

Breast Surgery Unit  
Helsinki University Central Hospital  
University of Helsinki  
Finland

# **QUALITY OF SURGICAL TREATMENT IN BREAST CANCER**

**Kaisu Ojala**

ACADEMIC DISSERTATION

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**Supervised by**

Professor Marjut Leidenius  
Breast Surgery Unit, Comprehensive Cancer Center  
Helsinki University Hospital  
Helsinki, Finland

and

Associate professor Tuomo Meretoja  
Breast Surgery Unit, Comprehensive Cancer Center  
Helsinki University Hospital  
Helsinki, Finland

**Reviewed by**

Associate professor Minna Tanner  
Department of Oncology  
Tampere University Hospital  
Tampere, Finland

and

Associate professor Ilkka Koskivuo  
Department of Surgery  
Turku University Hospital  
Turku, Finland

**Opponent**

Professor Malin Sund  
Department of Surgical and Perioperative Sciences  
Umeå University  
Umeå, Sweden

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# 1 List of original publications

This thesis is based on the following publications:

- I Ojala K, Meretoja TJ, Mattson J, Salminen-Peltola P, Leutola S, Berggren M, Leidenius MHK. The quality of preoperative diagnostics and surgery and their impact on delays in breast cancer treatment – a population based study. *Breast* 26:80–86, 2016
- II Ojala K, Vironen JH, Mattila K, Eklund AM, Leidenius MHK, Meretoja TJ. Feasibility of day surgery in patients with breast conservation and sentinel node biopsy – a randomized controlled trial. *Scand J Surg* 105:29–34, 2015
- III Ojala K, Meretoja TJ, Leidenius MHK. Aesthetic and functional outcome after breast-conserving surgery – comparison between conventional and oncoplastic resection. *EJSO* 43:658–664, 2017
- IV Ojala K, Meretoja TJ, Mattson J, Leidenius MHK. Surgical treatment and prognosis of breast cancer in elderly - A population-based study. Submitted.

The publications are referred to in the text by their roman numerals.

## 2 Abbreviations

ALND	axillary lymph node dissection
BCS	breast-conserving surgery
BCSS	breast cancer specific survival
BCTOS	Breast Cancer Treatment Outcome Scale
CT	computed tomography
DCIS	ductal carcinoma in situ
DDFS	distant disease-free survival
ER	oestrogen receptor
HER2	human epidermal growth factor receptor 2
IBR	immediate breast reconstruction
ITC	isolated tumour cells
MRI	magnetic resonance imaging
OS	overall survival
QoL	quality of life
PET	positron emission tomography
PR	progesterone receptor
RT	radiotherapy
SNB	sentinel node biopsy

## 3 Abstract

### **Aim**

The purpose of this study was to evaluate the quality of surgical treatment in breast cancer in various aspects: treatment processes, surgical procedures, waiting times, day surgery and aesthetic and functional outcomes. In addition, a special emphasis was put on the surgical treatment of elderly breast cancer patients.

### **Patients and methods**

In study I, the study population consisted of 1307 patients undergoing primary breast cancer surgery during 2010 in five hospitals in the Helsinki and Uusimaa Hospital District. The study population of study III included 637 patients receiving breast-conserving treatment due to unilateral primary breast cancer during 2010 in the Helsinki and Uusimaa Hospital District. In study IV, 446 patients older than 80 years of age with primary breast cancer between January 2005 and December 2010 were included. In studies I–III, patients were retrospectively identified using electronic patient records using ICD-10 codes C50 and D05.1. The data were checked and completed with additional information from electronic patient records. Data on survival were collected from the Finnish Cancer Registry. In Study III, aesthetic and functional outcomes were evaluated with two separate questionnaires: the Breast Cancer Treatment Outcome Scale (BCTOS) and an author-created questionnaire.

In Study II, 85 patients receiving breast-conserving surgery (BCS) and sentinel node biopsy (SNB) in a single breast cancer unit were prospectively included and randomised to day surgery or overnight stay. The patients and their spouses or other relatives received study questionnaires evaluating their perceptions of day surgery and physical and psychological recovery within discharge.

### **Results**

In Study I, the final rate of BCS was surprisingly low (51%), unaffected by hospital volume ( $p=0.781$ ). Oncoplastic resection (33% of BCS in a high-volume unit vs. 0–12% in lower-volume units) and immediate breast reconstruction (IBR) (11–20% of all mastectomies in high-volume units vs. 0% in lower-volume units) were performed more often in high-volume units ( $p<0.001$ ). The quality of axillary surgery varied with unit size; the rate of axillary lymph node dissection (ALND) in node-negative patients

was higher at 14–27% in low-volume hospitals compared to 5–8% in high-volume hospitals ( $p=0.009$ ). The median waiting time for primary surgery was 24 days, significantly prolonged by additional magnetic resonance imaging (MRI) (34 days;  $p<0.001$ ) and diagnostic biopsies (37 days;  $p<0.001$ ). Low-volume hospitals provided primary surgery significantly faster (15–17 days vs. 26–27 days;  $p<0.001$ ). The median waiting time from the primary operation to the initiation of any adjuvant treatment was 47 days. Wait times for the initiation of adjuvant treatment were significantly affected by the type of primary surgery and the number of cancer operations, that is, immediate breast reconstruction (54 days;  $p=0.011$ ) and re-excisions (57 days on patients with two cancer operations;  $p<0.001$ ), naturally.

In study II, the day surgical discharge rate was lower than expected; 18 (47%) patients randomised to day surgery were discharged the same day. The most common reason for overnight hospital stay was ALND, which occurred in 9 (24%) patients. Questionnaire results on perceptions of day surgery were analysed both according to randomisation and actual treatment groups. Patients in both groups had rather similar experiences on the first postoperative day. Also, spouses' or relatives' perceptions after discharge were similar in both groups.

In study III, the questionnaires concerning aesthetic and functional outcomes after BCS were returned by 379 (59%) patients. Of these, 293 (77%) had conventional breast resection and 86 (23%) had an oncoplastic resection. Patients in the oncoplastic resection group had significantly larger tumour diameters (16.0 mm vs. 12.0 mm;  $p<0.001$ ), more often multifocal tumours (12% vs. 5%;  $p=0.032$ ) and node-positive cancer (30% vs. 22%;  $p=0.029$ ). Accordingly, resection specimens were larger (97 g vs. 61 g;  $p<0.001$ ). In the oncoplastic resection group, lower quadrant tumour localisation (25% vs. 19%;  $p=0.007$ ) was more frequent. ALND was performed significantly more often in the oncoplastic resection group ( $p=0.007$ ), reflecting a difference in nodal status between the groups. There was no statistical difference between the groups as regards receiving radiotherapy (RT) and those receiving tumour bed boosters. In univariate analysis, larger tumour diameter ( $p=0.033$ ), multifocality ( $p=0.022$ ), weight of the resection specimen ( $p<0.001$ ) and oncoplastic surgery ( $p<0.001$ ) were predicting a poor aesthetic outcome when all patients were included.

In study IV, 401 (90%) patients received surgery. The median follow-up time was 52 months. The overall survival (OS) of patients was significantly better in the surgical



treatment group, five-year OS being 50.6% in the surgical treatment group and 15.2% in the non-surgical treatment group ( $p<0.001$ ). Also, breast cancer-specific survival (BCSS) was significantly better in patients with surgery, five-year BCSS being 82.0% in patients with surgery and 56.0% in patients without ( $p<0.001$ ). Altogether, 122 (30%) patients in the surgical treatment group died within three years of surgery.

### **Conclusions**

The quality of preoperative diagnostics greatly impacts the timely treatment of breast cancer. The positive impact of high-volume hospitals becomes evident when novel or skill-demanding surgical techniques like oncoplastic surgery and breast reconstruction are used. Day surgery is feasible in breast surgery after BCS and SNB. Overall patient satisfaction after BCS is high. Conventional resection provides good aesthetic outcomes in appropriately selected patients. Oncoplastic resection enables BCT in patients with larger, multifocal tumours with a favourable aesthetic outcome. In elderly breast cancer patients, OS and BCSS were better in surgically treated patients. Surgical treatment was safe in elderly population.

## **4 Introduction**

Worldwide, breast cancer is the most common cancer in women and the leading cause of cancer death. In Finland, the annual incidence of breast cancer was 5161 in 2015. However, breast cancer survival in Finland is one of the highest in Europe. According to the Finnish Cancer Registry, the predicted breast cancer-specific five-year survival rate from 2012 to 2014 is 91% and the ten-year survival rate is 85%. The age-adjusted breast cancer mortality rate has decreased by 30% since 1990 and was 27/100 000 in 2014.

The aim of breast cancer surgery is to provide excellent oncological outcomes with minimal risk of local and regional recurrences. Quality of life (QoL) is the second most important aim in breast cancer treatment. Today's breast cancer treatment with an effective screening program, improved diagnostics, better quality of surgery and more effective adjuvant treatments has resulted in increased breast cancer survival. The significance of QoL after breast cancer treatment is thereby extremely important.

To achieve better oncological outcomes and QoL, timely treatment and high-quality surgery are crucial. Delays in adjuvant treatment are associated with worse breast cancer outcomes (Gagliato et al. 2014, Richards et al. 1999); a four-week delay in systemic adjuvant treatment increases the risk for recurrence by 16% and mortality by 15% (Yu et al. 2013). Furthermore, many surgery-related factors may delay the initiation of adjuvant treatments and thus increase recurrence risk. Although many factors associated with delays in breast cancer treatment have been identified, the impact of organisational factors is also recognised and remains to be evaluated (Liederbach et al. 2015).

Both aesthetic and functional outcomes after breast cancer surgery influence QoL (Mansel et al. 2006, Heil et al. 2010). Therefore, an aesthetic outcome after BCS is an important goal (Heil et al. 2011, Santos et al. 2015). Several factors are associated with poor aesthetic outcome: central, medial or inferior tumour locations, larger tumour size, larger specimen volume, reoperation due to positive margins, radiation therapy and radiation boost (Foersteling et al. 2014, Hennings et al. 2015, Heil et al. 2012, Immink et al. 2012, Vrieling et al. 2000). Recognising the negative effects of poor aesthetic outcomes on QoL has facilitated the development of various oncoplastic

techniques. The oncoplastic approach also enables BCS for patients with larger and multifocal tumours without compromising aesthetic and functional outcomes. Previous studies implicate that oncoplastic surgery provides better aesthetic outcomes than conventional wide local excision (Losken et al. 2014). However, evaluation of aesthetic outcomes after breast cancer surgery lacks a gold standard, and methodology varies greatly (Chen et al. 2010). Further research is needed to establish the role of oncoplastic surgery in breast-conserving treatment.

However, the benefits of improved breast cancer treatment and increasing survival are not distributed equally in the breast cancer patient population. In elderly patients, breast cancer treatment guidelines are less often followed (van de Water et al. 2012, Kiderlen et al. 2015, Angarita et al. 2015, Shumway et al. 2017). Accordingly, not only OS but also BCSS have been inferior when compared to younger breast cancer patients. This is important since the number of elderly breast cancer patients is increasing due to ageing of the population. Altogether, 3179 women aged 80 years and older were diagnosed with primary breast cancer in Finland between 2011 and 2015 (Finnish Cancer Registry).

The impact of adjuvant radiotherapy (RT) on survival and local recurrences has been investigated (Matuchek et al. 2017, EBCTCG 2011), but there is less evidence regarding the benefits of surgery on local disease control and survival in elderly breast cancer patients (Hamaker et al. 2013). However, local disease control markedly affects QoL. Moreover, QoL is extremely important in elderly patients with limited life expectancy. Individualising treatment on the heterogeneous elderly breast cancer patient population is highly important.

The aim of the present study was to evaluate the quality of surgical treatment and the impact of surgery on aesthetic outcomes and delays in breast cancer treatment. The feasibility of day surgery in breast cancer was also investigated. A further aim was to evaluate surgical treatment and prognosis of elderly patients over 80 years of age.

## **5 Review of the literature**

### **5.1 Breast cancer incidence and survival**

Breast cancer is the most common cancer in women worldwide. In Finland, breast cancer incidence is among the highest in the world; the annual incidence in 2015 was 5161 and the age-adjusted incidence 177/100 000. The age-adjusted breast cancer incidence has increased by 2.3 times in Finland during the past 40 years (Finnish Cancer Registry, 2018).

Several factors have been identified to increase breast cancer incidence: menarche is starting earlier, childlessness is more frequent, and first pregnancies are at an older age. Hormone replacement therapy increases the risk of breast cancer, especially if used over five years' time. Obesity and alcohol use are also known to increase breast cancer incidence. Overdiagnosis caused by breast cancer screening may further increase the incidence slightly (Berry et al. 2005, Bleyer et al. 2012, Miller et al. 2014).

In elderly patients, breast cancer incidence is increasing due to ageing of the population. Breast cancer incidence in elderly patients in Finland is high: from 2011 to 2015, the incidence was 221/100 000 in women from 80 to 85 years and 247/100 000 in those 85 years and older. Altogether, 3179 women aged 80 years and older were diagnosed with primary breast cancer in Finland between 2011 and 2015 (Finnish Cancer Registry).

Worldwide, breast cancer is the most common cause of cancer death in women. In Finland, breast cancer survival is one of the highest in Europe. According to the Finnish Cancer Registry, the predicted breast cancer-specific five-year survival rate from 2012 to 2014 is 91%, and the ten-year survival rate is 85%. The age-adjusted breast cancer mortality rate has decreased by 30% since 1990 and was 27/100 000 in 2014. The high survival rate is due to early detection of breast cancer, particularly in the biannual screening program for women between 50 and 69 years of age, and improved quality of multimodality treatment (Berry et al. 2005, Bleyer et al. 2012).

## 5.2 Diagnosis and staging of breast cancer

Triple diagnosis is the gold standard in breast cancer diagnosis. The triple diagnostic approach consists of a clinical examination, breast imaging and a core needle biopsy. Breast imaging usually consists of mammography combined with breast and axillary ultrasound. Breast magnetic resonance imaging (MRI) can be used in selected cases, for example in invasive lobular cancer or in women with dense breasts. Breast MRI is the most sensitive imaging modality in breast cancer diagnostics, with over 90% sensitivity (Berg et al. 2004). However, false-positive findings in MRI occur in 10–15% of patients, leading to additional needle biopsies. Breast imaging should be conducted prior to biopsy, since haematoma may interfere with image interpretation. If any component of the triple diagnosis is suspicious of malignancy, a repeated core needle biopsy or surgical biopsy should be conducted.

Core needle biopsy is taken from the suspicious lesion in the breast, frequently guided by ultrasound. Sometimes, mammography or MRI are used in biopsy guidance. Core needle biopsy usually provides a tissue sample that allows for histological typing of the cancer and enables determination of tumour oestrogen, progesterone and human epidermal growth factor receptor 2 (HER2) status as well as Ki-67 expression. The diagnostic accuracy of fine needle aspiration cytology is inferior when compared to core needle biopsy (Hukkinen et al. 2008).

Axillary nodal status is the single most important prognostic factor in breast cancer. Axillary ultrasound is performed as part of the diagnosis, and fine needle biopsy is taken from suspicious nodes. Specificity of a positive ultrasound and needle biopsy is as high as 98% with 80% sensitivity (Houssami et al. 2011). Axillary staging with ultrasound and needle biopsy can optimise surgical treatment in node-positive patients by utilising a single axillary procedure, the gold standard currently being ALND. In patients with node-negative breast cancer, SNB is the gold standard in nodal staging.

For patients at high and intermediate risk of distant relapses, imaging the chest, abdomen and bone is recommended before administering systemic treatments. This is mainly done through computed tomography (CT) of the chest, CT or ultrasound of the abdomen and isotope bone scintigraphy. Positron emission tomography (PET) may reveal regional or distant metastases not detected by other methods and may thus be

helpful when findings of commonly used imaging are unclear. PET may also show an earlier response to systemic therapy.

### **5.3 Multidisciplinary treatment in breast cancer**

The management of early breast cancer involves several medical specialities. Therefore, treatment is best performed with a specialist multidisciplinary team to ensure optimal outcomes in terms of patient survival and QoL. The treatment of early breast cancer usually starts with surgery. The postoperative multidisciplinary meeting gives adjuvant treatment recommendations based on treatment guidelines and patient and tumour characteristics. If adjuvant chemotherapy is recommended, it is initiated postoperatively within four to six weeks. Endocrine treatment and/or radiotherapy follow chemotherapy. In Finland, neoadjuvant systemic therapy has been generally used in inflammatory breast cancer and in locally advanced disease to facilitate surgery. Neoadjuvant treatment also enables effective early treatment in aggressive breast cancer (i.e. HER2 positive and triple negative disease). In addition, neoadjuvant treatment is also currently used to facilitate BCS by tumour downsizing.

The multidisciplinary meeting is an important step in coordinating breast cancer treatment. The multidisciplinary team consists of the breast surgeon, clinical oncologist, pathologist, radiologist and breast cancer nurse. The plastic surgeon, physiotherapist and research nurse can also take part in multidisciplinary meetings. Multidisciplinary teams are noted to make better clinical decisions, evidence-based practice and improved quality of treatment (Biganzoli et al. 2017). The multidisciplinary meetings also serve teaching purposes.

### **5.4 Surgical treatment**

#### **Aims of surgical treatment**

The aim of surgical treatment is to minimise the risk of local and regional recurrences and thereby increase survival. Surgery also enables pathological assessment and staging of the tumour, facilitating tailoring the adjuvant treatments and providing information regarding prognosis.

The development of diagnosis and adjuvant treatments has markedly improved breast cancer survival, thus emphasising the value of QoL. Both functional and aesthetic outcomes after surgery influence QoL (Heil et al. 2010, Santos et al. 2015). Therefore, an important aim of surgery is tailoring the treatment individually by accounting for both local-regional disease control and aesthetic and functional outcomes.

Today, breast cancer surgery is markedly more conservative than ever before with equal or even better oncological outcomes. Not only physical recovery but also psychological and social recovery after breast cancer surgery are important. BCS itself has possibly reduced both early and late psychological implications of the disease (Moyer et al. 1997, Wapnir et al. 1999). Accordingly, hospitalisation after breast cancer surgery has decreased, and even day surgery is possible. However, the patient's preferences and perceptions regarding day surgery have not been widely evaluated (Marla et al. 2009, Bonnema et al. 1998).

## **Mastectomy**

Radical mastectomy was described in 1882 by Halsted and by Meyer in 1884. It consisted of removing the breast glandular tissue and in addition, the pectoralis major and minor muscles with axillary lymph nodes. In 1932, D.H. Patey first performed a mastectomy that preserved the pectoralis major muscle. Patey and W.H. Dyson described the technique in their 1948 article. In 1972, JL Madden published the mastectomy technique for saving both pectoral muscles.

Mastectomy was the standard treatment for all breast cancer patients until the 1980s. Today, it is still recommended for patients with tumours too large for breast conservation with acceptable aesthetic outcomes or is performed upon patient request. Mastectomy is also indicated if RT is contraindicated after BCS, as in patients with earlier RT on the same field. In inflammatory breast cancer, mastectomy is always performed after neoadjuvant treatment. Risk-reducing mastectomy can be performed in patients with a genetic predisposition to breast cancer, like BRCA1 and BRCA2 mutation carriers. However, even in gene mutation carriers, if breast cancer is already diagnosed, tumour biology and cancer prognosis define the treatment and extent of the surgery.

## **Breast-conserving surgery**

In the 1930s, Finnish professor Sakari Mustakallio started performing breast-conserving surgery. However, it was not until the 1970s that this more conservative form of surgery began to be more widely accepted. When the randomised trials of professors Umberto Veronesi and Bernard Fisher in the 1980s reported similar survival in patients treated by BCS combined with either radiation therapy or mastectomy, breast conservation became a standard treatment option in breast cancer surgery (Fisher et al. 1985, Veronesi et al. 1981).

Indications of BCS have extended since early on. It was initially recommended only to patients with small (<2 cm) unifocal tumours with a low risk of lymph node metastases. Since then, breast conservation has shown to be feasible and safe in larger and even multifocal tumours with axillary metastases when tumour-free margins are achieved (Gentilini et al. 2007). The consensus regarding acceptable tumour-free margins has also changed over time. Currently accepted are the tumour-free resection margin (i.e., no tumour on the ink) in invasive cancer and the 2 mm margin in ductal carcinoma in situ (DCIS). Nowadays, the rate of BCS is considered a central quality indicator in breast cancer treatment.

Contraindications of BCS are a large tumour-breast ratio, contraindication of radiotherapy or poor co-operation regarding radiotherapy. However, in elderly patients with comorbidities, radiotherapy can sometimes be omitted after BCS (EBCTCG 2005b).

In BCS, the tumour is resected with acceptable tumour-free margins to ensure oncological safety. Non-palpable tumours are preoperatively marked with a guide wire, radioactive isotope or radioactive seed utilising proper imaging modalities. The resection of breast tissue is performed with adequate mobilisation and closure of tissue to reach the best possible aesthetic outcome.

Neoadjuvant treatment is an option for patients who desire breast conservation, but their tumour size is too large. It can be considered especially for patients with HER2-positive or triple-negative breast cancer. Neoadjuvant treatment has equivalent overall survival outcomes with adjuvant therapies, but BCS can be performed more often after neoadjuvant treatment because of tumour downsizing (Fisher et al. 1998, van der Hage et al. 2007). Recent meta-analyses from EBCTCG noted an increased risk of local recurrences after neoadjuvant treatment (Biganzoli et al. 2017). However, the results



might have been affected by subgroups of patients without any surgery after neoadjuvant treatment due to clinical complete response. Not surprisingly, these patients had more local recurrences at their follow-up. Interestingly, recent studies suggest that despite the increased use of neoadjuvant therapy, conversion from a planned mastectomy to breast conservation after neoadjuvant therapy has not always been adopted. A recommendation for mastectomy before neoadjuvant therapy, combined with the option of reconstructive surgery, may in fact drive more extensive surgery, that is, risk-reducing contralateral mastectomy and bilateral IBR. A study by Karakatsanis et al. (2018) showed that breast surgery performed after neoadjuvant therapy does not reflect tumour response. However, even after complete pathological response, the original extent and possible multifocality of the tumour should be kept in mind when planning surgery after neoadjuvant treatment.

### **Oncoplastic surgery**

A satisfactory aesthetic outcome is the second most important goal in BCS after oncological safety. However, unsatisfactory cosmetic outcomes are still observed after conventional resection in up to 20–40% of patients (Haloua et al. 2013, Dahlback et al. 2016). Several factors associated with poor aesthetic outcomes have been identified: central, medial or inferior tumour locations, larger tumour size, larger specimen volume, reoperation due to positive margins, radiation therapy and radiation boost (Foesterling et al. 2014, Hennings et al. 2015, Heil et al. 2012, Immink et al. 2012, Vrieling et al. 2000).

Since the 2000s, numerous oncoplastic techniques have been developed to improve aesthetic outcomes and enable breast conservation in patients with larger tumour-breast ratios or with tumours in challenging locations. In oncoplasty, breast tissue is reshaped, replaced or rearranged after tumour removal to produce a better aesthetic outcome (Clough et al. 2010). Oncologic safety of oncoplastic breast-conserving surgery seems to be as good as after conventional wide local excision (Clough et al. 2017).

Although oncoplastic surgery includes also IBR, a direct comparison between these types of breast cancer operations is seldom made. Previous studies have demonstrated that with oncoplastic surgery, selected patients could achieve breast

conservation and avoid mastectomy and IBR with similar or even better psychosocial and aesthetic outcomes as well as QoL compared to IBR (Kelsall et al. 2017, Nicholson et al. 2007, Howes et al. 2016).

### **Aesthetic outcomes after breast-conserving surgery**

Evaluating aesthetic outcomes is lacking in standardised methods. A wide variation in the methodology makes comparing different study results difficult. Objective evaluation methods are based on either direct clinical evaluation or on the evaluation of photographs. Objective methods are costly, but at least some are reproducible (Cardoso et al. 2007). When evaluating treatment outcomes, patient self-evaluation is a valuable method since the subjective experience is central in the assessment of QoL (Stanton et al. 2001, Heil et al. 2010). However, even self-evaluation instruments vary from a single question to validated multi-item questionnaires. Previous studies also show that patient-reported aesthetic outcome questionnaires may provide more favourable aesthetic outcomes than objective aesthetic outcome measurements (Heil et al. 2011, Santos et al. 2015).

The most appropriate time to evaluate aesthetic outcomes after BCT and RT is not clear (Vrieiling et al. 2000, Haloua et al. 2013). Evaluating too soon after surgery and RT may produce falsely good results because of swelling after radiotherapy. Fibrosis and retraction after RT can increase up to three years (Immink et al. 2012).

### **Breast reconstruction**

Mastectomy without reconstruction results in inferior QoL. Breast reconstruction following mastectomy has benefits in body image, self-esteem and sexuality, leading to a better QoL (Elsahir et al. 2013). Breast reconstruction after mastectomy is one quality indicator in breast cancer treatment, and every patient receiving mastectomy should be informed about breast reconstruction.

Breast reconstruction can be performed immediately with mastectomy or in a delayed fashion after adjuvant treatments. It is important to remember that mastectomy with IBR is a more extensive operation than mastectomy alone. Breast reconstruction has risks: wound healing problems, infection, anastomosis problems in microvascular settings, thromboembolic complications and longer hospital stays.

After IBR, adjuvant treatments may be delayed due to healing problems, possibly negatively affecting oncological results (Vandergrift et al. 2013). In patients with a high risk of recurrence, IBR should be carefully considered to prevent delays in adjuvant treatments.

Radiation of the reconstructed breast is known to lead to suboptimal aesthetic outcomes, fat necrosis, fibrotic changes and capsular contracture after implant-based reconstructions. If the patient needs post-mastectomy RT, delayed breast reconstruction should be considered instead of IBR. IBR is ideal for low-risk invasive cancer patients or for patients with DCIS. Delayed breast reconstruction is usually performed one to three years after mastectomy. If the patient is uncertain about breast reconstruction at the time of their diagnosis, delayed breast reconstruction is a better option.

Nowadays, multiple techniques for breast reconstruction are available. The aim of breast reconstruction is to create a natural appearance of the reconstructed breast with the simplest possible technique. The main reconstruction options are prosthesis reconstruction and autologous tissue reconstruction or a combination of the two. Several local, pedicular and microvascular flaps are available for breast reconstruction. The most common autologous reconstruction options are the pedicular latissimus dorsi flap and microvascular flaps of the lower abdominal region.

### **Axillary lymph node dissection**

Surgical treatment of breast cancer consists not only of the breast surgery but also of axillary surgery. ALND was the gold standard in axillary staging for decades. A diagnostic ALND includes Berg levels I and II (lymph nodes lateral to and underneath the pectoralis minor muscle). Berg level III includes lymph nodes medial to the pectoralis minor muscle and should be included in dissection, when the patient has overt axillary metastases. The accuracy of axillary nodal staging is dependent on the number of examined nodes (Schaapveld et al. 2004), and ALND has been considered accurate if at least ten lymph nodes have been examined. The number of examined nodes is dependent both on quality of surgery and on pathology. ALND is therapeutic only in node-positive patients, and until recently, it has been routine in sentinel node–

positive patients. Axillary recurrences are rare after ALND, at 0.6–1.0% over a five-year follow up (Gentilini et al. 2007, Siponen et al. 2012).

ALND leads to acute and long-term morbidity such as upper arm lymphoedema, pain, numbness, loss of strength and impaired range of motion in the involved arm (Mansel et al. 2006). These symptoms affect 20–80% of women who undergo ALND and axillary RT.

### **Sentinel lymph node biopsy**

Today, breast cancers are detected earlier without axillary involvement due to mammography screening and improved diagnostics in general. With clinically node-negative patients, morbidity after ALND compromises QoL. Therefore, less invasive but equally accurate axillary staging methods have been sought. Different imaging modalities are not sensitive enough to exclude axillary lymph node metastases, although axillary ultrasound in combination with needle biopsy can detect positive axillary nodes in approximately 80% of node-positive patients (Houssami et al. 2011).

During the 1990s, SNB was introduced in nodal staging in breast cancer (Giuliano et al. 1996). The safety of SNB was further proved in randomised trials, the first of which was published in 2003 (Veronesi et al. 2003). SNB became the standard of care after innumerable validation studies showed an average false negative rate of 7.3% (Kim et al. 2006). Originally, SNB was indicated in invasive T1 and small T2 clinically node-negative tumours. Nowadays, SNB is also indicated in larger tumours whenever they are clinically node-negative.

In pure DCIS nodal staging is not needed. However, in 13 to 35 % of cases with preoperative DCIS diagnoses invasive breast cancer is detected in final pathological examination of surgical specimen. In these cases, SNB can be performed as a second operation after breast conservation. However, SNB is performed in DCIS patients undergoing mastectomy.

Numerous studies have clearly proven lower postoperative morbidity after SNB when compared with ALND (Mansel et al. 2006, Galimberti et al. 2013, Rönkä et al. 2005, Leidenius et al. 2005). After ALND, both short-term and long-term morbidity are more common than after SNB (Haid et al. 2002, Rönkä et al. 2005). The ALMANAC study showed better QoL after SNB than ALND (Mansel et al. 2006).

The number of ALND performed in node-negative patients should remain low and is considered a quality indicator in breast cancer treatment.

Until recently, ALND has been the routine treatment after positive SNB. However, previous studies have demonstrated only about a 40% rate of additional metastatic nodes in ALND after positive SNB (van la Parra et al. 2011). In addition, a few randomised trials have evaluated the role of ALND in the treatment of sentinel node-positive patients. ACOSOG Z0011 was a prospective randomised controlled trial evaluating the need for completion ALND after positive SNB (Giuliano et al. 2011). In this study, patients with micro- or macrometastases were randomised either to ALND or observation only after the detection of one or two positive lymph nodes in SNB. In the ACOSOG Z0011 trial, no differences in local or regional recurrence rates or in survival were observed in the 9.25-year follow-up (Giuliano et al. 2016). In the IBCSG 23-01 trial, patients with micrometastases ( $\leq 2$ mm) were randomised to ALND or no ALND with no difference in five-year disease free survival (Galimberti et al. 2013). Another study, AMAROS, compared ALND with axillary RT after a positive SNB (Straver et al. 2014). This study concludes that after a positive SNB, ALND and axillary radiotherapy provide excellent and comparable axillary control for patients with T1–2 primary breast cancer and no palpable lymphadenopathy.

Results of recent randomised trials have already changed treatment guidelines throughout the world. In Finland, ALND is no longer recommended in patients with ITC or micrometastases in SNB. In macrometastatic findings in SNB, the Finnish national treatment guideline discourages replacing ALND routinely with axillary RT since the follow-up period of the AMAROS study is limited concerning disease-free survival.

## **5.5 Systemic adjuvant treatment**

Systemic adjuvant treatment reduces the risk of breast cancer recurrence and improves survival. Without any systemic adjuvant treatment, ten-year recurrence-free survival has been 65% in node-negative patients and 43% in node-positive patients (EBCTCG 2011). Systemic adjuvant treatment is individually planned based on tumour and patient characteristics. Adjuvant chemotherapy reduces the recurrence rate in all biological subtypes of breast cancer. In EBCTCG meta-analyses (2005), the

anthracycline-based chemotherapy regimens produced relative mortality reductions of 20–38% on average. Endocrine treatment for ER-positive patients adds a further relative mortality reduction of 31%. However, comorbidities and advanced age may restrict chemotherapy use. Usually, six cycles of adjuvant chemotherapy are administered prior to radiotherapy. In HER2-positive patients, trastuzumab treatment is initiated simultaneously with chemotherapy. The duration of trastuzumab treatment is usually one year.

According to the Finnish National Breast Cancer Treatment Guideline, an estimated recurrence rate of over 10% in ten years is considered an indication for systemic adjuvant treatment. Histological tumour type and stage, nodal status, oestrogen and progesterone receptor status, HER2 amplification status and proliferation index are cancer-related factors that affect treatment decisions. Patient age, comorbidities and general conditions are evaluated as well.

Timely treatment without delays is considered a core quality indicator in breast cancer treatment (Del Turco et al. 2010). No consensus exists on the optimal time interval between surgery and adjuvant treatment. The Finnish Ministry of Social Affairs and Health has recommended that the time interval from surgery to the initiation of adjuvant treatment should be from four to six weeks. Delays in adjuvant treatment are associated with worse breast cancer outcomes in stage III breast cancer and especially in aggressive HER2 positive or triple negative disease (Gagliato et al. 2014, Richards et al. 1999); a four-week delay in systemic adjuvant treatment increases the relative risk of recurrence by 16% and mortality by 15% (Yu et al. 2013). Furthermore, many surgery-related factors such as number of cancer operations and complications may delay the initiation of adjuvant treatments and thus increase the recurrence risk.

In oestrogen receptor (ER)-positive breast cancer, endocrine treatment reduces the relative risk for recurrence by 50% and mortality by 30% (EBCTCG 2005a, 2005b). For ER-positive disease, endocrine treatment reduces the annual breast cancer death rate by 31%, respectively. Systemic endocrine treatment is considered in all patients with hormone receptor-positive cancer. Endocrine treatment is usually initiated after chemotherapy and simultaneously with RT. Tamoxifen and aromatase inhibitors are used depending on menopausal status. In premenopausal patients, ovarian suppression with tamoxifen or exemestane may be used according to the risk of recurrence. Recent

meta-analyses showed that using an aromatase inhibitor for five years reduces ten-year breast cancer mortality rates by about 15% compared with five years of tamoxifen, hence by about 40% proportionately compared with no endocrine treatment (EBCTCG 2015). Prolonged endocrine treatment for up to ten years should be considered for patients with a high risk of recurrence.

## 5.6 Radiotherapy

Whole-breast RT is recommended for all patients after BCS. The impact of adjuvant RT on survival and local recurrences is well defined. RT decreases local recurrences by 65–75%, prolongs disease-free survival and reduces breast cancer mortality. After a 15-year follow-up, about one breast cancer death is avoided for every four local recurrences avoided. RT also reduces 15-year overall mortality (EBCTCG 2000, 2005). A radiation booster to the resection site is recommended for high-risk patients as it decreases the risk of local recurrences but does not affect survival (Kindts et al. 2017). The radiation booster may have a negative impact on aesthetics after breast conservation, however (Immink et al. 2012, Vrieling et al. 2000).

In elderly patients, RT after BCS does not provide a survival benefit but lowers the risk of local recurrence (EBCTCG 2005, Matuschek et al. 2017). In this elderly patient group, RT-induced adverse effects and negative impacts on QoL should be understood when planning treatment. However, mastectomy should not be routine in elderly patients if adjuvant RT after BCS is not possible.

RT after mastectomy decreases the risks of recurrence and breast cancer death in all patients with node-positive cancer. In these patients, RT after mastectomy provided a significant decrease in the 10-year risk of local-regional recurrence (8.1% vs. 26.0%;  $p < 0.00001$ ). RT also significantly decreased 20-year breast cancer mortality (58.3% vs. 66.4%;  $p = 0.001$ ). However, in patients with node-negative cancer, RT improved neither local-regional disease control nor BCSS (EBCTCG 2014).

Based on these results, RT is recommended for mastectomy patients with node-positive disease. RT is also recommended in node-negative T3 and T4 tumours and can be considered even in T2 tumours if specific risk factors exist.

The RT of nodal regions (axillary, parasternal and supraclavicular regions) is indicated in patients with nodal involvement. The treatment of nodal regions is

individually based on tumour size, biology, number of involved nodes and type of axillary surgery. Axillary surgery in breast cancer treatment is evolving rapidly, and a more conservative approach is adopted: the number of patients with ALND is decreasing. Naturally, this reflects in the planning of nodal radiotherapy.

## **5.7 Breast cancer in the elderly**

Breast cancer in the elderly differs from the disease in younger women both in the diagnosis stage and in biological tumour characteristics. The biological features of breast cancer are often more favourable, with lower-grade tumours and more frequent oestrogen receptor expression (Diab et al. 2000). This is counterbalanced by larger tumours as well as higher rates of locally advanced and metastatic disease in diagnoses of older women (Bastiaannet et al. 2010, Gennari et al. 2004). These differences may be explained by missing screenings in older women and less breast cancer awareness.

The definition of an elderly patient varies greatly in the literature, ranging from 65-year-olds to over 80-year-olds. Naturally, this makes interpreting and comparing the results difficult. Moreover, in elderly patients, chronological age does not always correlate with biological age. Functionality and QoL may persist at the same level for years despite several comorbidities and frailty. Therefore, evaluating life expectancy even in the presence of serious comorbidities is difficult. Geriatric assessment tools may provide additional useful information for decision-making. Nevertheless, usability of geriatric assessment tools in clinical practice is suboptimal and needs further development (Huisman et al. 2017, Parks et al. 2015, Thomas et al. 2017).

Treatment guidelines are followed less often in elderly breast cancer patients, leading to under-treatment (van de Water et al. 2012, Kiderlen et al. 2015, Angarita et al. 2015, Shumway et al. 2017, Biganzoli et al. 2017). This can partly be explained by comorbidities and the frailty of older patients, preventing the use of adjuvant treatments, chemotherapy particularly. Accordingly, not only OS but also BCSS are inferior when compared to younger breast cancer patients. Naturally, OS is worse in older women with breast cancer due to other causes of death. On the other hand, BCSS in the elderly is also decreased, implicating the undertreatment of breast cancer. Tailoring breast cancer treatment without compromising survival or QoL is a significant clinical challenge. Local control influences QoL and is thus of high



importance in the elderly. However, physicians' nihilistic attitudes may also affect treatment decisions.

### **Local treatment**

Local treatment, that is, RT and especially surgery, is the cornerstone of treatment in early breast cancer, even among the elderly. One of the most important aims of breast cancer treatment in the elderly is to provide local disease control. However, elderly patients receive surgery markedly less often than younger patients, and over time, it has become more common to omit surgery in older women (Kiderlen et al. 2017). On the other hand, surgical procedures in the elderly have often been more extensive; mastectomy and ALND are performed instead of BCS and SNB (Sierink et al. 2014, Eaker et al. 2006, Kiderlen et al. 2015). Previous trials have shown that RT after BCS does not provide survival benefits but lowers the risk of local recurrence in elderly women (Hughes et al. 2013, EBCTCB 2005). Adverse effects of RT may also be more common in the elderly population.

### **Systemic adjuvant treatment**

With increasing age, a decrease in provision of any adjuvant treatment except for endocrine treatment is reported (Kiderlen et al. 2017). Chemotherapy in elderly breast cancer patients is used only after thorough patient evaluation and general treatment guidelines cannot be utilised on older, fragile patients. The role of the multidisciplinary team and physician is emphasised in clinical decision-making.

### **Primary endocrine treatment**

Primary endocrine therapy is an alternative to surgical treatment in elderly patients with ER-positive cancer. The use of primary endocrine treatment has increased significantly over the past decade, leading to the omission of surgery for elderly patients with resectable breast cancer (Hamaker et al. 2013). Primary endocrine treatment has been proven to result in inferior local disease control compared to primary surgery (Hind et al. 2006, Syed et al. 2011, Hughes et al. 2013). Moreover, endocrine treatment also has side effects: fatigue, dizziness, nausea, muscle weakness

and pain as well as increased risk in thromboembolic complications. Advanced age, comorbidities and frailty—all reasons to consider non-surgical treatment—affect the patients' ability to tolerate endocrine treatment and may lead to a poor QoL and decreased compliance. These long-term negative effects should be taken into account in patient counselling and decision-making.

## **6 Aims of the study**

1. The quality of preoperative diagnostics and hospital volume influence the quality of the surgical treatment process and waiting times in breast cancer patients
2. Day surgery is feasible in breast cancer surgery
3. Oncoplasty improves aesthetic outcomes compared to conventional breast resection
4. Surgical treatment in elderly breast cancer patients is well tolerated and improves oncological outcomes

## **7 Patients and methods**

This work was conducted at the Breast Surgery Unit, Comprehensive Cancer Center of the Helsinki University Hospital. Study I included 1307 patients undergoing primary breast cancer surgery during 2010 in the Helsinki and Uusimaa Hospital District. Patients with recurrent breast cancer, other malignant tumours in the breast or secondary surgeries were excluded. If bilateral breast cancer was detected, the tumour in a more advanced stage was used as the index tumour.

Study II was a randomised controlled trial and included 78 patients receiving BCS and SNB between January 2008 and March 2011. Patients were randomised in two groups: day surgery discharge and overnight stay. Results were analysed according to randomisation and actual treatment.

In study III, 637 patients receiving breast-conserving treatment due to unilateral primary breast cancer in 2010 were included. These patients received a questionnaire regarding aesthetic and functional outcomes: 379 patients answered the questionnaire and were included in the analysis. Patients with mastectomy as reoperation due to insufficient free tissue margin were excluded.

Study IV included 446 patients older than 80 years with primary early breast cancer between January 2005 and December 2010. The follow-up period ended on December 31<sup>st</sup>, 2014, and patients' survival status (alive, breast cancer-related death, death for other cause) as of that date was obtained from the Finnish Cancer Registry. Data on cancer recurrences were collected from hospital records. The follow-up period was calculated from the day of surgery until the end of the follow-up period or death.

The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital.

### **7.1 Surgery**

Breast and axillary surgery were performed or supervised by expert breast surgeons. In patients with breast conservation, a conventional wide local excision was performed, aiming at 1 cm free lateral margins and usually including the underlying

pectoral fascia and a slice of skin overlying the tumour. After resection, adequate mobilisation and closure of breast parenchyma were performed. Oncoplastic resection refers to first- and second-level oncoplastic procedures (Clough et al. 2010). In Study III, the following oncoplastic resection techniques were used: racket mammoplasty, reduction mammoplasty techniques, round block, rotationplasty techniques, extensive dual plane undermining and other oncoplastic techniques.

SNB was performed on patients with invasive breast cancer who had clinically node-negative breast cancer. The indications and contraindications for SNB according to the tumour size varied during the study period. In patients with DCIS, SNB was performed when mastectomy was performed. Also, if invasive cancer was suspected in breast imaging or core needle biopsy, SNB was recommended. ALND was omitted whenever the SNB was negative. SNB was performed using preoperative lymphoscintigraphy, intraoperative identification of the sentinel nodes with gamma probe and blue dye.

ALND was performed in node-positive patients, either after positive SNB or after axillary ultrasound with a tumour-positive needle biopsy of a suspicious node. ALND included the evacuation of Berg levels I and II nodes. Berg level III was palpated and evacuated if clinically suspicious for metastases.

**Table 1. Patient and tumour characteristics**

Study I: 1307 patients with surgery for primary breast cancer

Study II: 78 patients with breast-conserving surgery and SNB

Study III: 379 breast cancer patients with breast-conserving surgery

Study IV: 446 patients older than 80 years with primary breast cancer

		Study I	Study II	Study III	Study IV
Age, median (range)	years	62 (22–100)	56 (40–69)		84.5 (80.0–101.9)
Histological T-stage	Tis & T1mi	97 (7%)		23 (6.1%)	15 (3.4%)
	T1	813 (62%)		302 (79.7%)	207(46.4%)
	T2	306 (23%)		51 (13.5%)	194 (43.4%)
	T3-4	71 (5%)		0	26 (5.8%)
	NA	20 (2%)		3 (0.8%)	4 (0.9%)
Axillary lymph node status	N0	774 (59%)	62 (79.5%)	270 (71.2%)	187 (42%)
	N1mi	82 (6%)			7 (2%)
	N1	237 (18%)	16 (20.5%)	91 (24.0%)	94 (21%)
	N2-3	156 (12%)			66 (15%)
	NA	58 (4%)		18 (4.7%)	92 (21%)
Histological grade	1	306 (24%)	24 (30.8%)	111 (29.3%)	84 (21%)
	2	537 (42%)	36 (46.2%)	165 (43.5%)	155 (39%)
	3	433 (34%)	17 (21.8%)	100 (26.4%)	160 (40%)
	NA	31 (2.4%)	2 (2.6%)	2 (0.5%)	47 (10.5%)
Tumour ER content	positive	1025 (85%)	68 (87.2%)		370 (88%)
	negative		3 (3.8%)		50 (11%)
	NA		7 (9.0%)		26 (5.8%)
Tumour PR content	positive	797 (66%)	60 (77.0%)		268 (65%)
	negative		11 (14.1%)		146 (33%)
	NA		7 (9.0%)		31 (7.0%)
HER2 amplification	positive	158 (13%)	21 (27.0%)		39 (9%)
	negative		41 (52.6%)		341 (76%)
	NA		11 (14.1%)		66 (15%)
Tumour multifocality	positive			17 (4.4%)	
Histological type	DCIS	96 (7%)	4 (5.1%)	24 (6.3%)	15 (4%)
	Ductal	871 (68%)	68 (87.2%)	298 (78.6%)	294 (69%)
	Lobular	185 (14%)	6 (7.7%)	39 (10.3%)	67 (16%)
	other invasive	144 (11%)	0	42 (11.1%)	51 (12%)

## 7.2 Histopathology

The breast surgery specimens were oriented by the surgeon and were sent unfixed to the specialised breast pathologist for assessment. The primary tumour diameter, presence of multifocality, histological tumour type and grade, ER and PR status, MIB-1 proliferation index and HER2 amplification status were analysed as described in Leidenius et al. (2010).

Sentinel nodes were sent to the pathology laboratory separately from the primary tumour for frozen section analysis. Tumour deposits were classified as micrometastases at  $\leq 2$  mm in diameter and as ITCs at  $\leq 0.2$  mm in diameter. The longest diameter of the largest metastasis was recorded as the size of metastasis. The assessment of sentinel nodes and the nodes from the axillary lymph node dissection specimen is described in detail in a previous study (Meretoja et al. 2010).

## 7.3 Adjuvant treatment

Systemic adjuvant treatment and RT were individually planned by the multidisciplinary breast cancer team based on patient and disease characteristics according to national guidelines. RT to the ipsilateral breast was given after breast-conserving surgery using a linear accelerator to a cumulative dose of 50 Gy in 25 fractions. A booster dose of 10–16 Gy given in five to eight fractions was given to premenopausal women as well as in patients with close resection margins. The whole breast was treated from two tangential fields. Post-mastectomy RT was given to patients with a large primary tumour (pT3 or pT4) and to patients with axillary lymph node-positive cancer. RT was based on computer-based dose planning and was given in a linear accelerator with 2 Gy daily fractions, five fractions per week for a cumulative dose of 50 Gy.

For systemic adjuvant treatment, an estimated recurrence rate of over 10% across ten years was considered a threshold value. In addition to cancer-related factors, patient comorbidities, general condition and age were also taken into account when evaluating the advantages and disadvantages of systemic adjuvant treatment. Patients with HER2-positive breast cancer received trastuzumab concomitantly with chemotherapy if no clinical contraindications existed. Hormone therapy was initiated

after chemotherapy or simultaneously with RT if chemotherapy was not planned. Premenopausal women with ER- and/or PR-positive cancer received tamoxifen, and postmenopausal women received either tamoxifen or an aromatase inhibitor for five years. Only a few study patients received neoadjuvant treatment.

## **7.4 Anaesthesia and day surgery**

Study II was a randomised controlled trial. All patients were eligible for day surgery in the preoperative assessment. Patients who were randomised to the day surgery group were discharged on operation day if day surgery criteria were met and their condition allowed it. Criteria for day surgery discharge on the operation day were as follows: BCS and SNB without drainage, stable blood pressure and pulse level, no respiratory problems, patient mobilised to the preoperative level, no or only mild nausea, postoperative pain controlled by oral pain medication, either non-steroidal anti-inflammatory analgesic, paracetamol or paracetamol-codeine, no or minimal postoperative bleeding, normal urination, adult companion at home and patient being first on the operation schedule.

In study II, general anaesthesia was induced with propofol and fentanyl and maintained with propofol and remifentanyl infusions. All patients were intubated and received rocuronium for muscle relaxation. Dexamethasone and granisetron were given for prophylaxis of postoperative nausea and vomiting. To manage pain at home, ibuprofen and paracetamol or paracetamol with codeine were prescribed.

## **7.5 Quality indicators**

There are no validated and tested quality indicators for breast cancer patients in Finland. In Study I, the following parameters were modified from the EUSOMA recommendations (Del Turco et al. 2010) and used as quality indicators:

- proportion of patients having BCS
- proportion of mastectomy patients receiving IBR
- proportion of oncoplastic resections of all BCS
- need for re-operation due to insufficient resection margins



- need for re-operation due to false-negative sentinel nodes in the intraoperative assessment
- failure in identifying sentinel node
- ALND in node negative patients
- time from referral to surgery
- time from surgery to adjuvant therapy
- number of cancer operations.

Municipal authorities organize breast cancer screening in Finland. Biannual screening is offered to all women aged 50–69. According to the Health and Social Services Ministry statistics, screening participation in 2010 was 85% nationally and 79% in the Helsinki and Uusimaa Hospital District. Patients are referred to breast surgery units either from population-based screening or by other public or private healthcare providers. Before referral to the hospital for breast cancer surgery, diagnostic mammogram and ultrasound together with percutaneous needle biopsy of the primary tumour are required.

## **7.6 Hospital volume and facilities**

In Finland, the treatment of malignant diseases is almost exclusively performed by the public health care system. Regional healthcare districts organise the treatment. The number of breast cancer operations in each hospital is mainly dependent on the size of the population and incidence of breast cancer within its well-defined area. Some special cases, such as those with IBR, are referred to high-volume hospitals.

The Helsinki and Uusimaa Hospital District is the largest hospital district in Finland based on a population of more than 1.6 million people (2017). In 2010, breast cancer surgery was performed in five hospitals receiving patients mainly from their own defined areas. In Study I, hospitals A and B were high-volume (>150 patients annually), hospital C was medium-volume (100–150 patients), hospital D low-volume (50–99 patients) and hospital E very low-volume (<50 patients). Hospitals A and B are located in big cities, whereas hospitals C, D and E are located in smaller towns, surrounded by more rural-like areas. Nuclear medicine as well as MRI facilities are

located in Hospitals A and B. All hospitals performed SNB using similar surgical principles and histopathological methods.

Systemic adjuvant treatment and RT were individually planned by the multidisciplinary breast cancer team based on patient and disease characteristics according to national guidelines. All study patients receiving adjuvant or neoadjuvant therapies were referred to a single institute, the Department of Oncology at Helsinki University Hospital.

## **7.7 Questionnaires**

In study II, the patients and their spouses or other relatives received study questionnaires. These questionnaires evaluated their perceptions of day surgery and physical and psychological recovery within discharge. The questionnaires were not validated. They were filled out on the first postoperative day and returned by mail. Questionnaire results were analysed for patients receiving BCS and SNB only. Altogether, 44 (72%) patients returned the questionnaires, including 20 patients randomised to the day surgery group and 24 to the overnight stay group. Results were analysed according to randomisation and actual treatment received, that is, per protocol. When analysed according to actual treatment, 18 patients received day surgical treatment and 26 received an overnight stay.

In Study III, aesthetic and functional outcomes were evaluated with the use of two separate questionnaires: BCTOS and an author-created questionnaire (Appendix 1). Questionnaires and informed consent forms were sent three years after surgery by mail, with a prepaid return envelope included. Altogether, 379 (59%) patients agreed to take part in the study by returning questionnaires and signed informed consent forms. Of these, 293 (77%) had conventional BCS and 86 (23%) oncoplastic BCS. The proportion of conventional and oncoplastic procedures in the whole study population was similar at 79% and 21%, respectively.

BCTOS was designed to assess the woman's subjective evaluation of the aesthetic and functional outcomes after breast cancer treatment (Stanton et al. 2001). The BCTOS questionnaire addresses many important dimensions of post-treatment morbidity with respect to aesthetic and functional outcomes, specifically targeting the surgical aspects of BCS. We translated the BCTOS questionnaire into Finnish and

Swedish since, to our knowledge, it has not been used in Finland before. Patients rate different items according to symmetry between the treated and the untreated breast on a four-point scale (1 being no difference between the treated and untreated breast, and 4 being a large difference between the treated and untreated breast). BCTOS consists of three internally consistent scales, which are defined as Aesthetic, Functional and Sensitivity status. The score value of each subscale is the mean of items belonging to this scale. We defined the BCTOS aesthetic status cutoff value of  $\geq 3$  to be a poor aesthetic outcome. A BCTOS aesthetic score of 2.0–2.99 was considered intermediate, and  $< 2$  was considered a good aesthetic outcome.

Another author-created questionnaire focused on the aesthetic outcome of the operated breast. In this five-point questionnaire, patients were asked about their opinion of the aesthetic outcome of the operated breast in general and in some specific areas, such as breast size, nipple appearance and position, breast shape and position, scar tissue, fitting of bra and symmetry to contralateral breast. The questionnaire also asked if patients had any problems in everyday life due to the poor aesthetic outcome.

## **7.8 Statistical analyses**

The medians of continuous variables were compared using the Mann-Whitney U and Kruskal-Wallis tests. Categorical variables were compared using the Chi-squared test.

In Study II, four graded questionnaire answers were categorised into binomial variables for statistical analyses so that alternatives 1 and 2 were combined as well as alternatives 3 and 4. In the BCTOS questionnaire (Study III) to compare individual items between conventional and aesthetic groups, a four-point scale was categorised into two groups for statistical analyses, so that alternatives 1 and 2 (good or excellent outcome) were combined as well as alternatives 3 and 4 (intermediate or poor outcome).

Distant disease-free survival (DDFS) was calculated from the date of diagnosis to the date of the first occurrence of breast cancer metastases outside the regional lymph nodes. BCSS was calculated from the date of diagnosis to the date of death due to breast cancer and OS from the date of diagnosis to the date of death from any cause. Patients alive without cancer recurrence were censored on the completion date of the follow-up period. Life tables were constructed according to the Kaplan-Meier method,

*Patients and methods*

and survival between groups was compared with the log-rank test. P-values of  $<0.05$  were considered statistically significant.

## **8 Results**

### **8.1 Quality of preoperative diagnostics and surgery and their impacts on delays in breast cancer treatment (Study I)**

#### **Patient and tumour characteristics**

More than half of the patients (n=774, 59%) were node-negative with a significant difference between hospitals (p= 0.005). In hospital E, patients were eldest (median 66, range 44–89 years old), the proportion of T3-T4 tumours was significantly higher (20%; p<0.001) and these patients more often had grade 3 tumours (47%; p=0.029) (Table 8.1).

#### **Patient referral and preoperative examination**

The need for additional diagnostic imaging and biopsies was significantly different between hospitals, ranging from 33% in hospital D to 3% in hospital E (p<0.001). The need for additional diagnostic procedures was significantly different according to the referring institute (p<0.001) in both additional conventional diagnostic procedures and preoperative MRI (Table 8.2).

Table 8.1. Study population and tumour characteristics

		High volume hospitals		Medium volume hospital	Low volume hospital	Very low volume hospital		
		All n=1307	Hospital A n=697	Hospital B n=394	Hospital C n=125	Hospital D n=57	Hospital E n=34	p-value
Age, median (range)		62 (22-100)	62 (22-93)	60 (23-100)	62 (31-96)	62 (35-92)	66 (44-89)	0.005
Histological T-stage	Tis&T1mi	97 (7%)	50 (7%)	38 (10%)	5 (4%)	3 (5%)	1 (3%)	<0.001
	T1	813 (62%)	453 (65%)	231 (59%)	77 (62%)	33 (58%)	19 (56%)	
	T2	306 (23%)	157 (22%)	100 (25%)	26 (20%)	16 (28%)	7 (20%)	
	T3-T4	71 (5%)	25 (4%)	20 (5%)	16 (13%)	3 (5%)	7 (20%)	
	N.A.	20 (2%)	12 (2%)	5 (1%)	1 (1%)	2 (4%)	0	
Nodal stage	N0	774 (59%)	420 (60%)	224 (57%)	80 (64%)	33 (57%)	17 (50%)	0.005
	N1mi	82 (6%)	46 (6%)	24 (6%)	4 (3%)	5 (9%)	3 (9%)	
	N1	237 (18%)	118 (17%)	86 (22%)	21 (17%)	4 (7%)	8 (23%)	
	N2, N3	156 (12%)	77 (11%)	44 (11%)	19 (15%)	10 (18%)	6 (18%)	
	N.A.	58 (4%)	36 (5%)	16 (4%)	1 (1%)	5 (9%)	0	
Histological grade	1	306 (24%)	189 (28%)	79 (21%)	21 (17%)	12 (22%)	5 (15%)	0.029
	2	537 (42%)	262 (39%)	175 (45%)	61 (49%)	26 (48%)	13 (38%)	
	3	433 (34%)	228 (33%)	131 (34%)	42 (34%)	16 (30%)	16 (47%)	
ER	positive	1025 (85%)	558 (87%)	306 (86%)	92 (79%)	41 (77%)	28 (85%)	0.070
PR	positive	797 (66%)	431 (67%)	230 (64%)	80 (68%)	33 (62%)	23 (70%)	0.800
HER2	positive	158 (13%)	74 (12%)	47 (13%)	20 (17%)	10 (19%)	7 (21%)	0.173
Histological type	DCIS	96 (7%)	52 (7%)	35 (9%)	5 (4%)	3 (5%)	1 (3%)	0.117
	Ductal	871 (68%)	447 (66%)	274 (70%)	84 (68%)	43 (75%)	23 (69%)	
	Lobular	185 (14%)	98 (14%)	60 (15%)	14 (11%)	7 (12%)	6 (18%)	
	Other Invasive	144 (11%)	92 (13%)	13 (6%)	21 (17%)	4 (7%)	4 (12%)	
Adjuvant treatment	None	94 (7%)	51 (7%)	24 (6%)	12 (10%)	6 (11%)	1 (2%)	<0.001
	Endocrine only	169 (13%)	97 (14%)	38 (10%)	20 (16%)	8 (14%)	6 (18%)	
	Radiotherapy +/- endocrine	457 (36%)	261 (37%)	131 (33%)	42 (33%)	18 (32%)	5 (15%)	
	Chemotherapy +/- radio +/- endo	540 (41%)	265 (38%)	182 (46%)	49 (39%)	22 (38%)	22 (65%)	
	Neoadjuvant treatment	13 (1%)	9 (1%)	2 (1%)	0	2 (3%)	0	
	N.A.	34 (2%)	14 (2%)	17 (4%)	2 (2%)	1 (2%)	0	

Table 8.2. Patient referral and need for additional hospital diagnostics

			High volume hospitals		Medium volume hospital	Low volume hospital	Very low volume hospital	
		All n=1307	Hospital A n=697	Hospital B n=394	Hospital C n=125	Hospital D n=57	Hospital E n=34	p-value
Referring institute	Screening	459 (35%)	239 (34%)	145 (38%)	51 (42%)	18 (32%)	6 (18%)	0.132
	Public healthcare	350 (27%)	191 (28%)	95 (24%)	31 (25%)	22 (38%)	11 (32%)	
	Private clinic	487 (38%)	265 (38%)	147 (38%)	41 (33%)	17 (30%)	17 (50%)	
Need of additional hospital diagnostic	None	1054 (81%)	552 (80%)	314 (80%)	117 (94%)	38 (67%)	33 (97%)	<0.001
	MGR, US, core needle biopsy	139 (11%)	80 (11%)	36 (9%)	8 (6%)	14 (25%)	1 (3%)	
	MRI	114 (8%)	65 (9%)	44 (11%)	0	5 (8%)	0	
Surgical biopsy		23 (2%)	8 (1%)	10 (2%)	3 (2%)	1 (1%)	0	0.743

## Surgery

In 664 (51%) patients, the final breast surgery was BCS, with no difference between hospitals ( $p=0.781$ ). Of the 664 patients with BCS as the final surgery, 522 (79%) received conventional resection and 142 (21%) oncoplastic resection. The rate of oncoplastic resection varied significantly between hospitals: hospital A was clearly performing more oncoplastic surgery than others ( $p<0.001$ ). Between two high-volume centres (A and B), there was a significant difference in IBR rate ( $p=0.004$ , Table 8.3).

Altogether, 1259 (96%) patients underwent axillary surgery. Of these, 655 (50%) received SNB only and 362 (28%) received ALND after SNB. SNB was unsuccessful in 12 (1%) cases and 9 (75%) of these patients received ALND. Fifty-one node-negative patients underwent ALND, comprising of 7% of all node-negative patients. There was a significant difference between hospitals ( $p=0.009$ , Table 8.3). Of these 51 patients, 6 with upfront ALND received neoadjuvant treatment and were node-negative in postoperative pathological assessment. Nineteen patients with positive sentinel nodes (5% of all patients with positive SNB) had no ALND. Most often, these patients had isolated tumour cells (ITC) 14 (74%) or micrometastases 3 (16%). In 38 (10% of all ALND after SNB) cases, ALND was performed as a second operation due

to a false negative result in the intraoperative assessment of sentinel nodes with a significant difference between hospitals ( $p < 0.001$ , Table 8.3).

Complications demanding surgical intervention were rare: 1243 (95%) patients had none. Postoperative haematoma was the most common complication: 45 (3%) patients underwent haematoma evacuation.

Altogether, 1143 (88%) patients had only one cancer operation. Additional cancer operations were performed in 160 (12%) patients, of whom 151 (11%) received two operations and 9 (1%) received three operations. Reoperation due to an insufficient tumour-free tissue margin was performed in less than 8% ( $N=99$ ) of patients. The reoperation was a mastectomy in 77 (78%) patients, 28 (28%) of which had IBR. After secondary mastectomy IBR occurs more often than with primary mastectomy (46 patients, 9%;  $p < 0.001$ ).

### **Waiting time**

Waiting times from referral to primary surgery and from primary surgery to initiation of any adjuvant treatment are shown in Table 8.4. The waiting time for radiation therapy is shown for patients who did not receive chemotherapy. In this group, endocrine therapy may have been started before RT. Patients receiving neoadjuvant treatment ( $n=13$ ) were excluded from the waiting time analysis.

The median waiting time from referral to primary surgery was 24 days (range of 1–188) (Table 8.4a). Additional biopsies, preoperative MRI and IBR increased the median wait time significantly (Table 8.4b). Altogether, 1166 (89%) patients received adjuvant treatments. The median waiting time from primary operation to initiation of any adjuvant treatment was 47 days (range of 8–112), and it differed significantly between hospitals ( $p=0.005$ , Table 8.4a). Wait times for the initiation of adjuvant treatment were significantly affected by type of primary surgery and number of cancer operations (Table 8.4c). In eight patients, the delayed adjuvant treatment was due to complications requiring surgical intervention.



Table 8.3. Breast and axillary surgery

	High volume hospitals		Medium volume hospital	Low volume hospital	Very low volume hospital		
	All n=1307	Hospital A n=697	Hospital B n=394	Hospital C n=125	Hospital D n=57	Hospital E n=34	p-value
Final breast surgery							0.781
BCS	664 (51%)	358 (52%)	198 (51%)	58 (46%)	31 (54%)	19 (56%)	
Oncoplastic resection (% of BCS)	142 (21%)	118 (33%)	16 (8%)	7 (12%)	0	1 (5)	<0.001
Mastectomy	639 (49%)	337 (48%)	194 (49%)	67 (54%)	26 (46%)	15 (44%)	
IBR (% of all mastectomy)	74 (12%)	36 (11%)	38 (20%)	1 (1%)	0	0	<0.001
Final axillary surgery							<0.001
None	45 (3%)	31 (4%)	9 (2%)	0	5 (9%)	0	
SNB	655 (50%)	362 (52%)	189 (48%)	69 (55%)	24 (42%)	11 (32%)	
SNB+ALND	362 (28%)	199 (28%)	122 (31%)	29 (23%)	4 (7%)	8 (24%)	
ALND	207 (16%)	85 (12%)	66 (17%)	26 (21%)	16 (28%)	14 (41%)	
ALND as second operation	38 (3%)	20 (3%)	8 (2%)	1 (1%)	8 (14%)	1 (3%)	
SNB unsuccessful							0.698
	12 (1%)	7 (1%)	2 (1%)	3 (3%)	0	0	
ALND of N0 axilla							0.009
	51 (7%)	19 (5%)	16 (8%)	8 (10%)	4 (14%)	4 (27%)	
Positive SNB, no ALND							
	19 (5%)	14 (6%)	5 (4%)	0	0	0	

Results

Table 8.4a. Median waiting times (days)

			High volume hospitals		Medium volume hospital	Low volume hospital	Very low volume hospital	
		All	Hospital A	Hospital B	Hospital C	Hospital D	Hospital E	P-value
From referral to primary surgery N=1110	median (min-max)	24 (1-188)	26 (6-188)	27 (4-142)	19 (1-153)	19 (7-96)	15 (6-37)	<0.001
From primary surgery to initiation of any adjuvant treatment N=1148	median (min-max)	47 (8-112)	47 (14-95)	48 (9-112)	43 (8-82)	50 (29-83)	44 (19-70)	0.005
From primary surgery to initiation of systemic adjuvant treatment N=698	median (min-max)	47 (8-95)	48 (14-95)	48 (9-83)	42 (8-82)	50 (29-71)	42 (19-70)	0.126
From primary surgery to initiation of chemotherapy N=536	median (min-max)	48 (11-95)	48 (24-95)	49 (23-83)	45 (11-82)	50 (31-71)	49 (28-70)	0.834
From primary surgery to initiation of endocrine therapy N=162	median (min-max)	41 (8-90)	43 (14-90)	43 (9-79)	40 (8-46)	48 (29-56)	26 (19-55)	0.024
From primary surgery to radiotherapy N=264	median (min-max)	55 (26-125)	55 (26-113)	57 (31-125)	55 (35-77)	55 (41-99)	56 (47-63)	0.216

Table 8.4b. Waiting times for surgery

		Wait time for surgery, days median (range)	p-value
Additional biopsy	yes (N=90)	37 (22-153)	<0.001
	no (N= 1217)	23 (1-188)	
Preoperative MRI	yes (N=114)	34 (22-146)	<0.001
	no (N= 1193)	23 (1-188)	
Type of surgery	conventional resection (N=664)	23 (1-161)	0.146
	oncoplastic resection (N=142)	25 (8-126)	
	mastectomy (N=639)	25 (4-188)	0.002
	IBR (N=74)	30 (7-84)	

Table 8.4c. Waiting times for adjuvant treatment

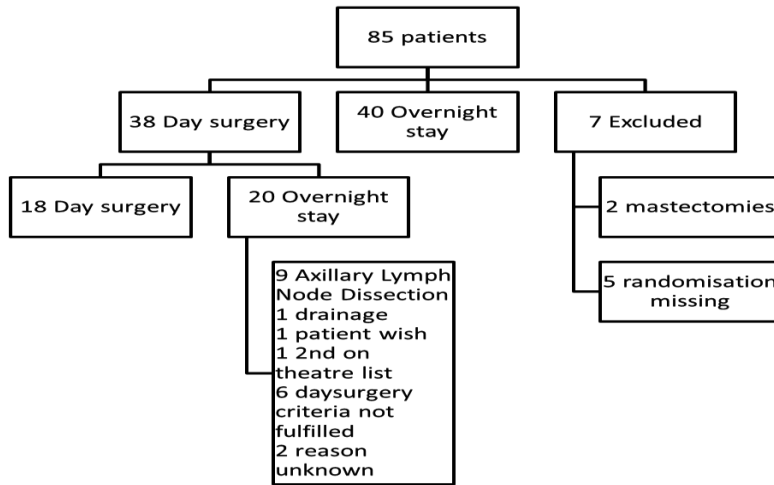
	Wait time from primary surgery to adjuvant treatment, days				p-value
Type of surgery, median (range)	conventional resection	oncoplastic resection	mastectomy	IBR	0.011*
	47 (8–112)	48 (19–90)	46 (11–95)	54 (30–83)	
Number of cancer operations, median (range)**	1	2	3		<0.001
	49 (5–120)	57 (26–125)	85 (56–90)		
*between mastectomy and IBR					
** Only patients receiving chemotherapy and/or radiation					

## 8.2 Feasibility of day surgery after breast-conserving surgery and SNB (Study II)

### Hospital discharge

In the day surgery group, 18 (47%) patients were discharged the same day, whereas 20 (53%) stayed at least one night in hospital (Figure 8.1). The most common reason for overnight hospital stay was ALND (9 patients). Other reasons included drainage (one patient), patient's wish for overnight stay after surgery (one patient) and not being first on the operation schedule (one patient). Day surgery discharge criteria were not met in six patients. Reasons for an overnight stay were missing for two patients. Altogether, 60 patients stayed one night or longer in hospital; 40 patients were randomised to the overnight stay and 20 to the day surgery group.

Figure 8.1. Patient randomisation and actual treatment groups



### Perception of day surgery

There were no statistically significant differences in physical and psychological symptoms between day surgical discharge and overnight stay groups regardless of whether they were analysed according to randomisation or actual treatment. For individual symptoms, see Tables 8.5 and 8.6.

All patients randomised to day surgery and treated accordingly would choose day surgery again. Similarly, their spouses' or relatives' perceptions of day surgery were positive. For both randomised and actual treatment groups, the majority of patients randomised to overnight stay (67%) or who had stayed overnight regardless of randomisation (61%) would not choose day surgery over overnight stay in the future ( $p < 0.0001$ ).

Patients in both groups had rather similar experiences regarding the first postoperative day and their psychological well-being. Also, spouses' or relatives' perceptions after discharge were similar in both groups (Table 8.6).

Table 8.5. Questionnaire results, actual treatment groups and percentages of answers

	Day Surgery N=18		Overnight stay N=26		P- value
	Not at all or a little	Quite or very much	Not at all or a little	Quite or very much	
Patient feels:					
tired	13(72%)	5 (28%)	14 (54%)	12(46%)	0.218
anxious	18 (100%)	0	22 (88%)	3 (12%)	0.128
nervous	18 (100%)	0	23 (96%)	1 (4%)	0.381
irritated	18 (100%)	0	24 (100%)	0	
depressed	18 (100%)	0	24 (96%)	1 (4%)	0.391
insecure	18 (100%)	0	23 (92%)	2 (8%)	0.219
desperate	18 (100%)	0	25 (96%)	1 (4%)	0.400
lonely	18 (100%)	0	25 (100%)	0	
weak	13 (100%)	0	13 (93%)	1 (7%)	0.326
short of breath	18 (100%)	0	25 (100%)	0	
pain	18 (100%)	0	22 (88%)	3 (12%)	0.128
sleepless	16 (89%)	2 (11%)	21 (81%)	5 (19%)	0.469
appetite loss	13 (87%)	2 (13%)	15 (100%)	0	0.143
nausea	18 (100%)	0	23 (92%)	2 (8%)	0.219
headache	18 (100%)	0	23 (92%)	4 (8%)	0.219
need for emotional support	18 (100%)	0	26 (100%)		
Spouse feels:					
tired	14 (82%)	3 (18%)	21 (88%)	3 (12%)	0.646
anxious	14 (82%)	3 (18%)	21 (88%)	3 (12%)	0.212
nervous	17 (100%)	0	21 (91%)	2 (9%)	0.394
irritated	17 (100%)	0	23 (96%)	1 (4%)	0.802
depressed	16 (94%)	1 (6%)	23 (96%)	1 (4%)	0.394
insecure	17 (100%)	0	23 (96%)	1 (4%)	0.394
sleepless	17 (100%)	0	23 (96%)	1 (4%)	0.482
lonely	16 (94%)	1 (6%)	21 (88%)	3 (12%)	
desperate	17 (100%)	0	24 (100%)	0	0.588
able to support patient	3 (19%)	13 (81%)	3 (12%)	21 (88%)	0.767
able to discuss with patient	1 (6%)	16 (94%)	2 (8%)	22 (92%)	0.767
need for more conversation with patient	16 (94%)	1 (6%)	22 (92%)	2 (8%)	0.718

Table 8.6. Questionnaire results, actual treatment groups and percentages of answers

	Day surgery N=18		Overnight stay N=26		P-value
	Yes	No	Yes	No	
Patient feels able to talk about cancer and her feelings during the first 24h after surgery	18(100%)	0	25(96%)	1(4%)	0.400
Patient feels that she has received enough support	18(100%)	0	24(92%)	2(8%)	0.228
Patient feels that she has received enough information	17(94%)	1 (6%)	25(96%)	1(4%)	0.789
Patient would choose day surgery in the future	18(100%)	0	10(39%)	16(61%)	0.000
Patient had to contact hospital after discharge	2(11%)	16(89%)	1(12%)	7(88%)	0.919
Spouse considers the length of hospital stay appropriate	17(100%)	0	23(96%)	1(4%)	0.000

### 8.3 Aesthetic and functional outcomes after breast-conserving surgery (study III)

#### Tumour and patient characteristics in conventional resection and oncoplastic resection groups

Patients in the oncoplastic resection group had significantly larger median tumour diameters (16.0 mm vs. 12.0 mm;  $p < 0.001$ ), and they had multifocal tumours more often (12% vs. 5%;  $p = 0.032$ ) and therefore also larger resection specimens (97 g vs. 61g;  $p < 0.001$ ) and node-positive cancer (30% vs. 22%;  $p = 0.029$ ). They also had lower quadrant tumour localisation more often (25% vs. 19%;  $p = 0.007$ ). ALND was performed significantly more often in the oncoplastic resection group ( $p = 0.007$ ), reflecting the difference in nodal status between groups. There was no statistical difference between groups in receiving radiation therapy and tumour bed boosters.

#### Surgery

Oncoplastic resection techniques were used as follows: 19 (22%) ratchet mammoplasties, 19 (22%) reduction mammoplasty techniques, 16 (19%) round block, 16 (19%) rotationplasty techniques, 12 (14%) extensive dual plane undermining and

4 (5%) other oncoplastic techniques. A contralateral breast symmetry procedure was performed in 20 (23%) patients in the oncoplastic group compared to 3 (1%) in the conventional resection group ( $p<0.001$ ). The re-resection rate due to tumour-positive margins was low in both groups: 12 patients (4%) in the conventional resection group and 3 patients (3%) in the oncoplastic group received a second resection. Due to the study plan, patients receiving mastectomy as a second operation were excluded. There was no difference in surgical complications requiring a reoperation, which were 5 (2%) in the conventional group and 3 (3%) in the oncoplastic group ( $p=0.309$ ). Axillary surgery, either SNB or ALND, was performed in 364 (96%) patients. Axillary surgery in the oncoplastic group was more extensive than in the conventional resection group: 35 (41%) received ALND in the oncoplastic group compared to 77 (26%) in the conventional resection group ( $p=0.007$ ).

### **Aesthetic outcome**

Aesthetic outcomes according to the BCTOS questionnaire were good in 284 (75%) patients. Good aesthetic outcomes were reported by 52 (61%) patients in the oncoplastic group and 230 patients (81%) in the conventional resection group ( $p<0.001$ ). The mean BCTOS aesthetic score was worse after oncoplastic resection than after conventional resection (mean 1.84 vs. 1.62;  $p=0.002$ ). Oncoplastic resection appears to be worse in almost every BCTOS aesthetic category (Table 8.7).

According to the author-created questionnaire, 217 patients (75%) in the conventional resection group and 61 patients (72%) in the oncoplastic resection group reported good or excellent aesthetic outcomes ( $p=0.441$ ). However, nipple position and appearance were significantly better in the conventional resection group; 112 (39%) patients reported excellent outcomes compared to 24 (29%) in the oncoplastic group ( $p=0.019$ ). The breast scar was also evaluated significantly better in the conventional resection group; excellent results were reported in 115 (40%) patients compared to 23 (27%) patients in the oncoplastic group ( $p=0.040$ ). For breast size, position and shape, there were no significant differences between groups.

Results in both the BCTOS and author-created questionnaires were in close agreement.

Table 8.7. BCTOS aesthetic subscale. Individual item comparison between groups

No difference or minimal difference in:	Conventional N=279 N (%)	Oncoplastic N=86 N (%)	p-value
Breast size	245 (86%)	60 (72%)	0.003
Breast texture	256 (90%)	65 (79%)	0.011
Nipple appearance	246 (88%)	59 (75%)	0.005
Breast shape	251 (88%)	63 (76%)	0.006
Breast position	260 (92%)	64 (77%)	<0.001
Breast Scar	237 (83%)	59 (72%)	0.024
Fit of clothing	266 (94%)	78 (93%)	0.706

### Factors influencing aesthetic outcomes

Patient and tumour characteristics were analysed more closely to examine reasons for poor aesthetic outcomes. Larger tumour diameter ( $p=0.033$ ), tumour multifocality ( $p=0.022$ ), weight of the resection specimen ( $p<0.001$ ) and oncoplastic surgery ( $p<0.001$ ) were predicting poor aesthetic outcomes in the BCTOS aesthetic subscale when all patients were included in the analyses. Aesthetic outcomes were not affected by tumour localisation ( $p=0.829$ ). Neither RT ( $p=0.261$ ) nor tumour bed boosters ( $p=0.231$ ) affected the BCTOS aesthetic outcome.

BCTOS aesthetic outcome results were analysed separately in the conventional and oncoplastic resection groups. Tumour multifocality ( $p=0.013$ ) remained a predictor of poor aesthetic outcomes in the conventional resection group but was not predictive in the oncoplastic resection group ( $p$ -value 0.836 for multifocality). Tumour localisation had no statistically significant effect on aesthetic outcomes. In the oncoplastic resection group, there was a significant difference in aesthetic outcomes between techniques ( $p=0.025$ ): extensive dual plane undermining provided poor aesthetic outcomes more often than others. Reduction mammoplasty and round block techniques provided good aesthetic outcomes most often.

The re-resection rate, surgical complication rate and contralateral breast symmetry procedure had no effect on BCTOS aesthetic outcomes.



### **Functional status**

Breast resection did not significantly affect functional status three years after surgery in the BCTOS questionnaire (BCTOS mean 1.345 in the conventional and 1.357 in the oncoplastic resection group;  $p=0.866$ ). Results were also analysed according to axillary procedure. As expected, the functional status was worse after ALND when compared with SNB only (BCTOS mean 1.255 after SNB and 1.547 after ALND;  $p<0.001$ ). In further analyses, we did not find other factors affecting functional status except the nodal stage, which determined the extent of axillary surgery.

## **8.4 Surgical treatment and prognosis in elderly patients of 80 years and older with breast cancer (Study IV)**

The median age of all patients was 84.5 years (range 80.0–101.9 years). The median age of patients receiving surgery was 84.1 years (range 80.0–101.9 years) and of those not receiving surgery, it was 86.5 years (range 82.2–90.8 years;  $p=0.347$ ). Altogether, 384 (86.1%) patients had one or more comorbidities: 254 (57.0%) had hypertension, 120 (27.0%) had ischaemic cardiac disease, 147 (33.0%) had another severe cardiovascular disease (i.e., atrial fibrillation, atherosclerosis), 65 (14.6%) had diabetes, 57 (12.8%) had dementia, 42 (9.4%) had pulmonary disease and 123 (37.0%) had some other severe disease such as rheumatoid arthritis, kidney failure or psychiatric disease. In 94 (21.1%) cases, the general condition of the patient influenced the treatment. Patient preference influenced the treatment in 43 (9.6%) cases.

### **Patients with surgery**

Surgery on the primary tumour was performed in 401 patients (90.0%). Surgery was performed under local anaesthesia in 12 patients (3%). Axillary surgery was performed in 352 (78.1%) patients. Altogether, 32 (26.2%) patients undergoing upfront ALND were axillary node-negative. In 69 (15.4%) patients, the general condition affected surgical treatment: surgery was either omitted or was less extensive. Recommended surgery was completely omitted in nine cases due to the patient's

preference. Altogether, 15 (3.7%) patients received mastectomy in order to avoid radiotherapy.

Adjuvant treatment was given to 302 (75.3%) patients. RT was received by 66 (56.4%) patients after BCS and 68 (23.9%) patients after mastectomy. Endocrine therapy was received by 259 (85.8%) patients. None of the patients received chemotherapy. In 27 (6.7%) cases, the general condition of the patient influenced the adjuvant treatment recommended by the medical oncologist. The patient's preference changed the recommended adjuvant treatment in 37 (9.2%) cases: 30 patients refused RT and 7 refused hormonal treatment.

### **Patients without surgery**

Surgery was not performed in 45 (10.1%) patients; it was omitted due to poor general condition in 31 (69%) of these patients. Nine (20%) patients refused surgery. In five (11%) patients' records, the reason for surgery omission was not clearly stated. Regarding comorbidities, patients without surgery had ischaemic heart disease (20 [44.4%] vs. 101 [25.2%];  $p=0.006$ ) and dementia (11 [24.4%] vs. 46 [11.4%];  $p=0.013$ ) significantly more often when compared to patients with surgery. There were no statistically significant differences between surgical and non-surgical treatment groups in the other recorded comorbidities. Endocrine therapy was given to 33 (73.3%) of the patients without surgery. None of the patients received RT or chemotherapy. Twelve (26.7%) did not receive any oncological treatment. Reasons for omitting treatment were very poor general condition in nine cases and patients' preference in two cases. In one case, the reason for omitting treatment was not clear from the patient report.

### **Survival**

For all patients, the median follow-up period was 52 months (range 0–117 months). For surgically treated patients, the median follow-up was 54 months (range 1–117 months) and for patients without surgery, it was 18 months (range 0–82 months). Overall, 226 (56%) patients receiving surgery died during the follow-up period. Of these deaths, 61 (27%) were breast cancer-related. None of the operated patients died within 30 days of surgery.

In patients with surgery, 81 (20%) had either histopathological T3-4 or N2-3 disease or both, and 41 (49%) had a postoperative CT scan. Nine patients had distant metastases diagnosed in their CT scans; four of the nine died of breast cancer 3–55 months after diagnosis, three died of causes unrelated to breast cancer and two were alive at the end of the follow-up at 49 and 83 months.

Of the non-surgically treated patients, 42 (93%) died during follow-up, 12 of (29%) died from breast cancer (Figure 8.2).

The OS was significantly better in patients who received surgical treatment than in patients who did not. Five-year OS was 50.6% in the surgical treatment group and 15.2% in the non-surgical treatment group ( $p < 0.001$ ; Figure 8.3a). Similarly, the BCSS was significantly better in patients with surgery when compared to patients without surgery. Five-year BCSS was 82.0% in patients with surgery and 56.0% in patients without surgery ( $p < 0.001$ ; Figure 8.3b), respectively.

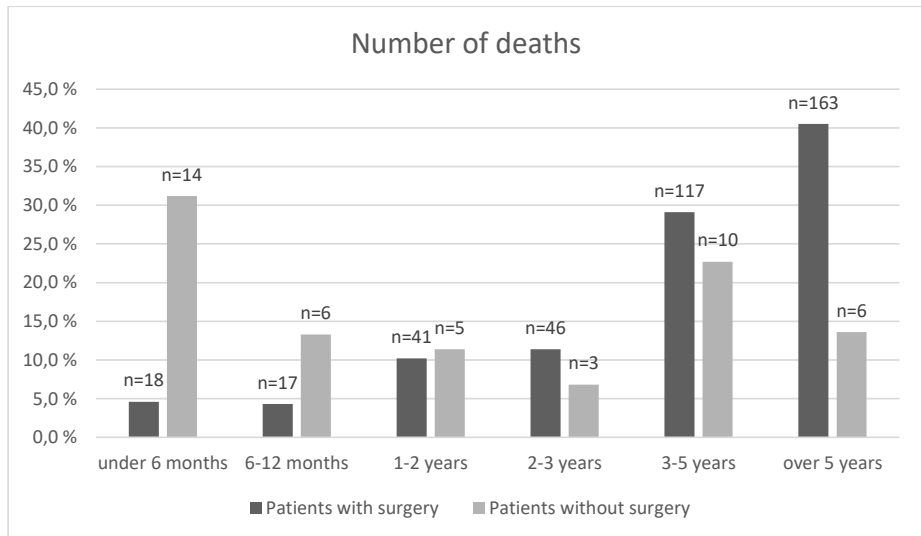


Figure 8.2. Number of deaths by treatment groups.

**Recurrences**

In the entire study population, local and regional recurrences were diagnosed in 16 (3.6%) and 6 (1.3%) patients, respectively. The median time from diagnosis to local recurrence was 13 months (range 3–49 months) and to regional lymph node recurrence 35 months (range 7–61 months). Distant metastases were reported in 80 (17.9%) patients. The median time from the primary diagnosis to distant metastases was 51 months (range 0–117 months), including the nine patients with distant metastases diagnosed in the postoperative CT scan. The five-year DDFS was 80.4% in patients with surgery and 53.3% in patients without surgery ( $p < 0.001$ ; Figure 8.3c). The number of breast cancer events by treatment groups is displayed in Table 8.8.

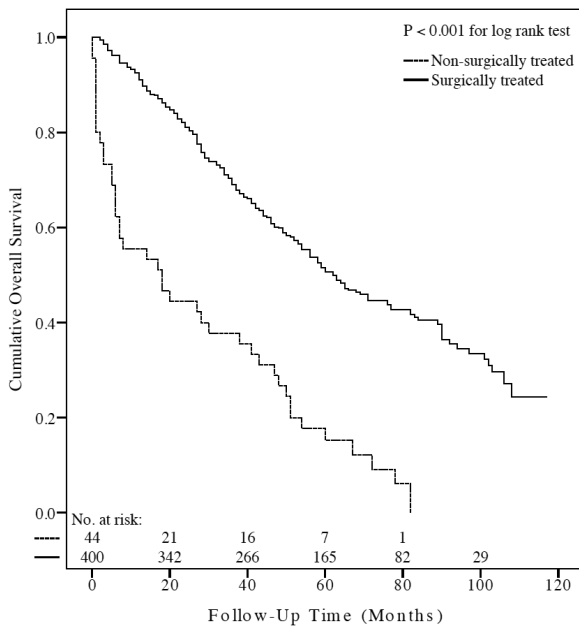


Figure 8.3a. Overall survival, comparison between surgical and non-surgical treatment groups.

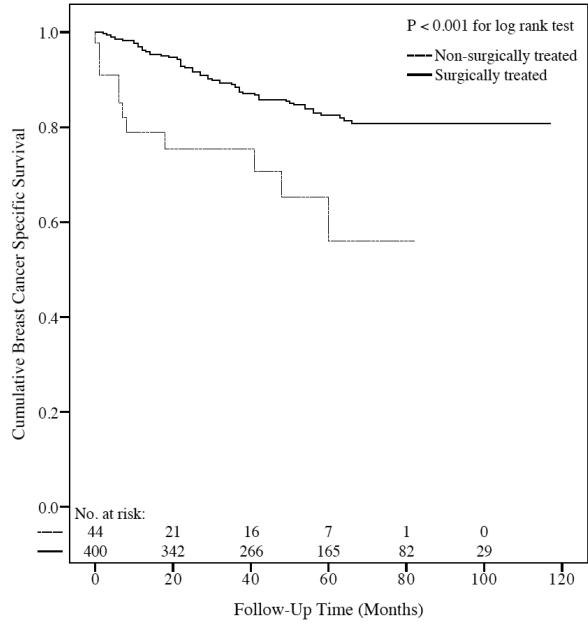


Figure 8.3b. Breast cancer-specific survival, comparison between surgical and non-surgical treatment groups.

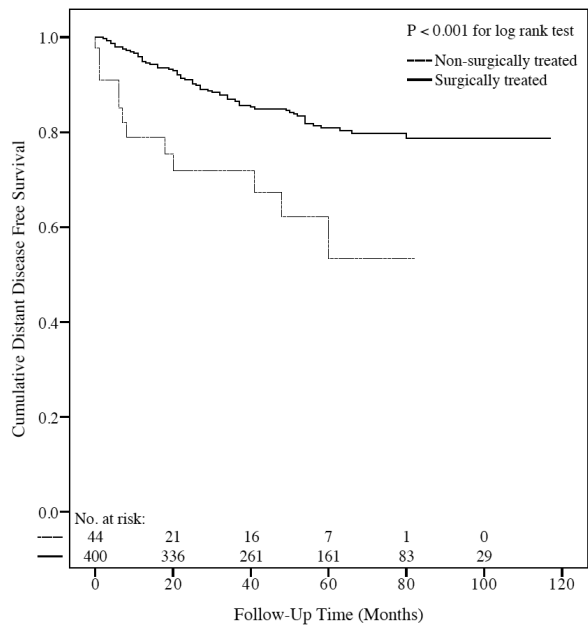


Figure 8.3c. Distant disease-free survival, comparison between surgical and non-surgical treatment groups.

Results

Table 8.8. Breast cancer events observed during follow-up according to treatment groups

		With Surgery	Without Surgery	
		N=401 (%)	N=45 (%)	<i>p (log rank)</i>
Follow-up (months)	Median	54	18	
	Range	1–117	0–82	
Events	Local recurrence	16 (4%)	0	0.298
	Contralateral breast cancer	0	0	
	Regional lymph node recurrence	5 (1%)	1 (2%)	0.218
	Distant metastasis	67 (17%)	13 (29%)	<0.001
	Breast cancer death	61 (15%)	12 (27%)	<0.001
	Death from other cause	165 (41%)	30 (67%)	<0.001

## 9 Discussion

### 9.1 Factors affecting breast cancer treatment and delays in treatment

#### Delays in surgical treatment

The referring institute has an impact on the breast cancer treatment process: patients referred by private clinics had significantly more additional diagnostic procedures. This possibly reflects differences in patient characteristics but also in clinical practice and expertise. Our study results confirm earlier findings that additional diagnostics, including biopsies as well as MRI, caused a delay in surgical treatment (Hulvat et al. 2010, Hukkinen et al. 2008.). The use of additional diagnostic procedures was not equivalent in hospitals treating breast cancer, with no plausible explanation from differences in population or tumour characteristics. We noted that variation in the use of additional diagnostic procedures between units places patients in unequal situations since the use of additional biopsies increases the waiting time until primary surgery.

#### Hospital volume

There are reports showing that the high surgical volume of a hospital is associated with better OS and a higher BCS rate (McDermott et al. 2013, Peltoniemi et al. 2011, Gooiker et al. 2010, Vrijens et al. 2012), whereas other studies indicate that the role of surgical volume is not substantial (Kuo et al. 2013, Siesling et al. 2014). In the present study, hospital volume had no effect on BCS rate. However, the overall BCS rate was surprisingly low at only 51%. Accordingly, the BCS rate has continuously increased since 2010, being approximately 70% in 2017. The positive impact of high-volume and treatment centralisation was seen in advanced oncoplastic and reconstructive techniques; most (83%) oncoplastic resections were performed in the two hospitals with the largest volumes. Similarly, IBR was clearly performed more often in patients treated in larger volume units.

Regardless of hospital volume, SNB appeared to be of high quality, with a proportion of unsuccessful SNB as low as about 1% and a rate of ALND of node-negative axillae acceptable. However, in low-volume hospitals, the rate of ALND in

node-negative patients was significantly higher without complete explanation from the study population, thus exposing patients to excess morbidity. During the last decade, indications for SNB have been extending rapidly (Mansel et al. 2006, Giuliano et al. 2011, Lucci et al. 2007, Rao et al. 2013). High-volume academic centres may have extended the indications of SNB faster, resulting in a higher quality of care. The role of SNB in axillary staging instead of ALND is well established, and a recent Cochrane review strengthens the SNB's status as the gold standard in axillary staging in clinically node-negative patients (Bromham et al. 2017).

In Finland, no official national quality criteria for breast cancer treatment have been established. The comparison of different breast cancer units as well as different countries is not simple since case-mix and organisational factors differ. In addition to tumour and nodal status-related factors, for example the existence of a screening program, national health insurance and funding policies as well as cultural differences may greatly influence treatment decisions.

### **Number of cancer operations**

A low number of cancer reoperations reflects optimal preoperative imaging, optimal preoperative diagnosis and the staging and surgical treatment itself. In our study, the re-excision rate due to insufficient resection margins was very low, less than 8%. It is clearly lower than in previous studies, reporting approximately 17–26% re-excision rates (McCahill et al. 2012, Wilke et al. 2014, Lovrics et al. 2010). On the other hand, the mastectomy rate was high, which may partly explain the low reoperation rate. Notably, the secondary mastectomy rate was almost 80%, even though the oncological safety of multiple excisions has been demonstrated earlier (Coopey et al. 2011), and secondary mastectomy rates reported earlier are clearly lower (McCahill et al. 2012, Lovrics et al. 2010). Also, only 12% of primary mastectomy patients received IBR, which is markedly less than the 40% recommended by the EUSOMA. However, national treatment recommendations are different in different countries, and for example, the need for postmastectomy RT influences treatment decisions. The IBR rate has significantly increased worldwide since the study period (Hong et al. 2018, Albornoz et al. 2013). In our unit, the rate of IBR was 19% in 2017. On the other hand, many patients who previously were



optimal candidates for mastectomy and IBR are currently treated with BCS, thanks to the oncoplastic approach.

### **Delays in adjuvant treatment**

Delays in the initiation of adjuvant treatments are associated with worse breast cancer outcomes in patients with grade III, HER2 positive and triple negative breast cancer (Gagliato et al. 2014, Richards et al. 1999), while no consensus exists on the optimal time interval between surgery and adjuvant treatment. In previous retrospective analyses, four weeks of delay in postoperative RT increases locoregional recurrences by 11% (Chen et al. 2008). Additionally, a four-week delay in adjuvant systemic therapies increases the risk of recurrence by 16% and mortality by 15% (Yu et al. 2013). In agreement with earlier studies, our results indicate that multiple cancer operations as well as IBR are causing delays in the initiation of adjuvant treatment. However, in our study, IBR was often performed as a second operation after failed BCS, which inevitably causes a delay in the initiation of adjuvant treatment. Currently at our institution, the patient will receive adjuvant chemotherapy before a second surgery to avoid delaying the initiation of chemotherapy. In the present study, the role of surgical complications in delaying adjuvant treatments could not be clarified properly since our data includes only complications that required surgical treatment.

## **9.2 Day surgery in breast cancer treatment**

Our study shows that patient satisfaction after BCS is equally good in day surgery patients as in patients with overnight stay. The patients felt that they received sufficient information about their disease as well as counselling and emotional support regardless of the hospital stay. Patient satisfaction with day surgery was high; all day surgery patients would choose day surgery again in the future. However, two-thirds of patients in the overnight stay group would have chosen the same treatment again. In fact, patients may prefer the procedure they have already experienced but may fear the unknown.

The rate of day surgical discharge was surprisingly low. In earlier studies, the discharge rate from day surgery in breast cancer patients was higher, between 86% and 100% in selected study populations (Marchal et al. 2005, McManus et al. 1994,

Seltzer et al. 1995, Marrazzo et al. 2007, Dooley et al. 2002). In our study, the most common reasons for overnight stay were ALND, inability to fulfil day surgical discharge criteria and use of drainages. This study was started in 2008 when there was not much knowledge about day surgery in breast cancer patients. Currently, neither ALND nor drainage are contraindications to day surgery at our unit. Moreover, ALND is no longer routine in all sentinel node-positive patients. Furthermore, breast conservation is feasible more often due to the evolution of oncoplastic techniques. Therefore, day surgery is a feasible option in an increasing number of breast cancer patients. Despite increasing possibilities for day surgery, general day surgical criteria set limits for discharge. In urban areas, distance is rarely the problem in day surgical discharge. However, an adult companion may not always be available.

### **9.3 Aesthetic outcomes after breast-conserving surgery**

#### **Factors affecting aesthetic outcomes**

Our study results indicate that conventional wide local excision provides good aesthetic outcomes in correctly selected patients. Patient-evaluated aesthetic outcomes were good or excellent in the majority of patients. Contrary to previous studies (Santos et al. 2015, Foersterling et al. 2014, Rezai et al. 2015), the tumour location did not affect the aesthetic outcome, even in the conventional resection group. Successful patient selection and surgical technique may partly explain our better aesthetic results after conventional resection. Moreover, our conventional wide local excision includes adequate mobilisation and closure of breast tissue and actually represents level 1 oncoplastic surgery (Clough et al. 2010). A larger resection specimen weight appears to be a predictor of poor aesthetic outcomes in this study as well as in previous reports (Hennings et al. 2015), although opposite results have been reported (Rezai et al. 2015). However, we have no data on the tumour-breast volume ratio, which might represent the extent of resection better than resection specimen weight alone. In our study, either re-excision, complication surgery or radiation boost have no effect on aesthetic outcomes, differing from previous studies (Heil et al. 2012, Immink et al. 2012, Vrieling et al. 2000). Nevertheless, the number of patients receiving surgery

because of complication or re-excision was low in this population; thus, we consider these results unreliable and incomparable to earlier studies.

### **Oncoplastic surgery**

Interestingly, on the BCTOS aesthetic subscale, nearly all individual items were worse after oncoplastic resection than after conventional resection. However, this finding is most likely due to selection bias. Oncoplastic resection allows the excision of larger or multifocal tumours to obtain the best possible aesthetic outcomes. Accordingly, the oncoplastic resection group patients had large or multifocal tumours more often, and they also received more extensive axillary surgery, as reported in earlier studies (Santos et al. 2015). Larger tumour diameter and tumour multifocality had a negative effect on aesthetic outcomes as expected and previously reported (Heil et al. 2012), although a statistically significant difference was not found when analysing the oncoplastic resection group alone.

A more extensive remodeling of breast tissue, performed in oncoplastic surgery, possibly leads to a notable difference in breast firmness and shape. The main goal of oncoplastic BCS is to avoid deformity. Many oncoplastic techniques cause more visible and longer scars and include centralisation of the nipple-areola complex, which may affect the patient's appraisal. With no deformity, the patient focus is on the scar and symmetry. Moreover, patients receiving oncoplastic resection have no knowledge about how poor the aesthetic outcome could be after conventional resection in their case.

For the aforementioned reasons, candidates for oncoplastic resection need to be informed about longer scars and possible asymmetry of the breasts. The need for a symmetrising procedure of the healthy breast needs to be evaluated and discussed with the patient. Thorough information about the patient is crucial in setting realistic expectations. Even after excellent aesthetic results, the patient may be dissatisfied. On the other hand, many patients are happy with their aesthetic outcomes, even when evaluated as inferior by the surgeon.

Our study results indicate that oncoplastic surgery should not be a value itself. Conventional resection provides good or even excellent aesthetic outcomes in

correctly selected patients. The surgical technique in breast conservation should be the simplest and likely to provide a good aesthetic outcome.

### **Methods in the evaluation of aesthetic outcomes**

Although aesthetic outcome is an essential quality indicator and an important endpoint in breast cancer surgery, treatment outcome measurement and especially surgical issues after BCT are lacking in standardised evaluation methods. Wide variation exists in the methodology of previous studies evaluating aesthetic outcomes after BCT, making a comparison of results difficult (Heil et al. 2011, Santos et al. 2015, Foersterling et al. 2014). A systematic review by Chen et al. (2010) underlines the need for better evaluation tools. This need is recognised: the BCTOS questionnaire is further developed for better usability (Hennings et al. 2018) and the Breast-Q questionnaire has a new module (the Breast-Q: breast-conserving therapy) for women undergoing lumpectomy with and without radiation for the treatment of breast cancer. Patient self-evaluation is acknowledged as a valuable method since the subjective experience is central to the assessment of QoL (Heil et al. 2010, Stanton et al. 2001).

Objective outcome measures are another way of evaluating aesthetic outcomes after breast cancer surgery. Within trials, a panel evaluation of photographs of the breast(s) is commonly used to evaluate cosmetic outcomes. A panel evaluation is time-consuming and performed without a standardised measurement technique. In recent years, digitalised assessment techniques have been introduced. An example of one such technique is the BCCT.core software (Cardoso et al. 2007). A recent publication shows a good correlation between panel evaluation and BCCT.core as well as between these and Breast-Q. Thus, any of these methods could possibly be used in trials to evaluate aesthetic outcomes and QoL (Lagendijk et al. 2017).

The most appropriate time to evaluate aesthetic outcomes after BCT and RT is at least two years postoperatively, due to the long-term effects of irradiation (Vrieling et al. 2000, Haloua et al. 2013). Previous studies concerning aesthetic outcomes after BCT and oncoplastic surgery also differ greatly regarding the evaluation time-point of aesthetic outcomes, varying from the immediate postoperative time (Foersterling et al. 2014, Heil et al. 2012) to several years after surgery (Immink et al. 2012). A study by Hennings et al. (2015) did not find a difference in aesthetic outcomes postoperatively

after BCT versus at the 1–2 year follow-up. Aesthetic outcomes are commonly evaluated one year after surgery when the breast is still oedematic after RT, especially in patients who have received adjuvant chemotherapy before RT. Fibrosis and scar retraction occur later, deteriorating aesthetic outcomes. We evaluated aesthetic outcomes three years after surgery, thus waiting a sufficient amount of time after radiation therapy has passed to visualise the effects of irradiation and the booster.

## **9.4 Surgical treatment and survival in breast cancer patients over 80 years of age**

The management of elderly patients with breast cancer is complex. Treatment guidelines are based on trials including mainly younger patients; elderly patients are often excluded. Thus, treatment guidelines are not always generalisable to elderly patients. Also, treatment strategies for early breast cancer vary markedly, both nationally and internationally. In two recent studies, elderly patient populations from European countries were compared (Schuil et al. 2018, Derks et al. 2018). These studies found great variance in primary treatment: in the British population, 47.8% of patients received surgery in comparison to 90.5% in the Dutch population (Schuil et al. 2018). Evidently, older patients have more comorbidities and medications that possibly interact with cancer treatment. Several studies report undertreatment of elderly patients, and the latest EUSOMA update recognised that that level of treatment in elderly patients is partly below the minimum standards of care (Biganzoli et al. 2017, Angarita et al. 2015). However, there is strong evidence that a more conservative approach to primary surgery and postoperative radiation therapy may be adopted in older patients without affecting longer-term outcomes (EBCTCG 2005b, Tinterri et al. 2014).

### **Surgery and survival**

In our elderly population, the surgical treatment rate was high: 90% of patients received surgical treatment. Patients receiving surgical treatment had better OS when compared with patients without surgical treatment. BCSS was also significantly better in surgically treated patients. However, both five-year OS and BCSS are lower than Finnish national estimates for all breast cancer patients. The better survival observed

in the patients with surgery may also be due to selection bias, at least in part. Patients with better physical conditions and therefore also longer life expectancy received surgical treatment more often. Accordingly, deaths from any cause during the first year of diagnosis were more frequent in patients without surgery, confirming successful patient selection when omitting surgical treatment. Moreover, we really do not know what the outcome of the patients with surgical treatment would have been if treated with endocrine therapy only. In Derks et al. (2018), variation in treatment strategies among elderly patients over 70 years of age was found. Interestingly, in early stage breast cancer, potential overtreatment was detected. In advanced stages, however, potential surgical undertreatment was observed.

In the present study, the proportion of mastectomies was also high when compared to the Study I population. A similar trend towards more extensive procedures in the elderly can be seen in previous studies (Sierink et al. 2014, Eaker et al. 2006, Kiderlen et al. 2017, van de Water et al. 2014). Mastectomy has adverse effects: an imbalance due to the remaining heavy breast can cause functional impairment, postoperative seroma formation is more common, and self-evidently, the aesthetic outcome is also worse. Aesthetic outcomes after breast cancer surgery may be less important in elderly patients, but impairment of functional status should be considered carefully in this patient group to avoid negative effects in terms of QoL. Mastectomy was also performed to avoid RT after BCS, even though previous studies have clearly shown that RT after BCS does not provide a survival benefit but lowers the risk of local recurrence also in elderly women (Hughes et al. 2013, EBCTCG 2000, Tinterri et al. 2009, Tinterri et al. 2014, Kunkler et al. 2015, van de Water et al. 2014). For these reasons, mastectomy should not be routinely performed, even if RT after breast conservation cannot be given due to poor general condition or to patient preference. Lately, this was stated in the updated Finnish national guidelines of breast cancer treatment and in the EUSOMA treatment recommendation update in 2017 (Biganzoli et al. 2017).

In our study, surgical treatment in elderly patients was safe: there was no immediate post-operative mortality. One-third of the patients in the surgical treatment group died within three years of surgery, 35 within the first postoperative year. Most of the deaths were from causes other than breast cancer. We can assume these patients did not have any survival benefit from surgery and thus may be considered as

surgically overtreated. On the other hand, one of the most important aims of breast cancer treatment in the elderly is to provide local disease control. Patients may have benefited from surgery in terms of local disease control, even though surgery did not provide a survival benefit.

### **Local disease control**

Primary endocrine treatment instead of surgical treatment has become more common during the last decade in the treatment of breast cancer in the elderly (Kiderlen et al. 2017). If local disease progression during primary endocrine treatment occurs, surgery should be reconsidered. However, at the time of local disease progression, the patient is older and often also less physically fit than during the time of their primary diagnosis. Moreover, for local disease control, a more extensive surgery – mastectomy - may be needed. Therefore, local disease progression could seriously affect QoL, which is considered of major importance in elderly patients. Our results emphasise that local treatment, especially surgery, is the cornerstone of treatment in early breast cancer, even among the elderly. Although breast cancer treatment in elderly patients may become more conservative, the superior role of primary surgical treatment in local control as well as in OS and BCSS should be kept in mind.

### **Decision-making**

Breast surgeons and other members of the multidisciplinary team have an important role in tailoring the treatment (Angarita et al. 2015, Shumway et al. 2017, Morgan et al. 2015). However, evaluating life expectancy even in the presence of serious comorbidities is difficult. Functionality and QoL in the elderly may persist at the same level for years despite various comorbidities and frailty. It is highly important to tailor the treatment of elderly patients on a case-by-case basis, while still aiming for the best oncological outcome without sacrificing QoL.

It is noteworthy that elderly patients are less likely to search for information from other sources such as the internet and may rely strongly on their physician's recommendations. Interestingly, in a study by Shumway et al. 2017, nearly half the surgeons and radiation oncologists reported that it takes more effort to advise a patient that they do not need RT than it does to recommend it. Thus, in fact, a patient's

## *Discussion*

decision about treatment may actually reflect the physician's preference and attitude. The latest updates on breast cancer treatment recommendations have considered elderly patients' characteristics, thus supporting the physician's decision-making.



## 10 Limitations of the study

The major limitation of studies I, III and IV lies in their retrospective, non-randomised study setting. Data integration from multiple sources is time-consuming and prone to errors, which also delayed the publication of our results. In Study I, we focused on factors affecting the quality of surgery and their impacts on waiting times, but not their impact on survival and QoL. In Studies III and IV, selection bias due to the retrospective, non-randomised setting was detected. In study III, the number of patients in the oncoplastic group was small, and some significant associations may have remained undetected. The study period also coincided with the beginning of the oncoplastic era in our unit, and since then, oncoplastic knowledge and skills of our surgeons have improved. Additionally, in Study IV, no geriatric assessment tools were used in clinical decision-making. Therefore, a multivariable analysis evaluating the influence surgery, tumour characteristics and comorbidities of OS and BCSS could not be performed.

In Study II, the number of study patients was small, especially those who were actually discharged on the operation day. The small number of patients may have impaired the detection of some differences between the treatment groups. Moreover, the questionnaires were designed by the researchers, and validated QoL questionnaires were not used. The response rate was also rather low.

## **11 Conclusions**

The quality of preoperative diagnostics has a great impact on the timely treatment of breast cancer. The positive impact of high-volume hospitals became evident in the more frequent use of contemporary breast cancer surgeries, such as SNB, IBR and oncoplastic resection.

Day surgery is feasible in breast surgery after BCS and SNB.

Overall patient satisfaction after BCS is high. Conventional resection provides good or even excellent aesthetic outcomes in correctly selected patients. Oncoplastic resection enables BCT in patients with larger and multifocal tumours with a favourable aesthetic outcome.

In elderly breast cancer patients, OS and BCSS were better in surgically treated patients. Local and regional recurrence rates were low. Surgical treatment was safe in this elderly population.

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## Appendix 1

### Leikatun rinnan ulkonäkö - kyselylomake

1. Pyydämme Teitä arvioimaan rintasyöpäleikkauksen esteettistä tulosta eli valitsemalla vaihtoehdon joka mielestänne parhaiten kuvaa leikatun rinnan ulkonäköä

1. Erinomainen
2. Hyvä
3. Ei hyvä eikä huono
4. Huono
5. Erittäin huono

A) Rinnan koko

1                      2                      3                      4                      5

B) Nännin sijainti ja ulkonäkö

1                      2                      3                      4                      5

C) Rinnan muoto ja asento

1                      2                      3                      4                      5

D) Leikkausarpi

1                      2                      3                      4                      5

E) Rintaliivien istuvuus

1                      2                      3                      4                      5

F) Symmetria eli samankaltaisuus toisen rinnan kanssa

1                      2                      3                      4                      5

G) Yleisarvosana rinnan ulkonäölle

1                      2                      3                      4                      5

2. Aiheuttaako leikatun rinnan ulkonäkö Teille ongelmia, oletteko esim. joutunut luopumaan jostain harrastuksesta, kuten uimahallissa uimisesta tai onko vaikea löytää sopivia rintaliivejä

- 1) Ei lainkaan ongelmia
- 2) Jonkin verran ongelmia
- 3) Huomattavia ongelmia

3. Jos leikatun rinnan ulkonäkö aiheuttaa ongelmia, minkälaisia nämä ongelmat ovat?

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