation between the patient's score, the surgeon's score, and the BCCT.core score, as well as to evaluate the evidence against the null hypothesis of no correlation.

Wilcoxon's matched-pairs signed-rank sum test

Wilcoxon's matched-pairs signed-rank sum test, a nonparametric method based on ranks, measures evidence against the null hypothesis of equal distributions for paired observations of two variables. If the distributions of the two variables are the same, i.e., if the null hypothesis is true, we expect the same sum of ranks for the absolute values of positive and negative differences.

The Wilcoxon matched-pairs signed-rank sum test was utilised to test the differences in patient and surgeon cosmetic scores, as well as the difference between cosmetic scores of the cancer-affected and contralateral breasts in Study I of this thesis.

Mann–Whitney U-test

The Mann–Whitney U-test, a nonparametric test based on ranks, evaluates evidence against the null hypothesis of no difference in distribution between samples from two independent groups.

The Mann–Whitney U test was utilised in Study I of this thesis to compare the dichotomised BCCT.core scores and the subjective scores of the surgeon and patient.

Kruskal–Wallis test

The Kruskal–Wallis test is a generalisation of the Mann–Whitney U-test to more than two groups.

The Kruskal–Wallis test was utilised to test for differences in postoperative HRQoL scores between the surgical groups in Study IV of this thesis.

Chi-square test

The chi-square test is used to examine associations between categorical exposure and outcome variables. It compares the actual counts in the cross-table with what would have been expected if the null hypothesis had been true (no association between exposure and outcome). The purpose of the test is to determine the likelihood of the observed data or data deviating even more from the null hypothesis if the null hypothesis is true; that is, the P-value.

The chi-square test was utilised in Study III of this thesis to test for an association between patient and tumour characteristics and the final type of surgery.

McNemar's test

McNemar's chi-square test for paired data is based on the number of discordant pairs and is valid if there are at least 10 discordant pairs. For fewer discordant pairs, an exact version of the test, based on a binomial distribution, is recommended. The test contrasts the number of discordant pairs in the two directions (-/+ and +/-) which are expected to be the same under the null hypothesis of equal marginal probabilities.

McNemar's test was used in Study I of this thesis to compare postoperative complications between cancer-affected and contralateral breasts.

Logistic regression

Logistic regression is frequently used to determine the association between exposure variables and binary outcomes. The effects of the exposure variables on the log odds of the exposure category coded 1 are assumed to be linear. This so-called logistic transformation of the probability p of the outcome coded 1, that is, $\ln(p/(1-p))$, ensures that the predictions from the model, which are probabilities, remain in the interval from 0 to 1. The nonlinear function $\ln(p/(1-p))$ is shaped like an S-curve and ranges from 0 to 1. Model estimates are typically expressed as odds ratios (ORs). Hence, the effects of the exposure variables on the odds of the outcome coded 1 are multiplicative factors.

Univariable and multivariable logistic regression analyses were used in Study II of this thesis to identify predictors of non-radical surgery, and in Study III to test covariates of known clinical relevance associated with the binary outcome (BCS versus mastectomy).

Ordinal logistic regression

Ordinal logistic regression, also called proportional odds regression, is a type of regression analysis used for ordinal outcome variables (variables with arbitrary but ordered values). This model forces the estimated effects of the explanatory variables on the outcome to be the same for all possible dichotomisations of the ordered outcome variables.

Ordinal regression was used in Study I of this thesis to analyse the effects of predefined clinicopathological variables on BCCT.core scores.

Receiver operating characteristic curves

The receiver operating characteristic (ROC) graph shows the performance of the classification model for all classification thresholds. The curve is defined as sensitivity (true-positive rate; vertical axis) versus 1-specificity (false-positive rate; horizontal axis) for all cut-off values. The overall ability of the continuous measure to discriminate between true positive and true negative values is measured using the area under the ROC curve (AUC). For a perfect discriminator, the area would be 1. The null hypothesis, that is, no discrimination, corresponds to an AUC of 0.5.

ROC curves were used in Study II of this thesis to evaluate the discriminatory performance of the model in predicting non-radical surgery.

Hosmer–Lemeshow test

The Hosmer–Lemeshow test is a goodness-of-fit test for logistic regression models. The observations are grouped into deciles by expected probabilities, that is, the predictions calculated from the model. The average expected probability for each group is then compared with the corresponding observed relative frequency of the outcome. The expected and observed values will agree for a perfectly calibrated model, leading to a chi-square statistic of 0 and ten dots on a 45-degree line through the origin when plotting the observed versus expected values.

Hosmer–Lemeshow graphics and tests were used to assess the goodness of fit of the model for the nomogram in Study II of this thesis.

Analysis of variance

Analysis of variance (ANOVA) is a multiple linear regression model used to compare the means of a numerical outcome variable in groups defined by a categorical exposure variable at two or more levels. The null hypothesis is that the group means are equal, and the alternative is that at least one mean differs from the other. ANOVA was used to determine the differences in the changes in HRQoL between the different surgical groups in Study IV of this thesis.

ANCOVA

Analysis of covariance (ANCOVA) is a generalisation of ANOVA used to examine the differences between group means, adjusted for the effects of potential confounding variables. ANCOVA was used to adjust for confounders in Study IV of this thesis.

Methods in the studies

Study I

Study population

This retrospective cohort study included women who underwent bilateral therapeutic mammoplasty between 2011 and 2018 at Kristianstad Central Hospital. The primary aim was to study cosmetic outcomes and symmetry after surgery. The secondary aim was to investigate the changes in symmetry pre- and postoperatively.

Patients who had a secondary mastectomy, missing postoperative photographs, died before the 1-year follow-up, or whose nipple was removed during surgery were excluded. Photographs were taken by the surgeon at diagnosis and at the 1-year follow-up. The study was registered with the ISRCTN (identification number 82786416), and ethical approval was obtained from the Regional Ethics Review Board at Lund University, Sweden (2018/827).

Outcome measures

Cosmetic outcomes were evaluated using three different modalities: patient, surgeon, and BCCT.core. Change in symmetry was measured using BCCT.core pre- and postoperatively. The impact of predefined clinicopathological variables on the cosmetic outcomes and complication rates was also examined.

Statistical analysis

The correlation between the scores was calculated using Spearman's rank correlation coefficient (rs). Evidence of equal score distributions in the two groups was evaluated using the Mann–Whitney U-test. The patient's and surgeon's scores, as well as the difference between the scores of the affected and contralateral breasts, were compared using Wilcoxon's matched-pairs signed-rank sum test. Postoperative complications were compared between cancer-affected and contralateral breasts using McNemar's test. Ordinal regression was used to analyse the effects of predefined clinicopathological variables on BCCT.core scores.

Study II

Study population

This observational retrospective study included three cohorts: a development cohort from a university hospital in Sweden (Site A) between 2015 and 2016 and two cohorts from 2017—one was from the same hospital, and the other was an external cohort from a regional hospital (Site B). The inclusion criteria were patients who underwent surgery for invasive or in situ breast cancer with a primary procedure code for partial mastectomy. The exclusion criteria were male sex, neoadjuvant therapy, and a benign final diagnosis. The study was registered in the ISRCTN (identification number 32164784), and ethical approval was obtained from the Regional Ethics Review Board at Lund University, Sweden (2018/622).

Outcome measures

The primary outcomes were positive resection margins after BCS, and preoperative tumour and patient characteristics associated with BCS.

Statistical analysis

A list of potentially relevant predictors of non-radical surgery were identified based on the literature and clinical knowledge. Univariable logistic regression was used to study the associations between individual predictors and non-radical surgery and multiple logistic regression was used to develop the final prediction model. The variables included in the final model were chosen by stepwise backward variable selection. The discriminatory performance of the model was assessed by using AUCs for ROC curves for all three cohorts. The calibration of the prediction model was assessed graphically in the validation cohorts as suggested by Hosmer and Lemeshow. The fraction of non-radical surgery was plotted against mean predicted probability of non-radical surgery for each of ten deciles of the predicted probabilities. Perfect calibration will correspond to dots on a 45-degree line through the origin. Calibration slope, ideally 1.00, was used as a numerical summary of the validation performance. A nomogram was developed for the final model.

Study III

Study population

This prospective study included patients in the SCAN-B cohort who underwent NAC between 2014 and 2019. Patients who did not provide consent, retracted consent, never underwent surgery, or underwent primary surgery were excluded. The ethics application for this study was approved by the Regional Ethics Review Board at Lund University, Sweden (diary number: 658/09 LU; 742/2016).

Outcome measures

The primary outcome was the proportion of BCS, and the secondary outcome was to identify the variables of clinical significance associated with BCS after NAC.

Statistical analysis

Chi-squared tests were used to quantify the support for an association between patient and tumour characteristics and the final type of surgery, while a trend version of the test was used for ordinal variables. Subgroup analyses were conducted across hospitals to evaluate the homogeneity of associations. Univariable and multivariable logistic regression analyses were used, including covariates of known clinical relevance for the outcome (BCS versus mastectomy). The six variables included were age, tumour size on mammography, molecular subtype (St. Gallen), axillary nodal status, mammographic density, and histological subtype.

Study IV

Study population

This prospective, longitudinal cohort study included patients with primary breast cancer who underwent surgery between 2019 and 2020 in Kristianstad Central Hospital. Patients who could not read or write Swedish, could not understand the information provided, and those receiving palliative care were excluded. The patients were grouped according to the surgical method: OPBS, standard partial mastectomy, mastectomy, or mastectomy with reconstruction. The patients completed the Breast-Q questionnaire at diagnosis, then again at the 1-year follow-up, and the EORTC QLQ-C30 and QLQ-BR23 questionnaires at that time. The aim was to study the quality of life at baseline and at 1 year follow-up. The study was registered at ClinicalTrials.gov (Protocol ID: NCT04227613).

Outcome measures

The primary outcome measure of this study was the quality of life at diagnosis and 1-year follow-up.

Statistical analysis

The Kruskal–Wallis test and ANOVA were used to determine the differences in HRQoL score distribution between the surgical groups. ANCOVA was used to adjust for potential confounding factors. The QLQ-C30 score was compared with the norm values for a Swedish cohort.

Methodological consideration

All studies in this thesis were cohort studies, which means that their level of evidence according to the Oxford Centre for Evidence-Based Medicine is Level 3. This classification stands for individual cohort studies, including retrospective studies.

Few randomised studies have evaluated breast cancer surgery in relation to specific outcomes. This is largely due to the ethical challenges of randomising patients. Moreover, the preferred method of surgery is often chosen for each specific patient. Owing to the lack of randomised trials, prospective cohort studies are the second-best option. They are less likely to confer bias than retrospective studies and can provide better data quality when prospectively registered. The disadvantage, in addition to the lack of randomisation, is the time required to collect the data. This thesis included both prospective and retrospective studies. Prospective studies have obvious advantages. However, considering the time-consuming nature of a prospective study, a retrospective study becomes a feasible alternative within a limited time frame.

The study cohorts in this thesis included patients from one hospital for Studies I and IV. However, for Studies II and III, patients from two hospitals were included. An advantage of multicentre studies is that they enhance the generalisability of the data. In Study I, the surgeon who evaluated the postoperative picture for cosmetic results was involved in the patient's care and therefore biased in the evaluation.

If the opportunity to conduct the thesis studies again were available, the main modification would involve including a second or multiple cohorts from other hospitals. This addition would allow for result comparisons with an independent cohort for studies I and IV. Additionally, employing an objective panel for the evaluation of postoperative cosmetic results would be considered.

Results

Study I

Flowchart of Study I is showed in Figure 17. The results of the study showed that out of 146 women, 89% had good or excellent cosmetic outcomes after bilateral therapeutic mammoplasty, as measured using BCCT.core 11% had a fair result, and none had poor (Figure 18). When comparing the patient and surgeon scores, the patient was more satisfied with the cosmetic outcome in general, with a median score of 9 out of 10, compared to 8 out of 10 for the surgeon. No improvement in symmetry was observed postoperatively, except in a small subgroup with >25% asymmetry preoperatively, where improved symmetry was noted at the 1-year follow-up. The overall complication rate was 27%, most were minor complications. The breast affected with cancer had a higher frequency of complications (20/146) compared with the contralateral breast (10/146). No association was found between cosmetic outcomes and prespecified clinicopathological variables of relevance.

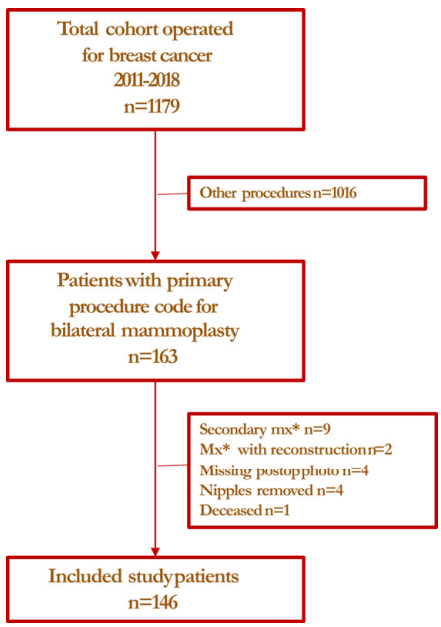


Figure 17. Flowchart of study I. (*Mx = mastectomy)

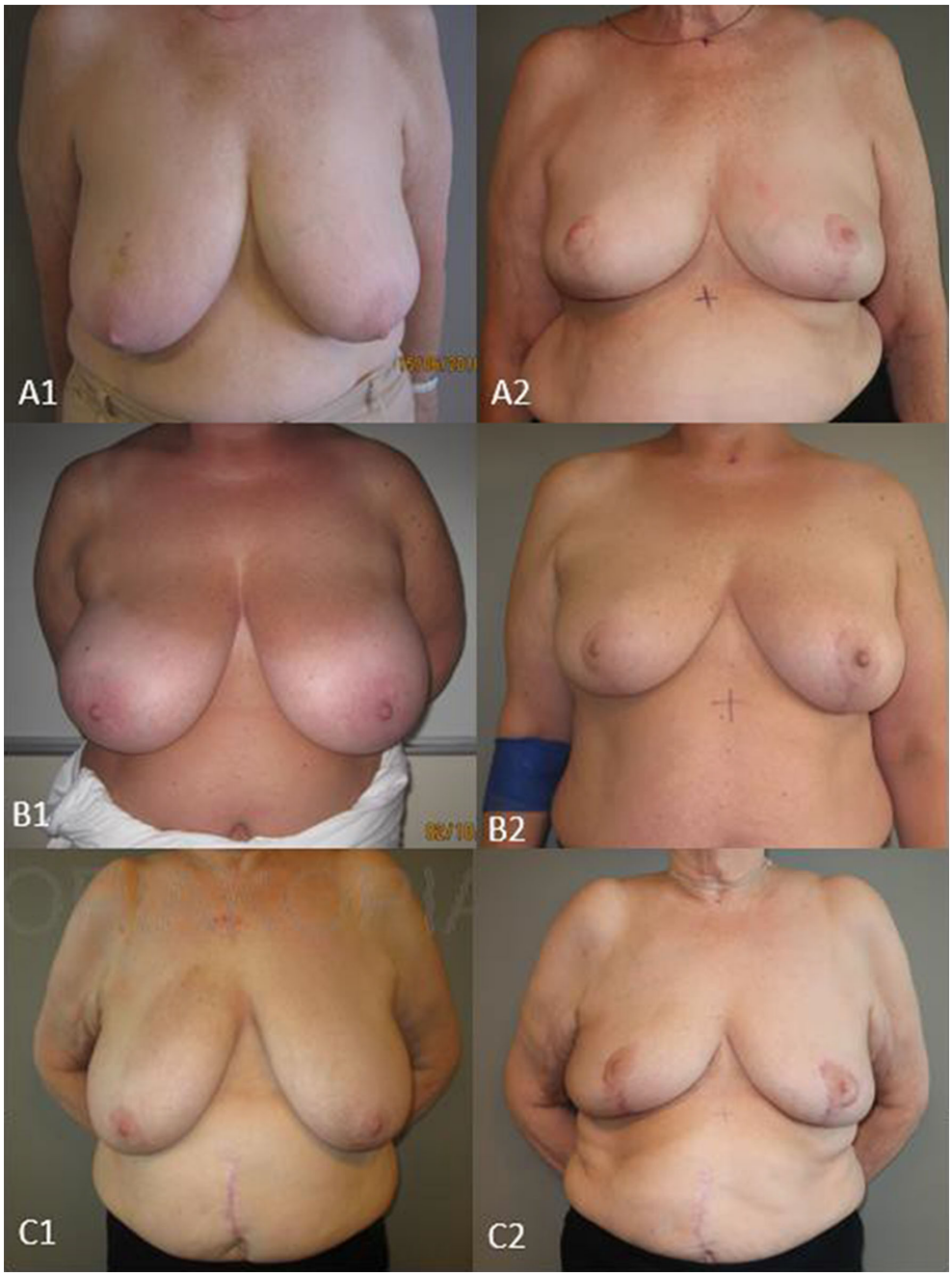


Figure 18. Pre- and postoperative pictures by BCCT.core scores. A2, excellent; B2, good; C2, fair.

Study II

The development cohort at Site A included 432 patients, while the validation cohorts included 190 patients at Site A and 157 patients at Site B (external validation cohort). The patient and tumour characteristics at baseline were largely comparable among the three cohorts. Positive margins were more common in the development cohort (17.8%) and temporal validation cohort from Site A (22.1%) than in the cohort from Site B (10.2%) (Figure 20). In the univariable logistic regression analysis, positive resection margins were strongly associated with mammographic tumour size, ultrasonographic tumour size, presence of mammographic microcalcifications, tumours less than 5 cm from the mamilla, and histological type on diagnostic core needle biopsy (invasive lobular cancer, pure DCIS, and benign biopsy). BMI, tumour palpability, tumour location in the breast, and axillary status had no statistically significant predictive value in the development cohort.

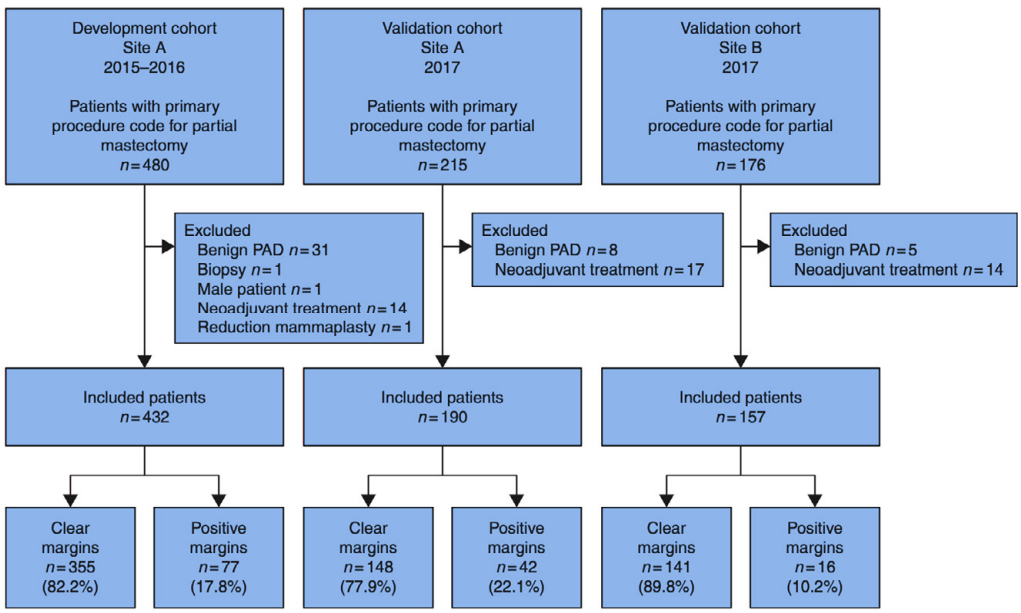


Figure 19. Flowchart of study II.

In the multivariable analysis, a nonlinear transformation of mammographic tumour size and six variables (visible on mammography, DCIS, lobular invasive cancer, distance from mamilla, calcification, and type of surgery) was conducted (Table 1). The best discriminator between positive and negative resection margins, as measured by P-values in the multivariable logistic regression model, was invasive lobular cancer, followed by DCIS and distance to the mamilla. The corresponding ROC curve had an AUC of 0.80 [95% CI 0.75-0.85].

The discrimination and calibration of the prediction model were assessed in the validation cohorts. In the temporal validation cohort from Site A, invasive lobular cancer showed no association with positive margins. In the external validation cohort at Site B, neither microcalcification nor the distance from the mamilla predicted positive margins. The prediction model discriminated between positive and negative resection margins in the two validation cohorts. However, the AUC was lower in both validation cohorts, and both calibration slopes were less than 1.00, indicating overfitting (Figure 20). The model appeared to underestimate the probability of positive resection margins in patients with a low risk of positive margins in the validation cohort from Site A and overestimate this risk in the validation cohort from Site B. The validation still suggested that the model could robustly identify patients at high risk of positive resection margins, and a nomogram was developed (Figure 21).

Preoperative characteristics	Odds Ratio (95% CI)	*P*-value
-30/(Mammographic tumour size, mm)	1.68 (1.21-2.32)	0.002
Visible on mammography		0.160
Yes	1.00	
No	2.33 (0.72-7.60)	
ILC[d] on needle biopsy		<0.001
No	1.00	
Yes	5.59 (2.71-11.50)	
DCIS[e] on needle biopsy		<0.001
No	1.00	
Yes	4.44 (2.00-9.83)	
Distance to mamilla ≥ 5 cm		<0.001
Yes	1.00	
No	2.96 (1.63-5.40)	
Oncoplastic surgery		0.015
Yes	1.00	
No	2.25 (1.17-4.32)	
Mammographic calcifications		0.205
No	1.00	
Yes	1.52 (0.80-2.89)	
Constant	0.06 (0.02-0.19)	

Table 1. A multivariable logistic regression model for prediction of positive resection margins based on preoperatively known characteristics in the development cohort (n=432).

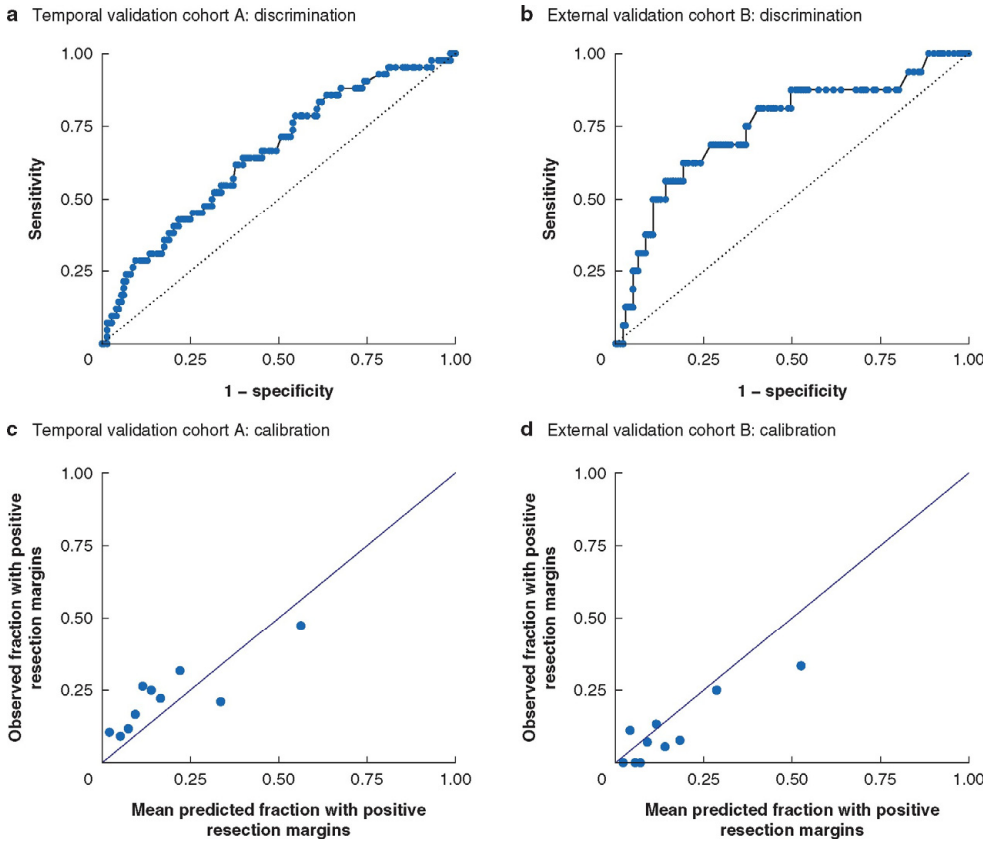


Figure 20. Discrimination and calibration plots for the temporal validation cohort at Site A and the external validation cohort at Site B.

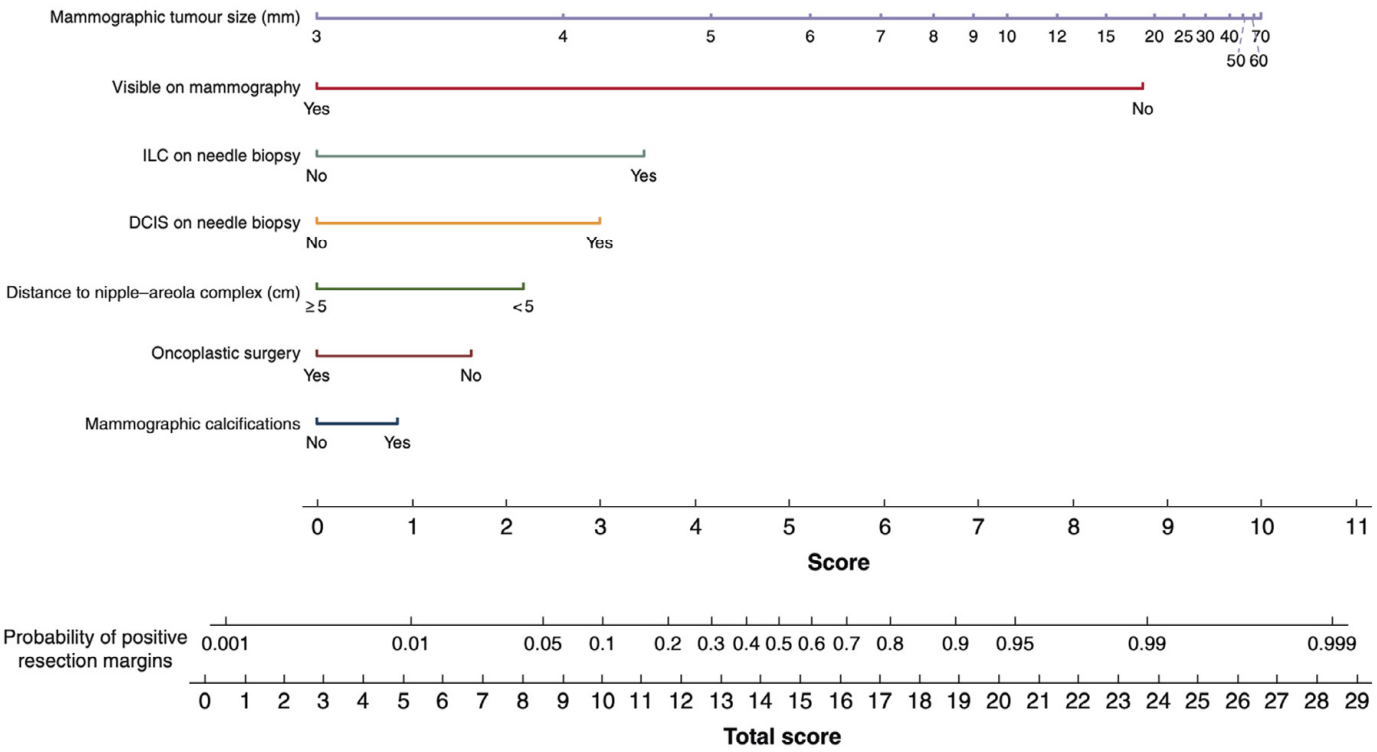


Figure 21. Nomogram for predicting positive margins.

Study III

In Study III, the cohort consisted of 226 women (Figure 22), and the rate of BCS after NAC increased from 37% to 52% during the study period (Figure 23). PCR was achieved in 30% of the cases. The conversion rates were 4% from mastectomy to BCS and 6% from BCS to mastectomy. The decision for conversion was based on the radiological size evaluated during NAC for all mastectomy cases.

Predictors of BCS were identified. Tumour size on mammography showed five times lower odds for the group with the largest tumour (OR=0.2). A similar negative correlation was observed with lack of visibility on ultrasound (OR=0.08) and lobular subtype compared with other subtypes (OR=0.2). The factors with a positive association with BCS were benign lymph node status at diagnosis (OR=2.26) and molecular subtype (St. Gallen), with triple-negative and HER-2 positive tumours having the highest probability of receiving BCS. Mammographic density indicated a trend toward a higher probability of BCS with low breast density (OR=4.2). The same trend was noted with a higher probability in younger women than in older women. In the multivariable logistic regression, the strongest associations with BCS were observed with tumour size on mammography (OR per mm=0.95), preoperative axillary nodal status (OR=2.05), and mammographic density (OR=0.51).

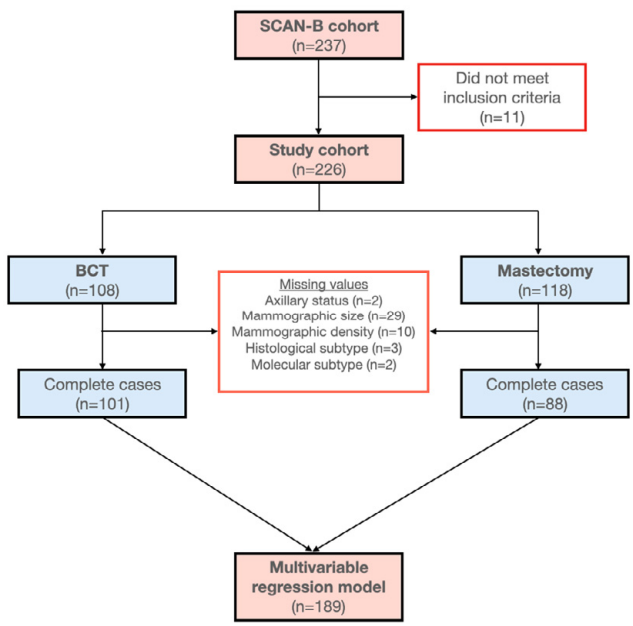


Figure 22. Flowchart of Study III.

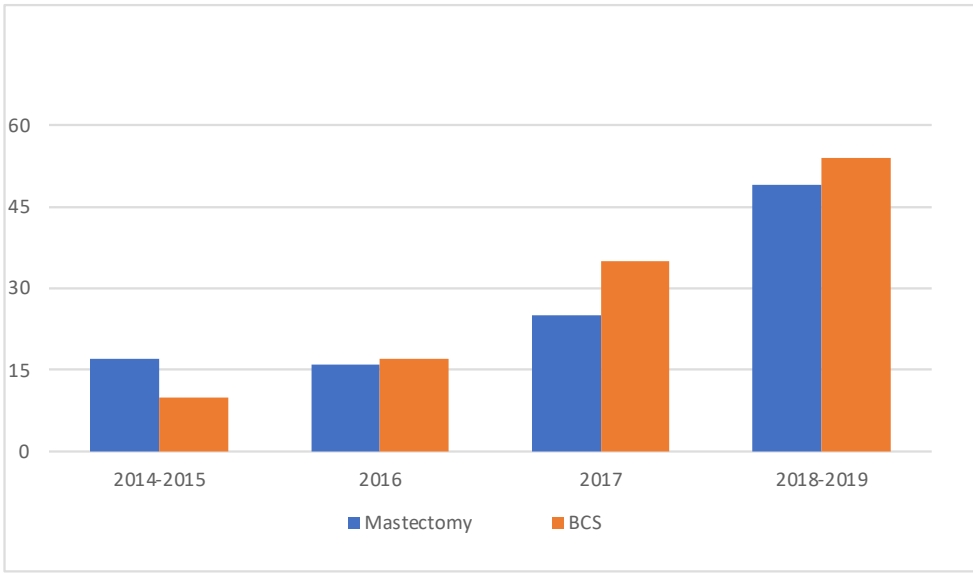


Figure 23. Annual comparison of BCS and mastectomy rates

Study IV

This study included 340 patients in the final cohort. Of the 160 patients who underwent OPBS, 112 underwent standard partial mastectomy, 42 underwent mastectomy, and 26 underwent mastectomy with immediate reconstruction. All patients attended the 1-year follow-up. The response rate for all questionnaires was approximately 95%.

The partial mastectomy and oncoplastic partial mastectomy groups were more satisfied with their breasts (Figure 24) and had better body image and higher sexual functioning scores than the mastectomy with or without reconstruction groups (Figure 25). The oncoplastic and mastectomy with reconstruction groups had more breast symptoms than the other groups. The mastectomy group had the least number of symptoms in the chest area (Figure 26). The other Breast-Q modules showed no differences between the surgical groups. The results of the ANCOVA analyses were similar to those of the unadjusted analyses in terms of the level of evidence for differences between the groups in the postoperative modules.

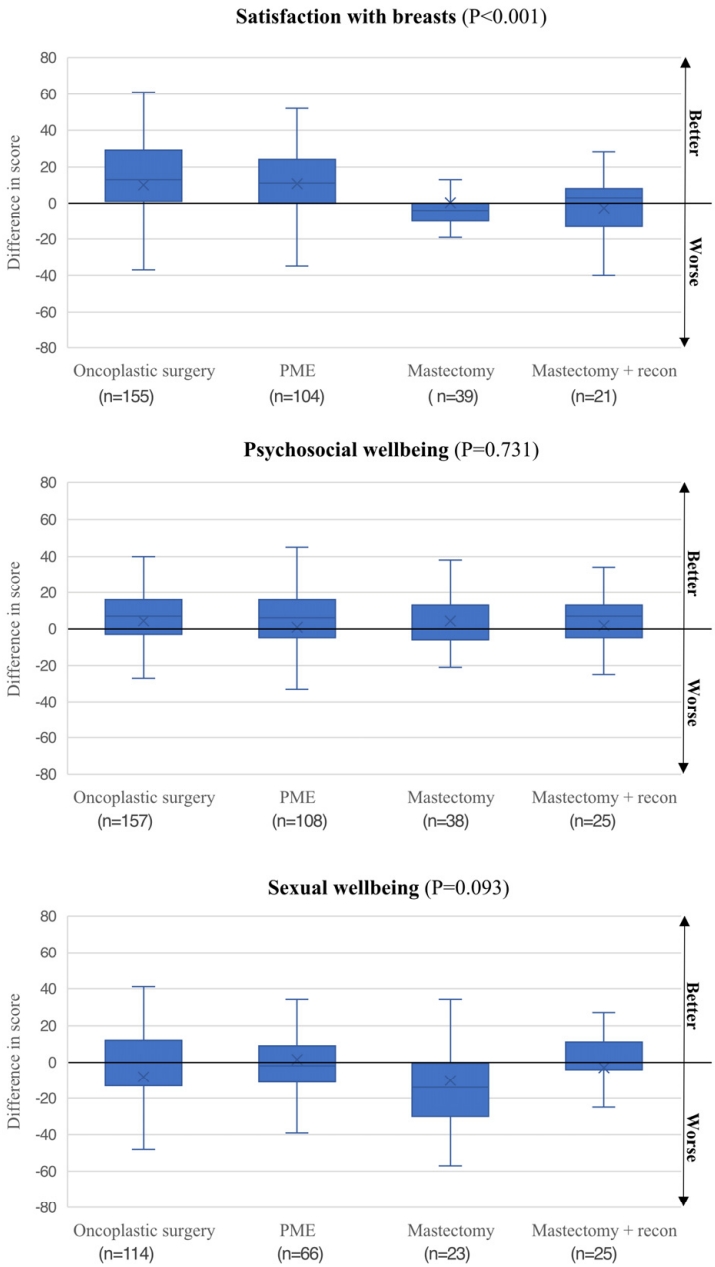


Figure 24. Difference in post- and preoperative Breast-Q scores between the surgical groups, analysed using ANOVA

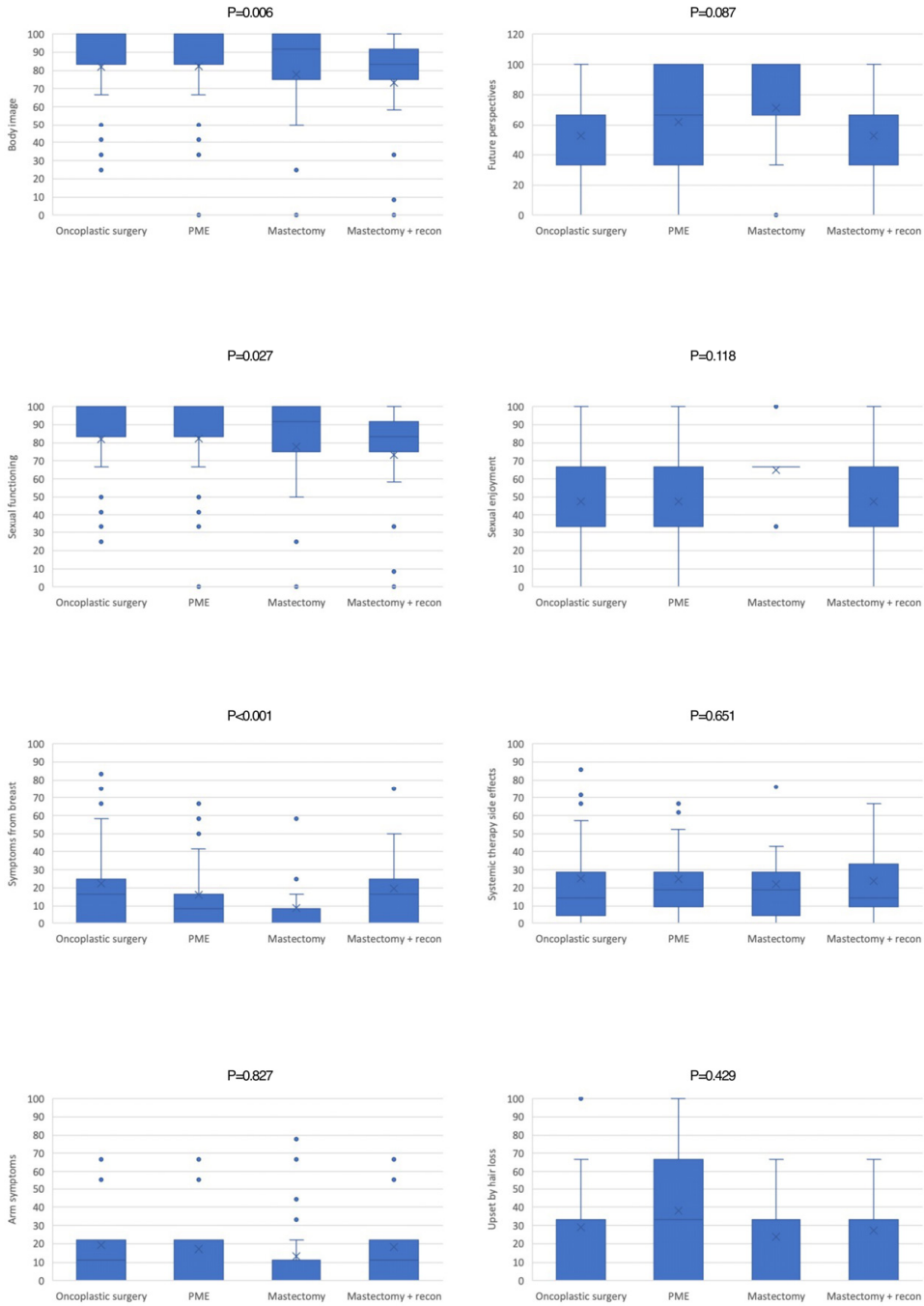


Figure 25. Comparison of postoperative QLQ-BR23 scores between the surgical groups, analysed using Kruskal–Wallis tests.

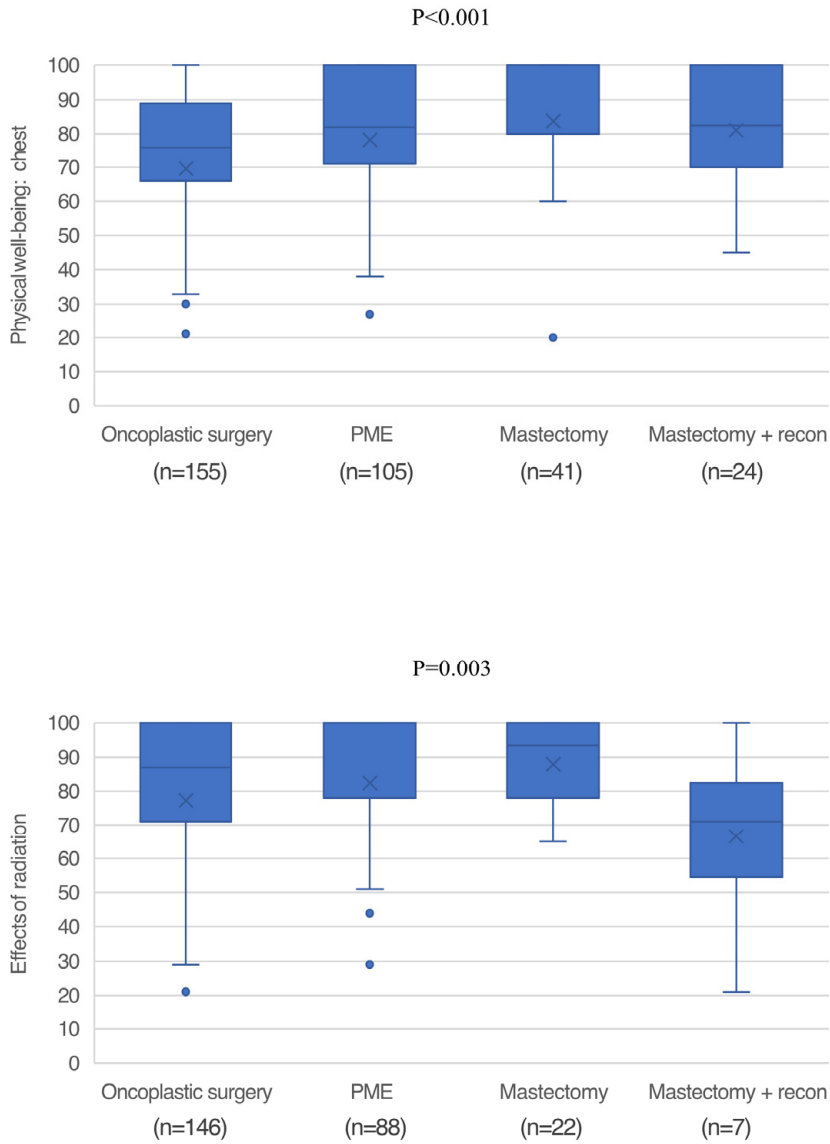


Figure 26. Comparison of postoperative Breast-Q scores between the surgical groups, analysed using Kruskal–Wallis tests.

The Breast-Q baseline scores were compared with normative data from a US population and showed the same mean scores for sexual well-being, as well as similar scores for satisfaction with breasts and psychosocial well-being.

The mean QLQ-C30 score for the study cohort was compared with the norm values for a Swedish cohort (Figure 27). The study cohort had slightly lower mean scores for cognitive and social function and higher insomnia and constipation scores than the Swedish norm. However, no difference or better scores were observed in all other subscales. The mean global health score was 7.7 points higher in the study cohort than in the reference cohort.

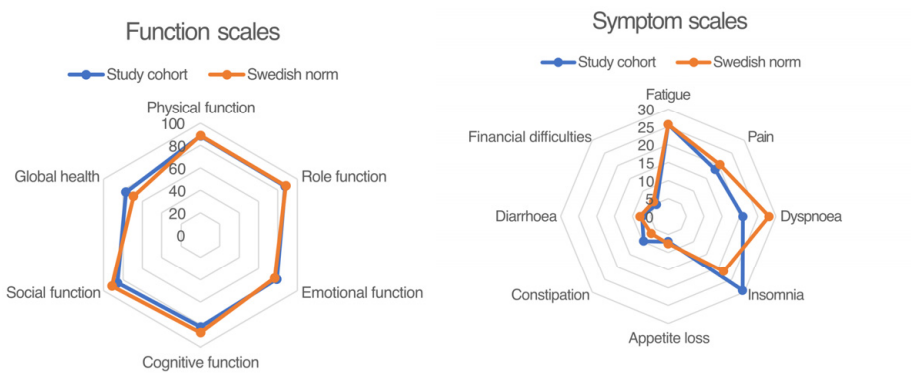


Figure 27. Comparison of postoperative mean scores for QLQ-C30 in the study cohort and norm values for QLQ-C30.

Discussion

Study I

Bilateral therapeutic mammoplasty has previously been studied in smaller cohorts [141-147] and in a larger retrospective study conducted by Grubnik et al. [148]. Consistent with the findings of the present study, previous studies have consistently reported favourable cosmetic outcomes. A meta-analysis also affirmed that bilateral therapeutic mammoplasty is oncologically safe [93]. In the late 90s, Clough et al. and Smith et al. suggested reduction mammaplasty as a viable option for larger tumours in patients with larger breasts [149-151]. The complication rates are reported to be 20–40% [152, 153], which is higher than those for standard partial mastectomy [154]. The current study, with 27% of patients documented to have complications, falls within the range of previous studies on bilateral therapeutic mammoplasty. For comparison, a meta-analysis of benign reduction mammoplasty reported complication rates of 40–50% [155].

Therapeutic mammoplasty potentially allows for wider excision of the tumour, improved outcomes of radiotherapy with fever complications, and improved quality of life in patients with macromastia. Differences in opinions regarding simultaneous bilateral surgeries persist. The concern is that a more extensive surgery leads to more complications; therefore, the healthy side should be delayed until adjuvant treatment is administered. This study showed that the cancer-affected breast had twice the number of complications compared with the healthy breast (20 vs. 10), and 7 were bilateral, indicating that most of the complications would still be present even with unilateral surgery.

Further research on this subject is warranted to determine whether there is any significant delay in adjuvant treatment with bilateral surgery. The advantages of only one surgical intervention are not insignificant: not needing a second surgery with a recovery period and not needing to have uncomfortable asymmetry for a year or longer. A systematic review conducted in 2016 summarised PROMs after breast cancer surgery. More than 90% of patients reported satisfactory or better outcomes with bilateral therapeutic mammoplasty, and complication rates were equivalent to those of benign bilateral reduction [156].

In summary, these results confirm previous findings of favourable cosmetic outcomes after therapeutic mammoplasty in patients with primary breast cancer.

Complication rates were comparable to those in previous studies, and importantly, cosmetic outcomes were not influenced by confounding factors, such as tumour size or BMI.

Study II

This study presented a nomogram for preoperative evaluation of the risk of positive margins. The final nomogram included variables that were preoperatively available without MRI assessment. This model can potentially decrease the proportion of second surgeries, including the negative side effects on postoperative complications, cosmetic outcomes, quality of life, healthcare costs, and delayed start to adjuvant therapy [157, 158].

For clinical use, the prediction model is presented as a nomogram to identify patients at high risk of positive margins. This allows the surgeon to adjust surgical planning according to the assessed risk.

The preoperative variables associated with positive margins in the model were mammographic tumour size, a diagnosis of invasive lobular cancer, microscopic calcifications, DCIS on core needle biopsy, and tumour distance from the mamilla. This is in line with previous studies that have found that central tumours [159, 160], invasive lobular cancer [160-169], DCIS [108, 161, 166, 168, 170], tumour size [108, 163, 165, 169-172], and microscopic calcifications [108, 170] on mammography are associated with positive margins.

Previous studies have reported predictive nomograms for positive margins [107-109, 170]. The results of the study in this thesis are comparable to other preoperative prediction models presented, ranging in AUCs from 0.7 to 0.82 [107, 108]. Validations of previously published nomograms vary in terms of performance [107, 170, 173-175]. Validation of the present study was performed in a manner similar to that of previously published studies.

MRI features have been included in these previously published models, but the importance of MRI in predicting positive margins was inconclusive in two larger studies [176, 177]. As in many centres worldwide, the patients in this study did not routinely undergo preoperative MRI. Presenting a nomogram that does not include MRI allows all breast surgeons to use it, irrespective of MRI availability.

OPBS is oncologically safer than standard BCS [93, 178-181]. The method of operation was included in the nomogram as a clinically important variable, although evidence for an association with positive margins was weak. The results of the regression model showed that OPBS was negatively associated with positive margins, and the risk of negative margins decreased when the patient was scheduled for OPBS. This is comparable to a previously published study showing

that OPBS decreased re-excision rates and was subsequently correlated with a lower risk of positive margins [181].

The re-excision rates in this study varied between 10% and 21%. When comparing these figures with those in international studies, the variability in those figures is even larger, ranging from under 10% to over 30% in some patient groups [162, 166, 182-187]. Several factors may affect the rates of positive margins, ranging from auxiliary service evaluations and routines, the proportion of primary mastectomies, and the criteria for positive margins, to surgical performance and experience.

The benefit of a tool for predicting positive margins before surgery is applicable to both surgeons and patients; surgical planning becomes easier and enables a wider excision margin or oncoplastic surgery in high-risk patients.

It should be noted that the model used in this study underestimated the risk of positive margins in low-risk patients. This is of low clinical value because patients with a low risk of positive margins can undergo standard BCS.

The external validation at Site B had a high AUC (0.75), indicating that it is externally applicable. Further external validation is required to strengthen this statement.

This novel predictive nomogram can provide clinical and surgical guidance for identifying high-risk patients with positive margins in settings where MRI is not available. The nomogram can be used to ensure that patients and surgeons are aware of the risk of positive resection margins and that a surgical approach is advised to match the level of risk.

Study III

In this study, more than half of the patients who underwent NAC also underwent subsequent mastectomy. The most important factors predicting BCS were the mammographic tumour size, mammographic density, and axillary nodal status. The overall rate of BCS in patients who underwent primary surgery and were included in the SCAN-B cohort during the same period was 70%. This indicates that NAC-treated patients had a lower rate of BCS than patients who only received adjuvant therapy.

OPBS extends the options for BCS in patients receiving NAC, especially when considering the potential of NAC to downstage the tumour size.

The International European Society for Medical Oncology guidelines state that BCS should be offered only when technically feasible. Mastectomy, such as for locally advanced disease or risk-reduction surgery, is recommended when BCS is

not technically feasible or inappropriate [16]. However, patient preferences regarding the type of breast surgery should always be considered.

Previous studies on BCS after NAC have reported similar rates (approximately 50%) [188, 189]. One study showed that BCS after NAC can yield improved outcomes regarding margin positivity, re-excision rates, and patient satisfaction compared to primary surgery [190]. A meta-analysis by Asselain et al. showed more local recurrences in patients treated with BCS after NAC than in matched patients receiving adjuvant therapy, though survival rates were equivalent [191]. De Boniface et al. evaluated patients receiving primary BCS with radiotherapy and showed that they had improved survival compared with those receiving mastectomy. This indicates that de-escalation of surgery can result in different oncological outcomes [21]. Importantly, a study conducted in 2023 showed that OPBS could help convert patients scheduled for mastectomy to BCS after NAC. In this study, 80% of the patients underwent BCS, and no positive margins were reported [192].

Only nine patients in the study converted from planned mastectomy before NAC to BCS after NAC. This highlights the persistence of the initial surgical plan, despite tumour shrinkage, as evidenced by imaging. This implies that tumour size at diagnosis and molecular subtype, rather than chemotherapeutic response, are important factors influencing the choice of surgical intervention. Another study reported a conversion rate from mastectomy to BCS of 36%, attributed to downstaging of the disease after NAC [79].

The rate of BCS increased from 37% to 52% during the study period. The reason for this is multifactorial, and specific reasons are difficult to define. However, possible explanations include advances in surgical techniques, such as oncoplastic surgery, increased awareness among patients and patient advocates, and advances in neoadjuvant treatment leading to better tumour response.

Mastectomy remains the preferred choice for a select group of patients, such as those with advanced tumours that do not respond to NAC, inflammatory cancer, and patients who are mutation carriers and require risk reduction surgery. Lastly, a small group of patients wanted mastectomy, even when BCS was feasible.

This is one of the few studies to present genomic subtypes related to NAC treatment and surgical outcomes. A recent study showed that gene expression-based and immunohistochemical biomarkers showed > 80% concordance [193]. Another study discussed the clinical relevance of gene expression signatures in a neoadjuvant setting to individually tailor NAC treatment [194]. In this study, gene expression signatures were not included in the multivariable analysis because they did not add any information compared with the molecular subtypes identified by St. Gallen.

In summary, there is room to increase the rate of BCS in patients treated with NAC. Active monitoring of patients during and after NAC, along with preoperative re-evaluation of BCS eligibility, can further aid in improving BCS rates.

Study IV

This longitudinal observational study presented data on HRQoL in patients with breast cancer and compared baseline scores with scores at the 1-year follow-up.

BCS was shown to result in better satisfaction with breasts and body image postoperatively than mastectomy with or without reconstruction. Patients who underwent mastectomy with reconstruction had worse sexual function outcomes than those in the other surgical groups. Most breast symptoms were observed in the oncoplastic surgery and mastectomy with reconstruction groups, whereas the mastectomy group had the fewest symptoms in the chest area. This could be partly explained by the fact that few patients who underwent mastectomy had indications for postoperative radiotherapy, except for those with malignant lymph nodes.

Oncological outcomes after BCS with radiotherapy are at least as good as those after mastectomy in patients undergoing primary surgery. Recent meta-analyses have even shown improved survival after BCS with radiotherapy [195, 196].

This study highlights the importance of surgeons trained in OPBS techniques for breast cancer care by demonstrating better HRQoL outcomes in the BCS group. Adjustment for known confounders did not change the interpretation of the results, indicating that the results were robust.

Patient selection and an individually tailored surgical approach are vital for breast cancer surgery. This was highlighted by the fact that patients who underwent extensive surgery reported more postoperative breast-related symptoms. Further prospective longitudinal studies are required to confirm these findings. Preservation of the breast should always be the first choice in breast cancer surgery, and OPBS provides patients who previously would have been at risk for mastectomy the opportunity to undergo BCS. With increasing survival rates, patients must live with the outcomes of surgery for long periods.

In 2019, a systematic review including six studies evaluated HRQoL and OPBS. Only one of the included studies provided data in favour of OPBS, and the authors recommended further cohort studies on HRQoL in connection with OPBS [197]. Another systematic review of PROMS after OPBS compared with BCS showed improved results with OPBS and recommended using OPBS to improve patient outcomes [198]. A scoping review of the application of Breast-Q indicated the need for prospective collection of centre-specific data for all types of breast

cancer, analogous to the current study design [199], same conclusion was drawn in a systematic review of HRQoL after OPBS [200].

A 2023 study involving over 700 patients compared OPBS with mastectomy and reconstruction and concluded that OPBS was to be preferred. Both patients and surgeons were more satisfied with the cosmetic results. The OPBS group had a lower frequency of complications and required fewer surgeries to complete their reconstruction [201]. Another study used Breast-Q to compare mastectomy and reconstruction with BCS. The study concluded equality in breast satisfaction and physical well-being but noted a relevant improvement in psychosocial and sexual well-being in favour of BCS [202].

Long-term data are important in HRQoL studies, and this study had a 5-year follow-up plan. A previous study conducted in 2022 measured HRQoL after 5–10 years and concluded that the majority (75%) of patients had high HRQoL and that there was a correlation between HRQoL and cosmetic outcomes [203]. Another study investigated long-term cosmetic sequelae (up to 10 years) after OPBS and concluded that up to 17% of patients had some form of cosmetic sequelae [204].

The current study was conducted at a single centre, and comparison with data from other centres would be beneficial for validating the findings.

Baseline data and longitudinal follow-up are needed to evaluate the HRQoL and changes in satisfaction and cosmetic outcomes in individual patients with breast cancer. Patients with different baseline HRQoL scores may experience different impacts of treatments, both surgical and oncological. This was demonstrated by a study involving over 100 patients evaluating preoperative and postoperative HRQoL using Breast-Q, EORTC-QLQC30, and QLQ-BR23 [205].

The evaluation of different surgical techniques should include oncological outcomes, PROMs, and HRQoL to determine whether the surgical outcomes are correctly selected and of value to the patient.

Strengths and limitations

The strengths and limitations of the four different studies are summarized in Table 2 below.

Study	Strengths	Limitations
I	- Relatively large cohort of breast cancer patients with breast cancer undergoing bilateral therapeutic mammoplasty - Three measurements for cosmetic outcomes	- Retrospective design - Long inclusion period (7 years) - Single-centre study
II	- Clinically relevant design only using preoperative variables - Model can identify patients at high risk of re-excision - Validation with external cohort	- Retrospective design - No data on breast density - Not all patients had reported calcifications
III	- Prospective design - Large cohort of breast cancer patients receiving neoadjuvant treatment - Included genomic subtypes - Multicentre study	- Three centres with heterogenous surgical approaches - Long inclusion period (6 years)
IV	- Prospective design with longitudinal data - Large cohort - Few patients were lost to follow-up - 1-year follow up	- Single-centre study - No long-term data yet

Table 2. Summary of strengths and limitations of the four studies

“You have your way. I have my way.
As for the right way, the correct way
and the only way, it does not exist”

– Friedrich Nietzsche

Conclusion

This thesis has explored different aspects of BCS in four different studies.

Study I showed that bilateral mammoplasty yielded good cosmetic outcomes with no overall difference in symmetry. Both the patient and surgeon were highly satisfied with the cosmetic results, with the patient scoring slightly higher than the surgeon.

Study II presented a nomogram for predicting positive margins, facilitating shared decision-making in the clinical setting by estimating the individual risk of non-radical surgery. The model demonstrated good predictive ability for positive margins after BCS in the validation cohorts. However, further external validation is required.

Study III concluded that, although the BCS rate increased during the study period, more than half of the patients receiving NAC underwent mastectomy. The factors influencing the choice of BCS were smaller tumour size, benign axillary status, and low mammographic density. This study highlighted the importance of preoperative re-evaluation of BCS feasibility after NAC.

Study IV showed that simple partial mastectomy with OPBS resulted in better cosmetic outcomes than mastectomy with or without reconstruction. Patients who underwent mastectomy had the fewest chest symptoms.

In summary, this thesis emphasises the importance of breast conservation, when technically feasible, to optimise HRQoL and cosmetic outcomes. The studies also showed that NAC-treated patients deserve an impartial re-evaluation for BCS after NAC, and that further development of OPBS and optimal margin assessment can aid in this endeavour. when it is technically feasible, to optimise the HRQoL and cosmetic outcomes. The nomogram is an example of technical aids to improve rates of BCS for breast cancer patients. Finally, this thesis highlights the fact that breast reconstruction is not equivalent to breast conservation. However, there are still gaps in knowledge regarding HRQoL and cosmetic outcomes for breast cancer patients, and the need for further research still exists.

“In the midst of chaos, there is also opportunity”

- Sun Tzu

Future perspectives

Research on HRQoL and cosmetic outcomes in patients with breast cancer is expanding exponentially. Data from the National Quality Register for Breast Cancer show that the rate of BCS in Sweden is gradually increasing. However, there is room for improvement. The results of BCS and OPBS should also be evaluated continually, with a critical focus on oncological outcomes, HRQoL, cosmetic outcomes and patient satisfaction.

The 5-year follow-up for Study IV is ongoing, and data collection will be completed in 2025. The prospect of evaluating whether an individual's HRQoL scores will persist for over 5-years or if any of the surgical groups will have a different outcome after 5-years is intriguing. Long-lasting results are more valuable than just 1-year follow-ups.

A second study, utilizing the cohort from Study IV is planned. The study will focus on the cosmetic outcomes of the same surgical groups and investigate whether cosmesis is associated with HRQoL outcomes.

The contralateral healthy breast is still an ongoing topic of discussion in Sweden. The debate revolves around determining the optimal surgical strategy for contralateral symmetrisation, exploring whether immediate bilateral surgery or delayed surgery on the contralateral side is the best course of action. The effects of radiotherapy on the breast can be unpredictable and can lead to shrinkage, persistent swelling, and oedema. The results of Study I showed very satisfied patients after bilateral surgery and post-radiotherapy, with no large differences in symmetry. This suggests that cosmetic aspects are not a cause for concern. This is an area open for further prospective studies, especially those measuring differences in the start of adjuvant treatment. In addition to HRQoL and cosmetic outcomes, exploring these aspects is crucial due to the oncological risks associated with delaying adjuvant treatment when opting for more extensive surgery. Grant et al. showed that contralateral symmetrisation can be performed simultaneously without delaying adjuvant therapy and is financially beneficial [206]. However, further studies are required to validate these findings.

The number of older patients with breast cancer is increasing, and age should not be the primary contraindication for OPBS. A systematic review from 2023 showed lower uptake of OPBS in older women (only 10% were 65 years or older) and

recommended further research regarding older individuals and their eligibility for OPBS [207].

Margin assessment in breast cancer surgery is a developing research field with new techniques emerging in the market, a few of which have been described in this thesis. With better intraoperative margin assessment, the risk of positive margins can be further reduced. This is beneficial both for the patient and from a surgical perspective. The important aspect when implementing new techniques is that they must improve the outcomes of margin assessment without being too time consuming or less cost effective, thus having limited use in the clinical setting. The future is exciting regarding the new possibilities within this field. An array of techniques is currently being evaluated, including the deep learning-based approach with ultrasound [208], fluorescence imaging [209], Raman spectroscopy [210], optical coherence tomography [211], radiofrequency spectroscopy [209], bioimpedance spectroscopy [212], micro-computed tomography [213], digital breast tomosynthesis [214], microscopy with ultraviolet surface excitation [215], and photoacoustic tomography [216].

The National Board of Social Affairs and Health in Sweden states that all patients in Sweden have the right to equal care, that the healthcare system should provide patient-centred care, and that the patient has the right to be involved and make informed choices about his or her care. This translates to shared decision-making in clinical care. A scoping review conducted by Oprea et al. on breast cancer in 2023 concluded that, although mounting evidence indicates the efficacy of shared decision-making interventions, knowledge to support sustained implementation in daily care remains limited [217]. Shared decision-making and its implementation in clinical practice is another area of research that warrants further investigation, especially in the evolving field of breast cancer surgery with many different techniques.

The differences in the available medical and surgical competencies in the field of breast cancer care in Swedish hospitals today are an issue in the prospect of offering equal care to all patients. One way to mitigate this inequality is for the Swedish Surgical Society and Swedish Society for Breast Surgery to set up norms and regulations for training in breast cancer surgery in Sweden. This would ensure that all surgeons working with breast cancer have received appropriate training.

The British Association of Breast Surgery has already implemented such a curriculum and has comprehensive breast surgery training that any specialist working within the field is expected to follow [218]. Additionally, oncoplastic breast surgery fellowships are available for application [219]. A review article published in 2021 highlighted how beneficial training and a comprehensive curriculum were for the breast cancer patients in the UK, with fewer mastectomies needed and fewer secondary surgeries [220]. This could be used as an inspiration to initiate the development of a similar training path for Swedish breast surgeons.

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