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SURGICAL TREATMENT OF BREAST CANCER AND PATIENT REPORTED OUTCOMES

SPECIAL EMPHASIS ON HEALTH-RELATED QUALITY OF LIFE AND THE COST OF CARE

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ACADEMIC DISSERTATION

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ABSTRACT

Breast cancer patients' health-related quality of life (HRQoL) is an important quality indicator in breast cancer care. HRQoL is recommended to be studied with both generic and disease-specific HRQoL measuring tools.

Different techniques in breast cancer surgery affect the patients' well-being in different ways. Patient-dependent factors and tumour biology both have their impact on treatment choices. Knowledge of breast cancer patients' HRQoL in relation to different surgical methods is still scarce. The method and timing of breast reconstruction is under debate between immediate breast reconstruction (IBR) and delayed breast reconstruction (DR). Pressure on societies caused by the rising incidence of breast cancer is associated with a need for health-economic evaluations to guide resource allocation on cancer treatment.

This thesis evaluates breast cancer patients' HRQoL in different states of the disease and compares different measuring tools to detect differences between them and produce data on their validity. Different surgical methods to treat breast cancer are studied in relation to HRQoL. All available breast reconstruction methods and the timing of reconstruction are evaluated. The cost of care from the care providers' perspective is also described during a two-year prospective follow-up. This thesis produces new information concerning HRQoL measuring tools and their usability in breast cancer; how breast cancer treatments performed in Finland affect the patients' HRQoL and how the costs of different surgical methods are generated.

This thesis is based on two study populations. 840 breast cancer patients treated in the Helsinki and Uusimaa Hospital district from 2009 to 2011 were recruited to a cross-sectional observation study as part of a study of prostate, colorectal, and breast cancer patients. Patients filled in an informed consent form and three different HRQoL measuring tools: EQ5D-3L (including VAS), 15D and EORTC QLQ C-30 BR23. Their answers were analysed with linear, stepwise regression analyses. Individual study population of 1065 patients with primary breast cancer were recruited to a prospective study from year 2008 to 2015 in Helsinki and Uusimaa Hospital District. Recruited patients filled in an informed consent form and two HRQoL questionnaires: the generic 15D and breast-cancer specific EORTC QLQ C-30 BR23. The questionnaires were handed out at the first hospital visit and repeated via mail at 3, 6, 12 and 24 months later. Clinical data were collected from hospital records, combined with HRQoL results and then analysed with statistical methods. Data on cost of care were obtained from the ECOMED database, analysed and presented according to the surgical method.

EQ5D was associated with a high ceiling effect with 41% of the patients reporting perfect health; other measuring tools performed with less ceiling. Breast cancer patients' HRQoL deteriorated along the disease progression with patients reporting fatigue, pain and sleeping disorder symptoms.

The prospective follow-up included 351 mastectomies, 415 breast resections, 248 oncoplastic resections and 51 immediate breast reconstructions (IBR). 402 patients went through axillary clearance. 840 patients (79% of all) received radiation therapy and 523 (49%) chemotherapy, 766 (72%) patients had endocrine treatment, and 119 (11%) patients had targeted therapy (anti HER2- medication). 41 patients had later corrective surgery and 34 patients had DR. HRQoL was affected by disease status and by the disease burden. Higher Grade, N-class and BMI (body-mass index) correlated with poorer HRQoL at 3 months. The effect of N- and M-class and receiving chemotherapy still correlated with poorer HRQoL at 24 months. Active smoking correlated with complications. Mastectomy patients had the poorest HRQoL throughout the study period and they reported the most pain and arm symptoms. Patients operated on with oncoplastic techniques had the best body image at 24 months. Reconstruction patients had the best physical and sexual functioning scores at 24 months. Reconstruction patients' recovery after treatments was the slowest. No difference was found between different autologous reconstruction methods. The lowest costs from surgery were observed in BCS patients (mean 6015 euros). Mastectomy was associated with mean costs of 8114 euros, IBR with 18 217 euros, and DR with 19 041 euros.

EQ5D-3L is associated with high ceiling effects. Consequently, care must be taken when choosing HRQoL measuring tools. Breast cancer patients frequently reported insomnia, pain and fatigue, indicating the main focus on symptom handling. Mastectomy patients are at risk of poor HRQoL and higher symptom burden. Oncoplastic techniques produce good HRQoL and body image. Breast reconstruction produces good HRQoL, physical - and sexual-functioning scores, but the improvement in HRQoL materialises later than in BCS patients. Breast reconstruction method and timing should be tailored individually, and no patient should be pushed toward reconstruction before being ready for it. The cost difference between IBR and DR is relatively small, so the cost of reconstructive surgery should not be a factor in the decision making.

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Appendix 1 : patient information and questionnaires for Study I

Appendix 2 : patient information and EORTC QLQ BR-23 questionnaire for Studies II-IV

1. ORIGINAL PUBLICATIONS

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

I Rautalin M, Färkkilä N, Sintonen H, Saarto T, Taari K, Jahkola T, Roine RP. Health-related quality of life in different states of breast cancer - comparing different instruments. Acta Oncol 57(5):622-628, 2018

II Rautalin M, Jahkola T, Roine RP. Surgery and health-related quality of life - A prospective follow up study on breast cancer patients in Finland. Eur J Surg Oncol 47(7):1581-1587, 2021

III Rautalin M, Jahkola T, Roine RP. Breast Reconstruction-Prospective Follow up on Breast Cancer Patients' Health-Related Quality of Life. World J Surg 46(4):836-844, 2022

IV Rautalin M, Jahkola T, Roine RP. The cost of breast cancer surgery – is the money spent reflected on health-related quality of life? In Vivo 36(5):2279-2286, 2022

2. ABBREVIATIONS

ACOSOG	The American College of Surgeons Oncology Group
AJCC	American Joint Committee on Cancer
AMAROS	After Mapping of the Axilla, Radiotherapy or Surgery?
BIA-ALCL	Breast Implant Associated – Anaplastic Large Cell Lymphoma
BCS	Breast Conserving Surgery
CCI	Charlson Comorbidity Index
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
DIEP	Deep Inferior Epigastric Artery Perforator
DR	Delayed Breast Reconstruction
EORTC	European Organization for Research and Treatment of Cancer
-QLQ C30	- Quality of Life Questionnaire
EQ-5D	Euro Quality of life (Group)- 5 Dimensional questionnaire
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
EUSOMA	European Society of Breast Cancer Specialists
HER-2	Human Epidermal growth factor 2 Receptor
HRQoL	Health Related Quality of Life
IBR	Immediate Breast Reconstruction
ICD-10	International Classification for Diseases, 10 th Revision
IMA	Internal Mammary Artery
LAP	Lumbal Artery Perforator
LD	Latissimus dorsi
MID	Minimal Important Difference
MRM	Modified Radical Mastectomy
NCSP	Nordic Classification of Surgical Procedures
NSM	Nipple Sparing Mastectomy
PR	Progesterone receptor
QI	Quality Indicator
SIEA	Superficial Inferior Epigastric Artery Perforator
SNB	Sentinel Node Biopsy
SSM	Skin Sparing Mastectomy
TMG	Transverse Musculocutaneous Gracilis
TNM	Tumour- Nodal-Metastasis classification
TRAM	Transverse Rectus Abdominis Muscle
UICC	Union for International Cancer Control
VAS	Visual Analogue Scale
WHO	World Health Organization
15D	15Dimensional HRQoL questionnaire

3. INTRODUCTION

Breast cancer is the most common cancer in women worldwide, and its incidence has been predicted to rise for a long time (Ferlay et al. 2020; Sung et al. 2021). This stresses the huge importance of setting standards for breast cancer treatments, for maintaining high quality of care, and for continuous evaluation of the quality of breast cancer treatments. HRQoL is an important outcome of breast cancer treatment alongside traditional endpoints of overall and disease-specific survival and response to treatments (Radice et al. 2003; Biganzoli et al. 2017). European guidelines suggest that HRQoL should be evaluated routinely as one of the listed Quality Indicators of breast cancer care (Biganzoli et al. 2017; Biganzoli et al. 2020; Cardoso et al 2019). An international group of experts listed knowledge gaps on oncoplastic surgery and highlighted HRQoL as a measure to be included in future studies and measured preferably by both generic and disease-specific measuring tools (Weber et al. 2020).

The treatment of breast cancer is tailored individually depending on the patient's health status and the specific features of the disease (Suomen Rintasyöpäryhmä 2022). Global and national guidelines set the framework for this individual planning, but differences exist between countries regarding treatment options, resources and availability (Sung et al. 2021). Breast conserving surgery has been proven to be equally as safe as mastectomy or even better when combined with radiation therapy (Early Breast Cancer Trialists' Collaborative Group 2011; Fisher et al. 2002; Kim et al. 2021; Veronesi et al. 2002). Oncoplastic techniques and breast reconstruction provide good cosmesis and HRQoL, but comparisons of all different surgical techniques are still scarce. Published studies have often compared allogenous methods (reconstruction with implants) to one or two different autologous methods (reconstruction with own tissue) and have often used single HRQoL measuring tool (Blackburn et al. 2018; Flanagan et al. 2019). The majority of studies have been retrospective. The need for prospective studies has been noted (Weber et al. 2020).

HRQoL can be measured with tools that are either generic or disease specific. Generic measuring tools produce health utility scores and can produce health profiles. Disease-specific measuring tools often produce symptom scores and knowledge on which specific areas of functioning are affected by the disease or by the treatment of the disease. A problem with HRQoL measuring tools is that they can be biased with gender, cultural or educational background and may produce floor or ceiling effects (Chopra et al. 2012). A floor effect means that the patient answers the question with the lowest possible value, whereas the ceiling effect is the opposite, i.e., the patient's answer indicates perfect health in that particular question. The use of both generic- and disease-specific

measuring tools reduces the problem of biased HRQoL results. The measuring tools should be validated in patients' native language.

Information about different treatment options is available for the patient from many different forums. Growing awareness of treatment options might generate demand for these options because the incidence of breast cancer is rising. This produces pressure on the societies with rising costs of care. Health economics play an important role as part of decision making in resource allocation. Data on costs of different treatment options is essential. HRQoL results combined with the oncological safety of treatments and the costs of care strengthen the planning of health-care systems as the costs are rising worldwide (Radice et al. 2003; Prager et al. 2018).

The aim of this study was to evaluate breast cancer patients' HRQoL in different states of the disease and to compare different measuring tools. The goal was to see how patients perceive different surgical methods used in breast cancer treatment in Finland, how HRQoL is affected over time, and to see if there are differences between surgical methods and HRQoL outcomes. Furthermore, the aim was to evaluate if there are differences in breast reconstruction methods and their timing regarding HRQoL and to describe the costs different treatments produce over a two-year follow-up from the care providers' perspective. This thesis strengthens the knowledge of the most prevalent symptoms that patients experience during breast cancer treatment and thus will help to optimise future cancer treatments and breast cancer surgeries.

4. REVIEW OF THE LITERATURE

4.1 Breast cancer incidence and prognosis

Female breast cancer has been recognised as the most commonly diagnosed cancer by 2020 worldwide cancer statistics. An estimated 2.3 million new cases of breast cancer diagnoses and 685 000 breast cancer-related deaths were recorded in 2020 globally. The highest incidence rates for breast cancer are recorded in Australia/New Zealand, Northern America and Western and Northern Europe. The global cancer burden is expected to rise to 28.4 million cases by 2040 (Sung et al. 2021).

Finland, with a population of 5.531 million, had 34 760 new cancer diagnoses in 2020. Of those, 4 885 were female breast cancers. 13 201 cancer-related deaths were recorded in 2020, and 968 of those were breast-cancer related deaths. The age-adjusted incidence of breast cancer was 161.2/ 100 000 life years and age-adjusted mortality 28.6/ 100 000 life years. The 5-year survival rate was 91% in all age groups for breast cancer patients (Pitkäniemi et al. 2022).

Mammography screening has been proven to reduce breast cancer mortality (Beckett et al. 2003; Tabar et al. 2003). Women in Finland aged 50 to 69 years are invited to participate in breast cancer screening every second year. Over 80% of those invited attend the screening. Approximately two thirds of breast cancers in Finnish women aged 50 to 69 years are found in screenings (Finnish cancer registry). Finland follows the WHO's recommendation for screening. Early detection of the disease and adjuvant treatments are the most affecting factors of breast cancer prognosis. Mammography screening is an important factor enabling early detection (Burstein et al. 2021).

Known risk factors for cancer also apply to breast cancer: excessive alcohol consumption, smoking, obesity and low physical activity all impact the morbidity and mortality of breast cancer and increase wound healing problems (Sung et al. 2021; Sørensen et al. 2002). In addition to active smoking, the exposure to smoke (passive smoking) has been linked to increased risk of breast cancer (Carreras et al. 2020; Macacu et al. 2015). Quitting smoking after breast cancer diagnosis may enhance the prognosis (Izano et al. 2015). Ageing, early menarche, childlessness, age at first delivery and dense breast tissue detected in mammography are also risk factors for breast cancer. A small part (5 to 10%) of breast cancers are related to dominantly herited mutations in genes, 30% of those being BRCA1 or BRCA2-gene mutations (Suomen Rintasyöpäryhmä 2022).

4.2 Factors affecting breast cancer treatment path

Breast cancer diagnostics is based on clinical examination, imaging, and pathological assessment of the tumour (Burstein et al. 2021). Treatment choices are based on international and national guidelines. The European Society for Medical Oncology (ESMO) released an updated version of guidelines for diagnosis, treatment, and follow-up for early breast cancer in 2019, as the Finnish breast cancer group also did (Suomen Rintasyöpäryhmä ry) for national guidelines (Cardoso et al. 2019; Jahkola et al. 2021; Suomen Rintasyöpäryhmä 2022).

The choice of surgical method is based not only on the guidelines but also on the patient's individual situation. The tumour characteristics, health status and personal preferences all affect each patient's treatment path. Oncological safety must be the top priority in all choices that are made (Chakravorty et al. 2012; Fisher et al. 2002; Mustonen et al. 2004; Rautalin et al. 2021).

Many aspects must be considered in the decision making for breast cancer surgery and treatments. The tumour is excised in a breast conserving manner (breast conserving surgery, BCS): either by straight-forward excision of the tumour; by more complex or larger excision of the tumour with reshaping or repositioning of breast tissue (oncoplastic surgery); or with total removal of the breast gland, mastectomy. The possibilities of surgery depend, among other things, on the size of the tumour, the size of the breast and their relation (Clough et al. 2010). Tumour biology sets its demands for treatment: small tumours with good prognostic features such as estrogen positivity or low proliferation activity are handled differently than bigger tumours with possible multicentricity, high proliferation activity and the absence of hormonal receptors (Cardoso et al. 2019; Veronesi et al. 2005). Tumour margins must be declared free of cancer (von Smitten 2008; Suomen Rintasyöpäryhmä 2022). The use of neoadjuvant treatments is increasing, and this partly enables BCS for large tumours that earlier led to mastectomy. Neoadjuvant treatments are recommended if the tumour is more than 5 cm in diameter or, in some cases, larger than 3 cm with susupision of positive nodes in the axilla (Suomen Rintasyöpäryhmä 2022).

BCS combined with radiation therapy is recommended when applicable, but other surgical options step in when this is not the case. The choice between mastectomy alone or breast reconstruction can be a challenging process. Breast reconstruction can be performed immediately at the first breast cancer surgery operation (immediate breast reconstruction, IBR) or in a delayed setting (delayed breast reconstruction, DR) after oncological treatments have ended. Patients should be offered a consultation regarding breast reconstruction if mastectomy cannot be avoided (Jahkola et al. 2021).

Adjuvant treatments are administered according to the patients' individual situation (Cardoso et al. 2019; Suomen Rintasyöpäryhmä ry 2022).

Comparison of different surgical approaches and the timing of corrective surgery is challenging and still lacks consensus on which choice to offer patients (Neyt et al. 2005; Rautalin et al. 2022; Santosa et al. 2018; Veronesi et al. 2005; Zhong et al. 2016). Numerous studies have addressed the question of timing and surgical method, yet the results remain debatable. Breast reconstruction produces good HRQoL, but past studies reporting this have mostly been retrospective or have compared limited different operating methods. The need for prospective studies has been stated repeatedly.

4.2.1 Prognostic and predictive factors

The staging of breast cancer is based on the TNM classification provided by the AJCC Cancer Staging Manual (8th Edition) and the TNM classification for malignant tumours (8th Edition) that the European classification UICC has developed (Brierley et al. 2017). The latest AJCC adjustments were presented in 2017 (Giuliano et al. 2017). Prognostic factors in early breast cancer include the size of the tumour, the presence of hormonal receptors, the proliferation activity of the tumour and whether the disease has spread to regional lymph nodes. Estrogen receptor positiveness is linked to better prognosis of the cancer, while triple negative (the tumour has no receptors to estrogen, progesterone or HER-2, human epidermal growth factor receptor 2) has the worst prognosis (Aaltomaa et al. 1991). High proliferation activity (Ki-67 expression) is also an indicator for poorer prognosis (Cuzick et al. 2011; Nielsen et al. 2021). Due to the development of targeted therapies, the prognosis of HER-2- positive disease has improved (Burstein et al. 2021; Cardoso et al. 2019, Tiainen et Utriainen 2022).

4.2.2 Patient-dependent factors that affect the choice of surgery

In planning and deciding the path of breast cancer care for each patient, individual characteristics influence the decisions. The patient's own wish is an important determinant, and the decision on the treatment choice should be made in collaboration with the surgeon and the patient (Mac Bride et al. 2013).

Age needs to be considered when assessing the treatment options (Rosenberg et al. 2020). However, age had no significant correlation with complications in an American study, and older patients had higher HRQoL than younger ones with autologous breast reconstruction. This indicated that high age should not independently rule out any surgical options (Santosa et al. 2016). A study of elderly breast cancer patients aged 80 years or higher presented 401 patients with a surgical intervention, 70% of which were mastectomies. The conclusion was that surgical treatment also offers better local disease control

in elderly people. Age should not be a determinant for the choice of mastectomy, for example, to avoid adjuvant treatment (radiation therapy) (Ojala et al. 2019).

Obesity affects the surgical results in terms of increased infections and wound-healing problems (Boczar et al. 2020; de Blacam et al. 2012; Lee et al. 2016). High BMI (body-mass index) might induce prolonged operation times and jeopardise surgical outcomes (Palve et al. 2020; Webb et al. 2020).

Comorbidities affect breast cancer patients' surgical options because a high comorbidity burden increases mortality and is associated with complications (Charlson et al. 1987; Palve et al. 2020). Diabetes has been mentioned as a risk factor for post-surgery healing (de Blacam et al. 2012). Charlson developed the Charlson Comorbidity Index (CCI) in late 1980s to evaluate which health conditions are important. It was especially designed to identify health conditions that put patients at risk of death (Charlson et al. 1987). Quan updated the CCI in 2011 since the treatments of certain conditions have evolved and the burden of some conditions has turned out to be less morbid (Quan et al. 2011). CCI can be used as a comprehensive way to describe patients' comorbidity burden. Table 1 lists the comorbidities with the original CCI and the updated index.

Table 1. Comorbidity index listing from highest index to lowest (Charlson et al. 1987; Quan et al. 2011).

Comorbidity	CCI index by Charlson	CCI index by Quan
Metastatic solid tumor	6	6
Liver disease (moderate to severe)	3	4
AIDS/HIV	6	4
Mild liver disease	1	2
Any malignancy	2	2
Hemi- or paraplegia	2	2
Dementia	1	2
Congestive heart failure	1	2
Chronic pulmonary disease	1	1
Rheumatologic disease	1	1
Diabetes with chronic complications	2	1
Renal disease	2	1
Diabetes without chronic complications	1	0
Myocardial infarction	1	0
Peripheral vascular disease	1	0
Cerebrovascular disease	1	0
Peptic ulcer disease	1	0

4.2.3 Availability of surgical options

All breast cancer patients are not equal in terms of surgical options availability. Patients' socioeconomic status and the admitting hospital's status have been recognised as influencing factors on the treatment path (Albornoz et al. 2012; Sung et al. 2021). The health care systems' funding varies greatly between countries, and payment issues might influence the choices surgeons make to some degree: in the USA, the number of implant reconstructions has risen along with the physician payments (Sheckter et al. 2018). Ethnicity has been under investigation in terms of whether women belonging to ethnic minority groups present late with their breast cancer, resulting in a higher number of mastectomies, and whether they seek breast reconstructions less often. Past studies have reported conflicting results –ethnicity did not seem to affect the surgical choice in England, whereas in the USA some inequities were associated with ethnic background in cancer treatment (Gathani et al. 2021; Zavala et al. 2021).

MacBride studied factors that influence the decision making in breast cancer surgery. The patients' age, imaging results, where they live and their distance from the possible radiation facility were influencing factors. The surgeon's role was also discussed. The surgeons' sex, experience and workplace were evaluated, but no firm conclusions could be made on how surgeons ended up deciding on the operational procedure. The importance of involving the patient in the decision-making process with relevant information about the effect of different approaches on HRQoL was highlighted (Mac Bride et al. 2013). Recent guidelines stress that decision making should be based on multidisciplinary meetings involving the patient (Burstein et al. 2021, Suomen Rintasyöpäryhmä 2022). The experience and annual volume of operations by surgeons affect the results. High-volume surgeons experience fewer complications, which was seen in a study in which 6675 free flap breast reconstruction operations were evaluated in terms of complications and reflected on the annual volume per performing surgeon (Ochoa et al. 2021).

4.2.4 Availability of recommended therapies

Expert groups have given global recommendations on how breast cancer therapies should be designed and administered. The ESMO Guidelines Committee in Europe set the standard for early breast cancer clinical practice guidelines for diagnosis, treatment and follow-up (Cardoso et al. 2019). The St. Gallen consensus from 2021 stated features that affect the decision making in breast cancer care, one of those being the response to neoadjuvant treatments before surgery, emphasising the evolving of the field of adjuvant and neoadjuvant treatments (Burstein et al. 2021). The ASCO guidelines in the USA report HER-2-positive patients therapies in a recent publication

(Giordano et al. 2022). How these recommendations are fulfilled is a big question. Countries have their own guidelines, as Finland does, but only thorough benchmarking would reveal how well these recommended treatments come into use in real life. Hospitals that treat breast cancer need to provide designated treatments to qualify as a breast center. The EUSOMA group reported substantial inequalities in Europe, especially in eastern Europe, in terms of oncological treatments' availability; neither expensive nor inexpensive drug therapies are available for all, and the same was reported for radiation therapy availability (Biganzoli et al. 2020).

4.3 Breast cancer surgery

Johns Hopkins Hospital in the USA started to perform the Halsted radical mastectomy in 1882 to treat breast cancer surgically, in which the pectoralis muscles and level I-III axillary lymph nodes were dissected in addition to removing the breast and overlying skin. A more conservative approach towards breast cancer surgery was practiced over the years as knowledge of cancer recurrence and the way the disease behaved increased: first, a mastectomy without removing the muscles, then partial removal of the breast (Mustakallio 1972; Shons et al. 2001; Veronesi et al. 1981;). Finnish Dr. Mustakallio performed BCS in the 1940s to 1950s and published a series of 702 patients in 1972 proving BCS to be oncologically acceptable with early-stage breast cancer patients when combined with radiation therapy. BCS seemed to produce content patients (Mustakallio 1972). Veronesi compared the Halsted mastectomy (n = 349) to partial breast resection (quadrantectomy, n = 352) in a patient series from Milan, Italy, from 1973 to 1980. No difference in disease-free survival or overall survival was found, indicating that BCS is the favorable surgical approach with a less-mutilating appearance for the patient (Veronesi et al. 1981; Veronesi et al. 1986; Veronesi et al. 2002).

There are numerous studies analysing the oncological safety of different techniques and different outcomes such as recurrence rates, morbidity, mortality, and patient reported outcomes (de Boniface et al. 2021; Geers et al. 2018; Heneghan et al. 2011; Pukancsik et al. 2017; Rutherford et al. 2022; Sorrentino et al. 2019). An extensive literature review emphasised the rapid and ongoing evolution of surgery and other treatment options for breast cancer (Riis 2020).

Breast reconstruction is an option both in an immediate and delayed setting (Jahkola et al. 2021). Based on HRQoL results, IBR outperforms mastectomy, both in prospective and retrospective studies (Dauplat et al. 2017; van Bommel et al. 2020). A comparison of breast-conserving surgery and breast reconstruction often found patients' HRQoL was equal but sometimes favoured one or the other (Heneghan et al. 2011; Howes et al. 2016). Breast

reconstruction should be offered to all patients going through breast cancer surgery. Patient-reported outcomes after breast cancer surgery support breast reconstruction (Cordova et al. 2019; Tykkä et al. 2002).

4.3.1 Breast-conserving surgery

Veronesi's pioneering study starting from the 1970s showed long-term results proving BCS to be safe and acceptable in breast cancer treatment when combined with radiation treatment (Veronesi et al. 2002). Fisher ended up with a similar finding; that breast resection (lumpectomy in USA) combined with radiation therapy is feasible (Fisher et al. 2002). The same finding was also reported by Curran and the EORTC group in the late 1990s, by van Dongen in 2000, and by Luini in 2008 (Curran et al. 1998; Luini et al. 2008; van Dongen et al. 2000). A comparison of BCS and mastectomy reported that BCS produced higher patient satisfaction and superior body image (Curran et al. 1998). Radiation therapy is associated with problems in aesthetic outcome for patients treated with BCS and with radiation, but long-term follow-up studies show that HRQoL impairment is transient (Batenburg et al. 2020; Jacobs et al. 2021; Kindts et al. 2019). De Boniface stated that BCS with radiation therapy produced better survival than mastectomy did, irrespective of adding radiation therapy to mastectomy (de Boniface et al. 2021). A Korean study with 45 thousand patients showed BCS patients with radiotherapy achieving a better overall survival rate and breast cancer-specific survival rate compared to mastectomy (Kim et al. 2021).

4.3.2 Oncoplastic breast surgery

Breast cancer resection combined with techniques of shaping the breast to achieve a more favorable outcome led to the development of oncoplastic techniques (Rainsbury 2007). Clough presented a classification for oncoplastic surgery in Europe 2010. The study introduced a way to classify BCS into two levels depending on the excision volume and the extent of breast reshaping. Level 1 techniques include excision of less than 20% of the breast volume, no skin excision, and no mammoplasty in a dense breast. Level 2 techniques include excision of 20 to 50% and more extensive breast reshaping (Clough et al. 2010). The American Society of Breast Surgeons presented a consensus classification system of oncoplastic surgery in 2019 in America with similar classification for level 1 and 2 techniques based on volume and reshaping (Chatterjee et al. 2019). Gilmour from the UK presented a guide to good practice because oncoplastic surgery has become standard care for breast cancer surgery. The guide aims to set quality criteria for high-quality treatment with oncoplastic techniques (Gilmour et al. 2021).

A series of 90 breast cancer patients were operated on with oncoplastic techniques and followed up in a prospective manner for a median of 26 months

in a study from Finland. The study revealed that oncoplastic techniques achieved negative margins and acceptable cosmesis with no local recurrences (Meretoja et al. 2010). A more recent study of Finnish breast cancer patients' oncological safety after surgery assessed 1800 patients: 1189 patients treated with traditional resection of breast cancer and 611 patients treated with oncoplastic surgery. No difference was found in local recurrences or re-operation rates (Niinikoski et al. 2019). The same comparison was made in the UK for 440 BCS patients and 146 oncoplastic resection patients. Oncoplastic resection was associated with reduced re-excision rates during the median 28-month follow-up of that study (Chakravorty et al. 2012).

Mansell suggested that, due to similar tumour burden, oncoplastic surgery should be compared to mastectomy (instead of wide excision of the breast) in terms of oncological safety and outcomes (Mansell et al. 2015). Comparing oncoplastic techniques with wide excision and mastectomy with or without IBR, Mansell later reported that oncoplastic surgery is safe even when the histopathological status of the disease is similar (Mansell et al. 2017). Chand compared therapeutic mammaplasty (comparable to oncoplastic techniques) to LD miniflaps (latissimus dorsi muscle flap, where the muscle is used partially or as a whole as volume replacement after wide excision of the breast) in a 150-patient series and found that therapeutic mammaplasty produced superior patient satisfaction (Chand et al. 2017). Campbell and Romics evaluated studies that had compared oncoplastic techniques to other surgical techniques regarding resection margin problems, re-operation rates and local and distant recurrence rates. The conclusion was that oncoplastic techniques provide superior aesthetic outcomes. However, they raised a concern of oncological safety not yet being firmly established. They stated that more evidence is needed, especially more prospective data to provide information on oncological safety and improved aesthetic outcome (Campbell et Romics 2017). Later, in 2019, Pearce stated that extreme oncoplastic surgery (large excisions and corrective procedures with oncoplastic techniques) is a safe alternative to mastectomy (Pearce et al. 2020).

The Oncoplastic Breast Consortium Initiative in 2020 published a review concerning knowledge gaps in oncoplastic surgery. First, 212 surgeons and 26 patient advocates from 55 countries prioritised the 15 most important aspects to focus on. Then a panel for a consensus conference was gathered from 20 countries in 2019. They selected the seven most important aspects as research strategies with a goal to enhance and unify the research and knowledge in oncoplastic breast cancer surgery. They pointed out the need for international-level prospective, randomised trials using patient-reported outcomes concerning the reconstruction type and timing, the use of a mesh, and positioning of implants. They viewed the BREAST-Q questionnaire as a suitable tool for HRQoL assessment but also acknowledged the need for

systematic evaluation of other patient-reported outcomes along with surgical morbidity (Weber et al. 2020).

4.3.3 Mastectomy

Mastectomy can be the best operating technique in certain situations. A patient's own wish is an important factor in the decision to remove a breast. The tumour size in relation to the breast size can yield towards mastectomy (small breast with large tumour). That could be the case also with multicentric tumors or in a situation where excision has not led to negative margins (Cardoso et al. 2019). Mastectomy techniques have evolved from radical removal of the breast, pectoralis muscles, skin, and lymph nodes towards modified techniques: skin sparing (SSM), nipple sparing (NSM), modified radical mastectomy (MRM) where the overlying skin is spared with or without the nipple, or mastectomy where the skin is excised but no muscles removed, maintaining oncological safety to treat breast cancer (Jones et Lancaster 2018; Meretoja et al. 2007; Patani et al. 2008). SSM and NSM performed with IBR provide good patient satisfaction and is oncologically safe in selected patients with no increase of recurrences compared to MRM (Howard et al. 2016; Valero et al. 2020).

4.3.4 Autologous breast reconstruction

Autologous reconstruction (reconstruction with own tissue) methods seem to be more favorable in terms of HRQoL, patient satisfaction and cosmetic outcome compared to allogenous reconstruction (reconstruction with implants) (Alderman et al. 2007; Pusic et al. 2017; Santosa et al. 2018). Long-term results, when comparing autologous vs allogenous methods, show radiation diminishing patient satisfaction, especially with allogenous reconstructions (Jagsi et al. 2015). Age itself does not seem to be a predictor of complications in patients with reconstruction (Santosa et al. 2016). The oncological safety of autologous breast reconstruction compared to mastectomy is adequate. Autologous reconstruction does not affect the distant relapse rate (Geers et al. 2018).

Latissimus dorsi flap

Breast reconstruction started to establish its position in breast cancer surgery by the 1970s into the 1980s. LD flap is a pedicular flap, in which the latissimus dorsi muscle is raised with the overlying skin and a subcutaneous island and transposed from the back to front to reconstruct the breast. As experience grew with reconstructive surgery, the results also started to be evaluated from different perspectives. Mansel et al. studied the cosmetic results of the transverse rectus abdominis muscle (TRAM) and latissimus dorsi (LD) flaps and rated LD as more favorable (Mansel et al. 1986). De Mey found LD to be a

good workhorse in breast reconstruction by 1991 but also saw a trend towards abdominal flaps in their institute in Belgium. Capsular contracture was often a problem; implants were normally combined with LD flaps (De Mey et al. 1991). Reefy studied the outcomes of skin-sparing mastectomy and immediate reconstruction with LD flap with or without an implant in a prospective trial. Patient satisfaction was good, and IBR with these methods seemed to be oncologically safe with smaller than T2 tumors (Reefy et al. 2010). Blackburn studied the effect of LD on shoulder dysfunction. The review included 24 articles from 2006 to 2016. This study revealed some concerns on musculoskeletal effects and stated the need for further studies in this specific area because the results were contradictory in revealing musculoskeletal problems (Blackburn et al. 2018). An Australian study evaluated possible shoulder dysfunction after LD reconstruction (n = 100) compared to mastectomy (n = 121). They learned that patient satisfaction with LD reconstruction was at a high level with no evidence of shoulder dysfunction (Koh et al. 2018). A Finnish study found association with postoperative complications and LD reconstruction (Palve et al. 2020).

Abdominal flap

Holmström first described autologous breast reconstruction with a free flap from the lower abdomen in 1979 (Holmström 1979). The evolution of abdominal flaps has gone from 1) pedicled TRAM flaps, where the rectus abdominis muscle was raised with a transverse skin-subcutaneous flap with pedicle and turned to reconstruct the breast to 2) a muscle-sparing TRAM, where only a part of the muscle was raised to 3) free flaps based on the skin-subcutaneous island and the pedicle that supports the islands perfusion and to 4) SIEA (superficial inferior epigastric artery) or DIEP (deep inferior epigastric artery) perforator flaps. Free flaps are then anastomosed to either axillary or internal mammary vessels (artery IMA and veins). Abdominal flaps have been regarded as the first choice of autologous breast reconstruction (Nieminen et al. 1999). Abdominal flap reconstruction produces good HRQoL (Hunsinger et al. 2016; Macadam et al. 2016).

Transverse musculocutaneus gracilis flap

Breast reconstruction from the gluteal fold or thigh are options for selected patients as described by Myers (Myers et al. 2021). The musculus gracilis is raised with a transverse skin-subcutaneus island and anastomosed as a free flap to either axillary arteries or IMA. The problem with TMG and gluteal fold flaps is mostly the limitation in volume and the length of the pedicle even though 30 years of experience especially with TMG flaps have proven to produce acceptable results. Patients with a low BMI who thus lack material for an abdominal flap have a choice with TMG for autologous breast reconstruction (Weitgasser et al. 2021).

Fat grafting

The breast can be reconstructed with fat harvested from the patient in a delayed setting. Patient selection for this reconstruction method is crucial; patients should have enough fatty tissue to be extracted and a moderate volume to be reconstructed. Tissue damage after radiation therapy might result in poorer results (Kauhanen et Höckerstedt 2019). Fat grafting can also be used to correct BCS deformities in addition to total reconstruction of the breast after mastectomy. The procedure is considered oncologically safe in both cases (De Decker et al. 2016; Sorrentino et al. 2019). Fat grafting as a corrective procedure after BCS does not increase local recurrence, indicating this procedure is safe (Tayeh et al. 2022).

4.3.5 Allogenous breast reconstruction

The breast can be reconstructed with implants. The permanent implant can be placed at the first operation in an immediate setting, but with DR an expander is often needed first to allow tissue expansion, followed later by placing the permanent implant. Detection of recurrence is not hampered with implants, indicating that implant reconstruction is an oncologically safe procedure (McCarthy et al. 2008). Implant reconstructions nowadays increasingly use a mesh or acellular dermal matrix to secure the implants' positioning (Kalstrup et al. 2021).

HRQoL has been found to improve after implant breast reconstruction, but patients may have concerns about the aesthetic outcome; thus, the final results assessment should be first made after enough recovery time and healing (Elder et al. 2005). HRQoL results favoured BCS over implant reconstruction when comparing BCS to IBR with implants. Radiation therapy seemed to diminish HRQoL (Flanagan et al. 2019). The use of implants varies between countries, and cultural differences exist regarding reconstruction methods. The Mayo Clinic reported implant reconstruction was associated with significant reoperation rates, but no difference was found between IBR implant reconstruction, tissue expanders and autologous reconstruction methods (Hammond et al. 2022).

Breast implants were found in 2011 to have an association with anaplastic large cell lymphoma (BIA-ALCL), especially the rough-surfaced implants (McCarthy et al. 2019). Given the rising awareness over BIA-ALCL, several countries have given instructions to avoid rough surfaced implants and favour smooth surfaced implants, which seem to have no association with ALCL. Smooth-surfaced implants may have more rippling than rough-surfaced implants, but HRQoL seems to be similar using either material (Vorstenbosch et al. 2021). An EU-level, multinational expert group gave a statement about

the safety of breast implants in relation to BIA-ALCL in 2021 and regarded smooth implants as safe (SCHEER 2021). The majority of patients are treated in a curative manner when the capsule around the implant is removed surgically en-block and the long-term prognosis is good with this rare condition (Turton et al. 2021).

4.4 Axillary surgery

Axillary surgery has undergone big changes from routine axillary clearance to sentinel node biopsy (SNB). The American College of Surgeon's Oncology Group (ACOSOG) stated in 2011 in their phase 3 trial that patients with lower disease burden can be safely treated with SNB when accompanied with adjuvant treatments and that axillary clearance does not increase survival (Giuliano et al. 2011). The same resulted in long-term results: the ACOSOG study found no difference in long-term survival compared to axillary clearance in T1 -T2 primary breast cancer patients when one or two nodes have been found with metastases and patients have received adequate oncological treatments (radiation therapy and chemotherapy) (Giuliano et al. 2017). A multicenter, randomised, phase 3 non-inferiority trial AMAROS (After Mapping of the Axilla, Radiotherapy or Surgery?) also provided information about the safety of SNB and radiotherapy after a positive SNB finding compared to axillary clearance in early breast cancer patients. Axillary clearance can result in various problems such as pain and lymphedema (Donker et al. 2014). The International Breast Cancer Study Group reported the same finding with long-term follow-up: early breast cancer patients with a low disease burden are not candidates for axillary clearance (Galimberti et al. 2018). Guidelines in Finland regarding axillary surgery follow the international guidelines (Suomen Rintasyöpäryhmä ry 2022).

4.5 Outcomes of breast cancer surgery

The traditional endpoints in breast cancer research have been disease-free and overall survival and the response to treatments (Radice et al. 2003). Even though the focus of treating potentially lethal illness is on curing the disease and producing as long a disease-free time as possible, there are also other highly important outcomes to address. The psychological and economic burden generated by the disease are relevant in breast cancer. The treatment of breast cancer aims to provide high-quality care, meaning an efficient surgical procedure that removes the cancer safely in a manner that produces the best possible HRQoL and cosmetic outcome for patients of all ages and health states (Park et al. 2021; Rosenberg et al. 2020).

Contralateral side symmetry should be considered when planning breast surgery. Very different-sized breasts might indicate later physiological

problems, or problems in dressing, performing exercise, and social and sexual interactions. Poor asymmetry indicates poor HRQoL (Waljee et al. 2008). Cosmesis and patient satisfaction correlate with the BCS technique: it makes a difference how much of the breast is removed. The surgeon should make a notice on the volume that needs to be excised when planning BCS to achieve good patient satisfaction (Cochrane et al. 2003).

Outcomes of breast surgery can be evaluated in numerous ways. The EUSOMA Group Quality Indicators (QI), when fulfilled, will set a minimum standard of care (Biganzoli et al. 2017; Biganzoli et al. 2020). The number of mastectomies, re-operations, axillary surgery, or complications are amongst the outcomes to report and follow. HRQoL is an important outcome measure in modern breast cancer care. The appearance of the breast – the cosmetic outcome – can also be an outcome measure, but how to measure this remains still unsolved. Some studies have used expert panels to evaluate the breasts with certain criteria (Ueda et al. 2008). There are also software programs to evaluate the aesthetic results of breasts after conserving surgery. Software programs are based on photographs in which breast symmetry is measured with different parameters (for example, the measure from jugulum to mamilla, from mamilla to inframammary fold, or differences in breast volume) (Cardoso et al. 2007; Krois et al. 2017). The software might be useful in some research settings (Cardoso et al. 2007; Lagendijk et al. 2017).

The way complications are recorded and reported still varies between institutes and countries. The Clavien–Dindo classification for complications offers a comprehensive tool to assess complications (Dindo et al. 2004; Clavien et al. 2009). The classification includes five levels of complications according to their severity. Class I includes complications that are deviations from the normal recovering course but do not require antibiotics or revisional procedures. Class II are complications that require the use of antibiotics or revisional procedures (minor wound dehiscence or infections). Class III are complications that require surgical interventions either in IIIa under local anesthesia or in IIIb under general anesthesia. Life-threatening complications form Class IV and death Class V (Dindo et al. 2004).

4.6 Health-Related Quality of Life

Patient-reported outcomes began to rise as an important outcome measure of breast cancer treatments in the 1970s and 1980s. Patients were interviewed and asked to fill in questionnaires, and it soon became evident that the questionnaires should somehow be standardised and validated to produce scientifically sound data.

Health-Related Quality of Life (HRQoL) questionnaires that were developed in numerous studies all have their pros and cons. Hunt developed The

Nottingham Health Profile in the 1980s, which is a standardised tool for studies in health problems and evaluation of medical outcomes but is not specifically designed to reflect overall HRQoL (Hunt et al. 1980). SF-36 (Short Form -36) is a generic measuring tool developed in the 1990s (Ware et al. 1992). EQ5D-3L was developed by the EURO QoL group and published in 1990 (EUROQoL 1990). 15D was developed by Professor Sintonen and published in 2001 (Sintonen 2001). EQ5D and 15D are generic HRQoL measuring tools and produce a health utility score, a number that describes a patient's health status. The EORTC Quality of Life Group developed the EORTC QLQ C-30 questionnaire 2002 for studying cancer-related quality of life (EORTC Group 2002). The breast cancer-specific additional questionnaire BR-23 is a questionnaire specially designed to study breast cancer-related problems. An attempt to find the best HRQoL measuring tool also found other measuring tools, not listed here, that are not frequently used anymore. What is common for most measuring tools results is that mastectomy patients' HRQoL is the lowest and BCS and reconstruction patients present higher HRQoL in comparison studies (Zehra et al. 2020). Blumenschein studied how different HRQoL measuring tools could be compared in multiple regression analyses and stated that different health dimensions can be used as explanatory values of HRQoL (Blumenschein et al. 1996).

Numerous HRQoL questionnaires aim at a specific disease, procedure, or health status. The BREAST-Q was published by Pusic in 2009. This tool specifically addresses breast surgery and can be used to study effectiveness and impact of breast surgery – not only in breast cancer patients (Pusic et al. 2009). Different HRQoL measuring tools give different HRQoL scores and some measuring tools present high ceiling or floor effects (Rautalin et al. 2018). Ceiling effect means that the answer a patient chooses to a question is the highest possible option and floor effect is the lowest. Some measuring tools produce many of their answers this way, indicating poor selection of the measuring tool in the chosen situation or a possibility exists that the measuring tool is not valid. All measuring tools used in medical studies should be validated and presented to patients in their native language. The BREAST-Q was not yet validated in Finnish at the onset of this thesis.

4.6.1 Generic measuring tools

The generic measuring tools readily available at the onset of this thesis are presented in more detail:

EQ5D-3L and VAS

EQ5D-3L comprises questions from 5 dimensions. Patients answer by ticking a numeric value for each question from one (best) to three (worse situation), with best describing their status in that area of the question (EUROQoL 1990).

EQ5D-3L includes VAS, a visual analogue scale from 0 to 100 mm (100 being the best imaginable health situation and 0 the worst). The minimum important difference in the score (MID) is 0.08 for EQ5D and 7 to 12 for VAS (Pickard et al. 2007).

15D

15D comprises questions from 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech (communication), excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity). Patients tick a numeric value from one (best) to five (worse situation), with best describing their status in the area of the question at the moment. The 15D score represents the overall HRQoL, ranging from 0 to 1 (Sintonen 2001). The MID for 15D is 0.015 (Alanne et al. 2015).

4.6.2 Disease-specific measuring tool

The disease-specific measuring tool readily available at the onset of this thesis is presented in more detail:

EORTC QLQ C-30 and BR-23

EORTC QLQ C-30 is a cancer-specific measuring tool that produces symptom and functioning scores and an overall quality of life score. Symptoms addressed are nausea/vomiting, diarrhea, constipation, sleeping disturbances, pain and breathing. Patients evaluate their health during the past week on a numeric scale from one (not at all) to four (very much) in specific symptom-related questions. Patients also evaluate their health status and life quality on a scale from one (poor) to seven (excellent) in functional status-related questions. The measuring tool produces values for functional scores concerning physical, social, mental, role and sexual functioning. BR-23 is designed especially for breast cancer patients, and the questionnaire addresses concerns about body image and sexuality, specific breast cancer-related symptoms and psychological distress. The BR23 questionnaire produces symptom scores about Systemic therapy side effects, Breast and Arm symptoms and Hair loss. The questionnaire produces functional scores about Body image, Sexual functioning, Sexual enjoyment, and Future perspective. The scores range from 0 to 100: high score indicates good health for functional scores but problems with that particular symptom for symptom scores. (EORTC Group 2002). A MID has not been established for EORTC. A suggestion for the interpretation of the changes of scores is described as a minimal significance for changes from 5 to 10, intermediate from 10 to 20 and large significance for changes over 20 points (Cocks et al. 2012; Osaba et al. 1998).

4.7 Economical evaluation of breast cancer treatment

The cost of breast cancer care is remarkable for both the patient and the society. A review almost 20 years ago drew attention to the economic burden breast cancer produces, especially in industrialised countries. Breast cancer is the most common cancer in women, so it generates a huge part of overall health care costs (Radice et al. 2003). The cost of cancer care is rising globally along with the growing incidence. The ESMO group has set recommendations for low-income countries on how national resources should be prioritised and how systematically collected, standardised data provide evidence-based information to help decisionmakers in their work towards fair and sustainable health-care systems (Prager et al. 2018). Cancer registries and systematic research are imperative in the efforts to enhance the quality of health care. Economic evaluations produce useful outcome results that might weigh in the decision-making processes (Marseille et al. 2015; Palve et al. 2022; Prager et al 2018; Radice et al. 2003; Ziolkowski et al. 2013).

A systematic review of economic evaluations in plastic surgery included 95 articles in the analysis from 1986 to 2012. Breast surgery studies comprised 20% of the studies. The research revealed that full economic evaluations are needed in future studies (Ziolkowski et al. 2013).

Guidelines exist on how to design and report health-economic studies (Husereau et al. 2013; Weinstein et al. 1996). A group from the USA published guidelines concerning the methodological aspects of cost-effectiveness analyses in 1996 with a scope to improve and unite the research scene. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) is a guideline formulated by an international group of experts from different areas of expertise. Their goal is to enhance the quality of reporting health-economic research and thus lead to better quality health decisions. A guideline from 2013 listed a 24-item checklist to help standardise the reporting of health-economic studies (Husereau et al. 2013). Tessler focused on the methodology used in plastic surgery and health economic studies in 2012, resulting in recommendations for study designs of such studies to improve the quality of health economic research (Tessler et al. 2014). Miroshnychenko reviewed in 2021 how the CHEERS guidelines were being followed in plastic surgery. Breast surgery was the biggest domain (48% of the studies in this review). Checklist compliance was 15/24, and the conclusion was that the quality of health economic studies could be higher, cost-utility analyses would be advisable and it is recommended to collaborate with health economists (Miroshnychenko et al. 2021). Marseille stated that cost-effectiveness analyses should include both the disease burden and the budget of the anticipated intervention if the purpose is to contribute to resource allocation (Marseille et al. 2015). This notion creates a difficulty when comparing breast cancer treatment options: patients with different disease burdens can be treated similarly or differently, presumably resulting in equal endpoints regarding

survival but very different endpoints regarding HRQoL. CHEERS guidelines were updated in 2022, with the checklist growing to 28 items. The leading idea in this update is that those studies that address economic aspects "should be understandable, interpretable, and replicable" (Husereau et al. 2020). The problem with breast cancer surgery and health economic studies is still that surgical options cannot be randomised.

It is advisable to routinely perform collection of patient-reported data combined with the hospital costs of cancer care (Hall et al. 2015). A study from the Netherlands evaluated different surgical approaches for breast cancer patients with a 10-year follow-up. BCS proved to be less costly and produced good HRQoL compared to reconstruction whose costs were higher. Breast reconstruction with either autologous or allogenous methods was more cost-effective than mastectomy (Kouwenberg et al. 2020). Australian early-stage breast cancer patients' treatment path was compared between BCS and mastectomy with or without adjuvant treatments, revealing BCS with radiation therapy to be more costly than mastectomy (Kenny et al. 2000). American research studied patients' economic status and revealed that breast cancer patients' wealth affected the choice of the surgical approach the patients eventually made (Greenup et al. 2019).

The possibilities of comparing health care productivities internationally were evaluated in 2013. The diagnostics and classification of diseases and treatments in Nordic countries are similar, as are the classification of expenses, thus enabling their comparison between Nordic countries. Comparing the quality of care is difficult, but well-established data sources in Nordic countries produce registered data that enable cost-effectiveness studies. According to Medin, the health care systems' cost-effectiveness is at a reasonably acceptable level in Finland (Medin et al. 2013). A study of costs of care for 10 different cancer sites in Finland between 2009-2014 revealed that approximately 20% of all cancer costs resulted from breast cancer. Treatment costs are the lowest in breast cancer (highest in prostate cancer) in the cost formation. Costs other than those of treatments, including screening costs, disability pensions and, for example, sick leaves, are high with breast cancer. With time it seems that the overall costs of cancer care diminish a bit, but there is variation between costs from different cancer sites. The recorded drop in costs does not indicate the deterioration of quality of care but rather points out that more treatments are given in an out-patient setting, and the length of a hospital stay is shortening nowadays. Patient-reported outcome measures, like health statuses, are advisable to be reported increasingly as the population is ageing (Torkki et al. 2018). The costs of breast cancer care at different stages of the disease were studied in Finland in a cross-sectional study of 827 patients from 2009 to 2010. The study included both direct and indirect costs and noted that the primary treatment phase, the first year after diagnosis, was the period of most costs building up (Roine et al. 2019). Encountering financial

difficulties negatively affects HRQoL (Koskinen et al. 2019). Breast reconstruction treatment costs between autologous and allogenous methods seem to build up more with certain autologous methods in Finland (Palve et al. 2022).

5 AIMS OF THE STUDY

The aim of the thesis was to evaluate different HRQoL measuring tools in different states of breast cancer, to study how different surgical methods affect HRQoL, and to describe the cost formation in breast cancer treatment from the care provider's perspective.

The specific aims were:

- To compare the results of three different HRQoL measuring tools in breast cancer patients in order to evaluate their validity in different states of the disease and to identify explanatory factors for HRQoL.
- To study how different surgical methods affect breast cancer patients' HRQoL and to find out whether some surgical methods provide more favourable HRQoL results than others. To explore the recovery process of breast cancer patients by repeated HRQoL measurements at different timepoints.
- To compare all available breast reconstruction methods, their outcomes, and the HRQoL they produce. To evaluate the timing of breast reconstructions by comparing IBR and DR in search of optimal reconstruction timing and method.
- To describe, from the care-provider's perspective, how breast cancer patients' costs of care are comprised in relation to the use of different surgical methods and to see if the costs are reflected in HRQoL.

6 MATERIAL AND METHODS

6.1 Patients

Study I

804 patients with histologically confirmed breast cancer were recruited in Helsinki and Uusimaa Hospital District into a cross-sectional observation study between 2009 — 2011. The study was approved by the Helsinki and Uusimaa Hospital District's Ethics Committee and is a part of a larger study with prostate, colorectal and breast cancer patients. Patients were asked to participate when visiting the hospital or via mail. One reminder was sent if there was no response.

Patients were grouped according to their disease state: primary treatment (n = 118), recovery (n = 150), remission (n = 382), metastatic state (n = 176), and palliative care (n = 14). The recovery group comprised patients whose diagnoses had been made 6 to 18 months prior to recruitment. The remission group comprised patients whose diagnoses had been made 18 or more months prior to the recruitment. The metastatic state group comprised patients who had a recorded distant metastasis at the time of the recruitment. The palliative care group comprised patients whose disease had advanced to the state that life-prolonging treatments had been terminated at the time of the recruitment.

Studies II – IV

1065 patients with primary breast cancer were recruited into a prospective observational study in the Helsinki and Uusimaa Hospital District between 2008 — 2015. The study was approved by the Helsinki and Uusimaa Hospital District's Ethics Committee and is an independent study with no other publications of this patient material. Patients were asked to participate at their first visit to the hospital and later approached via mail.

Patients were grouped according to their breast surgery method: breast-conserving surgery with either resection (n = 415) or oncoplastic resection (n = 248), mastectomy (n= 351), or breast reconstruction IBR (n=51). The surgical methods were identified using the Nordic Classification of Surgical Procedures (NCSP): the resection group comprised patients operated on with either HAB40- or HAB99-coded procedures and the oncoplastic surgery group with HAB50-coded procedures. Pedicled flaps were not included in the oncoplastic group (Level II techniques as described by Clough 2010). Breast reconstructions were performed at the Department of Plastic Surgery Helsinki and other breast cancer surgeries at the Breast Cancer Unit Helsinki.

41 mastectomy patients who had undergone additional surgery later after primary cancer surgery were identified and formed the DR group in *Study III*. *Study IV's* DR group comprised 34 patients; patients who had undergone mastectomy or breast reduction as a corrective procedure were excluded from the group so that the DR group comprised those mastectomy patients who had received breast reconstruction with either autologous or allogenous methods.

6.2 Questionnaires

Study I

Patients were asked to complete an informed consent form and a questionnaire regarding sociodemographic factors: education background, marital and occupational status. Patients were given three HRQoL questionnaires: EQ5D-3L (including VAS), 15D, and EORTC QLQ C-30.

Studies II – IV

Patients were asked to complete an informed consent form and two HRQoL questionnaires: 15D and EORCT QLQ C-30 BR-23. The baseline questionnaires were handed out at the first visit to the hospital, and subsequent questionnaires were mailed at 3, 6, 12 and 24 months.

6.3 Economic data collection

The data concerning the cost of care for the two-year follow-up were obtained from the administrative ECOMED database used in the hospital. Each patient's costs were identified using their social security numbers. Cost data were obtained for a period starting one month prior to their baseline answers and extending to 26 months thereafter to include all relevant costs.

6.4 Clinical data collection

Study I

Clinical data concerning the state and biology type of the disease and oncological treatments were collected from hospital records.

Studies II-IV

Clinical data concerning comorbidities, smoking status, BMI, and specific details concerning the state and biological type were collected from hospital records using their social security numbers to identify the patients. ER- and PR-hormone receptor status, HER-2 gene expression, Grade, and TNM-status were recorded. Details concerning breast and axillary surgery were also

recorded: BCS (*Study IV*) as a simple resection of the breast or oncoplastic resection, mastectomy, IBR (*Study II*), or DR (*Studies III-IV*). Sentinel node biopsy (SNB) and axillary clearance were recorded. Oncological treatments given (radiation therapy, chemotherapy, hormonal treatment, endocrine treatment, or targeted therapy) and the course of recovery were recorded. Complications were recorded from patient records; those having a deviation in the recovery process were noted and classified in *Study III* in more detail using the Clavien-Dindo classification for complications. Percentages of surgical interventions and the proportions of axillary surgery, re-operation rates and radiation therapy were calculated for BCS and mastectomy patients and in more detail, separating those with invasive cancer and DCIS. These were reflected by EUSOMA Quality Indicators regarding surgical care.

6.5 Statistical analysis

Study I

Statistical analysis was performed using SPSS version 22 (SPSS Inc., Chicago, Illinois, USA). The analysis was made in two phases as a linear stepwise regression analysis. The patients' clinical data and demographic factors along with the disease state were entered as potentially explanatory factors of HRQoL at *Phase 1*. Those factors that were significant in *Phase 1* were entered with EORTC symptom and functioning scores as potential explanatory factors of HRQoL in *Phase 2*. Independent samples T-test was used to study the differences between groups. P-values ≤ 0.05 were considered statistically significant.

Study II

Clinical data were combined with the HRQoL data using decoded patient IDs. Statistical analysis was performed using SPSS 25.0 software and partly using NCSS software. Analysis was performed as a stepwise linear regression analysis (One-way ANOVA). The distribution of the HRQoL results from both EORTC and 15D instruments was slightly skewed, which led to the use of Kruskal-Wallis non-parametric tests. Box-Cox-transformation was performed for the regression analyses to ensure the normal distribution of the data. The variables entered into the analysis were BMI, smoking status, having a complication, seroma aspiration more than 10 times, multiple surgery, axillary surgery, TNM and grade classification, radiation therapy, chemotherapy, endocrine treatment, and encountering a recurrence of the disease. P-values ≤ 0.05 were considered statistically significant.

Study III

Statistical analysis was performed using NCSS software. Clinical data were combined with the HRQoL results as in *Study II* and Box-Cox transformation was made to ensure the normal distribution of the data. Two-Sample tests were performed to compare IBR and DR group's overall HRQoL (Global health

score in EORTC and in 15D total score). The changes in these scores were studied from baseline to 12 months and 24 months. Breast-cancer specific BR23-answers, EORTC symptom and functional scores, and 15D health profiles were studied by comparing the results of the IBR and DR groups with the Mann-Whitney U-test.

The differences between the symptom and functional scores were studied at 12 and 24 months with Kruskal-Wallis non-parametric ANOVA to further study the surgical methods. Some surgical method groups were too small for comparisons: in IBR group four TMG; in DR group one LAP; and three implants. Patients whose corrective surgery was mastectomy or reduction of the healthy side (for balancing reasons) were not included in the analyses. The comparisons were thus made in IBR for abdominal flaps, LD, and implants and for DR abdominal flaps, LD, and fat grafting.

Study IV

Clinical data and HRQoL data were combined as in *Studies II-III*. Data retrieved from the ECOMED database were grouped according to the clinic that had generated the costs: the Breast Surgery Unit, Plastic Surgery Unit, and Oncological Unit. The billing codes were summed up so that all costs generated by different actions were studied separately (number of visits and the cost from outpatient clinics, number of surgeries and their costs, number and costs of days spent at wards, number and costs from diagnostics). Clinical data with HRQoL data and the ECOMED data were then combined with patient IDs to analyse the overall costs of each patient over the two-year follow-up. Analysis was made by NCSS software.

7 RESULTS

7.1 Patient characteristics

Five patients in *Study I* were male. The patients' age varied from 26 to 90 years (mean 61.7 years). Table 2 lists patient characteristics, demographic factors, hormonal status of the cancer type, location of metastases, and oncological treatments received during the preceding three months.

Table 2. Patient characteristics in Study I. Number of answers (N) and percentages (%) within each group. Reproduced with permission from Taylor & Francis group (Rautalin et al. 2018).

	Primary treatment n = 118 (14.0%)	**Recovery** n=150 (17.9%)	**Remission** n=382 (45.5%)	**Metastatic disease** n = 176 (21.0%)	**Palliative care** n = 14 (1.7%)
Demographic data					
Age in years, mean (SD)	56.9 (10.7)	60.8 (10.4)	63.1 (10.0)	62.7 (10.9)	64.6 (11.4)
Married or cohabiting, n (%)	81 (68.6)	99 (69.2)*	231 (61.1)*	101 (58.7)*	8 (61.5)*
Higher education, n (%)	73 (61.9)	91 (62.3)*	207 (54.5)*	104 (60.8)*	8 (61.5)*
Employed, n (%)	70 (59.3)	69 (47.3)*	149 (39.1)*	35 (20.2)*	2 (15.4)*
Unemployed, n (%)	9 (7.6)	8 (5.5)*	23 (6.0)*	10 (5.8)*	2 (15.4)*
Months from dg, mean	0.7	13.1	29.1	91.7	84.6
Cancer specific factors					
Estrogen positive, n (%)	73 (80.2)*	119(86.2)*	313 (85.3)*	135 (80.8)*	11 (78.6)
Progesterone positive, n (%)	54 (60.0)*	90 (65.7)*	248 (67.4)*	90 (55.6)*	9 (64.3)
HER-2- positive, n (%)	13 (14.6)*	17 (12.7)*	48 (16.6)*	52 (36.6)*	2 (15.4)*
Metastases n (%)	0	0	0	176	14
Bone, n (%)	0*	0	0*	129 (73.7)*	14 (100)
Lungs, n (%)	0*	0	0*	45 (25.9)*	6 (42.9)
Brain, n (%)	0*	0	0*	19 (10.9)*	4 (28.6)
Liver, n (%)	0*	0	0*	75 (43.1)*	8 (57.1)
Pleura, n (%)	0*	0	0*	30 (17.2)*	1 (7.1)
Peritoneal/ascites, n (%)	0*	0	0*	10 (5.7)*	0
Skin, n (%)	0*	0	0*	12 (6.9)*	0
Lymph nodes, n (%)	0*	1 (0.7)	4 (1.0)*	52 (29.9)*	2 (14.3)
Treatment received preceding 3 months					
Radiation therapy, n (%)	1 (0.8)	4 (2.7)	1 (0.3)	18 (10.2)	4 (28.6)
Chemotherapy, n (%)	7 (6.0)*	2 (1.3)	0	121 (68.8)	4 (28.6)
Endocrine therapy, n (%)	3 (2.6)*	106 (71.1)*	292 (76.4)	64 (36.6)*	6 (42.9)
Targeted therapy, n (%)	1 (0.9)*	7 (4.9)*	2 (0.5)*	40 (24.2)*	2 (16.7)*

In case of a missing answer, total N and % vary. Those are marked with an asterix *.

Two of all the 1065 recruited patients in the follow-up study (*Studies II-IV*) were male. The patients' age varied from 24 to 89 years (mean 59.7 years). The Comorbidity index (CCI) for the whole study group ranged from no significant comorbidities (0) to 7 comorbidities, with a CCI mean of 0.327, SD 0.733. 844 patients had no comorbidities (CCI 0). Table 3 shows the distribution of the CCI index by group.

Table 3. Charlson comorbidity index (CCI) distribution by groups Study II. N, percentages within group. The majority of patients had little comorbidities, whereas the proportion of patients with a heavy comorbidity burden are few.

CCI index	**Resection** n = 415	**Oncoplastic resection** n = 248	**Mastectomy** n = 351	**Reconstruction** n = 51
0, n (%)	341 (82.2)	195 (78.6)	266 (75.8)	42 (82.4)
1, n (%)	40 (9.6)	36 (14.5)	39 (11.1)	4 (7.8)
2, n (%)	29 (7)	15 (6)	37 (10.5)	4 (7.8)
3, n (%)	5 (1.2)	2 (0.8)	6 (1.7)	1 (2)
4, n (%)	0	0	1 (0.3)	0
5, n (%)	0	0	0	0
6, n (%)	0	0	1 (0.3)	0
7, n (%)	0	0	1 (0.3)	0

Diagnoses for diabetes were found with 72 (6.8%) and depression with 43 (4%) of all patients. Active smoking was reported for 107 (10%) and former smoking for 132 (12.4%) of all patients. Routine mammograph screening found 464 (43.6%) of the study population's breast cancers. BMI and smoking status were quite similar in all groups, as Table 4 indicates. 402 patients (37.7%) went through axillary clearance and 839 (78.8%) patients received radiation therapy, 523 (49.1%) chemotherapy, 766 (71.9%) endocrine treatment, and 119 (11.2%) targeted therapy in *Studies II-IV*.

Table 5 presents characteristics of reconstruction patients in *Study III*. The autologous IBR methods used were 19 LD flaps (10 with and 9 without an implant in addition to the flap), 19 abdominal flaps (9 TRAM and 7 DIEP flaps), and 4 TMG flaps. Allogenous patients were all implanted with an expander at the first operation and the permanent implant later. Axillary clearance was performed for 19 patients. The autologous methods were 10 LD flaps (three with additional implants), 14 abdominal flaps (6 TRAM and 8 DIEP flaps), one LAP, 6 fat graftings, and 7 balancing reductioplasties or mastectomies for the contralateral side for DR patients. Allogenous implant reconstruction was performed for three patients with expanders. 20 of the DR patients had axillary clearance at their primary cancer surgery.

Table 4. Patient characteristics in Study II. Means, SD, percentages within group. Reproduced with permission from Elsevier Ltd. (Rautalin et al. 2021)

	Resection n = 415	**Oncoplastic n = 248**	**Mastectomy n = 351**	**Reconstruction n = 51**
Demographic data				
Age mean (SD)	61.7 years (8.6)	59.4 years (8.6)	59.1 years (12.1)	48.5 years (11)
BMI at baseline, mean (SD)	27.5 (5.4)	27.4 (5.6)	26.1 (4.8)	25.2 (4.3)
Active smoking, n (%)	32 (7.7)	27 (10.9)	43 (12.3)	5 (9.8)
Cancer details				
Ductal, n (%)	296 (71)	167 (67)	218 (62)	27 (53)
Lobular, n (%)	58 (14)	41 (17)	96 (27)	13 (26)
DCIS, n (%)	18(4)	7(2.8)	11(3)	5(10)
T1, n (%)	348 (84)	170 (69)	152 (43)	31 (61)
T2, n (%)	60 (15)	75 (30)	159 (45)	16 (3)
T3, n (%)	1 (0)	2 (1)	28 (8)	3 (6)
T4, n (%)	0	0	8 (2)	0
N0, n (%)	317 (76)	150 (61)	154 (44)	32 (63)
N1, n (%)	83 (20)	73 (29)	122 (35)	16 (31)
N2, n (%)	12 (3)	20 (8)	54 (15)	3 (6)
N3, n (%)	3 (1)	5 (2)	20 (6)	0
Grade 1, n (%)	170 (41)	69 (28)	62 (18)	5 (10)
Grade 2, n (%)	151 (36)	105 (42)	131 (37)	20 (39)
Grade 3, n (%)	92 (22)	74 (30)	157 (45)	25 (49)
Treatment				
Axillary clearance, n (%)	86 (21)	87 (35)	210 (60)	19 (37)
Radiation therapy, n (%)	413 (100)	239 (96)	171 (49)	17 (33)
Chemotherapy, n (%)	131 (32)	129 (52)	231 (66)	32 (63)
Endocrine treatment, n (%)	279 (67)	187 (75)	266 (76)	34 (67)
Encountered recurrence	9 (2.2)	8 (3.2)	14 (4)	1 (2)

	Immediate					Delayed					
Reconstruction type, n	**Total** 51	**Abdominal** 16	**LD** 19	**Implant** 12	**TMG** 4	**Total** 41 (1LAP)	**Abdominal** 14	**LD** 10	**Implant** 3	**Fat graft** 6	**Reduction** 7
Age at time of reconstruction, mean	48.5 (25-64)	48.4 (25-63)	53 (32-64)	44 (28-62)	41 (27-56)	53.9 (26-79)	52.7 (36-65)	55.3 (41-75)	47 (33-55)	48 (34-55)	61 (26-79)
BMI at baseline, mean	25.2	26.3	25.5	23.6	23.9	24.6	25.1	24.4	21.6	22.5	27.4
Months from primary surgery, mean (range)	-	-	-	-	-	20.5 (10-24)	20.6 (12-24)	21.1 (15-24)	24	22 (19-24)	16.3 (10-23)
Axillary clearance n (%)	19 (37.3)	7 (43.8)	7 (36.8)	4 (33.3)	1 (25)	20 (48.8)	5 (35.7)	4 (40)	3 (100)	2 (33.3)	5 (71.4)
Ductal carcinoma n (%)	27 (52.9)	7 (43.8)	10 (52.6)	8 (66.7)	2 (50)	27 (65.9)	9 (64.3)	5 (50)	1 (33.3)	6 (100)	5 (71.4)
Lobular carcinoma n (%)	13 (25.5)	5 (31.3)	5 (26.3)	2 (16.7)	1(25)	11 (26.8)	3(21.4)	5 (50)	2 (66.7)	0	1(14.3)
DCIS n (%)	5 (9.8)	1 (6.3)	3 (15.8)	0	1 (25)	0	0	0	0	0	0
Stage 1a/1b n (%)	20(39.2)/0	6(11.8)/0	5(9.8)/0	7(13.7)/0	2(3.9)/0	16(39)/0	6(14.6)/0	6(14.6)/0	1(2.4)/0	1(2.4)/0	2(4.9)/0
Stage 2a/2b n (%)	10(19.6)/14(27.5)	6(11.8)/2(3.9)	1(2)/11(21.6)	2(3.9)/1(2)	1(2)/0	19(46.3)/4(9.8)	7(17.1)/1(2.4)	3(7.3)/1(2.4)	1(2.4)/0	5(12.2)/0	3(7.3)/2(4.9)
Stage 3a/3b n (%)	6(11.8)/0	2(3.9)/0	1(2)/0	2(3.9)/0	1(2)/0	0/0	0/0	0/0	1(2.4)/0	0/0	0/0
Radiation therapy n (%)	17 (33.3)	4 (25)	6 (31.6)	5 (41.7)	2 (50)	22 (53.7)	7 (50)	4(40)	1 (33.3)	4 (66.7)	5 (71.4)
Chemotherapy n (%)	32 (62.7)	10 (62.5)	8 (42.1)	11 (91.7)	3 (75)	26 (63.4)	7 (50)	7 (70)	2 (66.7)	4 (66.7)	5 (71.4)
Endocrine treatment n (%)	34 (66.7)	13 (81.3)	12 (63.2)	7 (58.3)	2 (50)	35 (85.4)	12 (85.7)	9 (90)	2 (66.7)	6 (100)	5 (71.4)
Targeted therapy n (%)	7 (13.7)	0	1 (5.3)	5 (41.7)	1 (25)	8 (19.5)	3 (21.4)	1 (10)	1 (33.3)	1 (16.7)	2 (28.6)
Recorded complication n (%)	18 (35.3)	4 (25)	8 (42.1)	6 (50)	0	13 (31.7)	7 (50)	3 (30)	0	0	2 (28.6)
Length of stay at reconstruction phase, mean days (range)	5.4 (2-9)	6.5 (2-9)	5.8 (2-7)	3.1 (2-6)	6.5 (6-7)	4.7 (1-14)	7.1(5-10)	5.2 (4-7)	3(2-4)	1.3 (1-2)	1.7 (1-2)
Smoking, active n (%)	5 (9.8)	2 (12.5)	3 (15.8)	0	0	3 (7.3)	2 (14.3)	1 (10)	0	0	0
Smoking, quitted n (%)	8 (15.7)	3 (18.8)	2 (10.5)	2 (16.7)	1 (25)	3 (7.3)	1 (7.1)	2 (20)	0	0	0

Table 5. Detailed patient characteristics for different breast reconstruction methods in Study III. N, means, percentages. Reproduced with permission from Springer Nature (Rautalin et al. 2022).

7.2 Response rate

The response rate was 59% in *Study I*. The response rate in *Studies II* and *IV* for those having answered at baseline was 93% at 3 months, 95% at 6 months, 94% at 12 months and 90% at 24 months. The response rate in *Study III* was for IBR 94/DR 93% at 3 months, IBR 98/DR 100% at 6 months, IBR 98/DR 95%, and IBR 92/DR 93% at 24 months.

Some questions were left unanswered, most often those regarding sexual wellbeing. Some answers were missing at baseline from approximately 5 % of the respondents and, depending on the question, from 7 to 14 % at 12 months and from 14 to 20 % at 24 months (*Studies II-IV*).

7.3 Follow up

Studies II-IV

139 (13.1%) patients encountered a complication (excluding seroma formation) during the two-year follow-up. 42 (3.9%) patients had to have seroma drained more than 10 times. One patient encountered a fatal complication (Clavien-Dindo V) after chemotherapy at four months postoperatively (wide cerebral infarction). One patient, who had earlier had an esophagus perforation after gastroscopy, encountered another esophagus perforation at 6 months after chemotherapy (Clavien-Dindo IV), resulting in esophagectomy, percutaneous gastrostomy, and later reconstruction of the esophagus. One patient encountered subarachnoid hemorrhage needing operative treatments (Clavien Dindo IV). Four patients encountered a pulmonary thrombosis, two deep venous thrombosis of a lower limb, and two an upper limb venous thrombosis (Clavien-Dindo IV). One patient had a pulmonary reaction from chemotherapy and another pneumonia requiring intensive care treatment (Clavien-Dindo IV). All but one Clavien-Dindo class IV and V complication occurred after oncological treatments. One pulmonary thrombosis was detected after implant replacement operation. The rest of the complications were not life threatening and ranged from minor immediate wound dehiscence to mild infections (Class I-II) and from hematomas to more severe infections or scarring problems that resulted in surgical interventions (Class IIIa-IIIb). Factors that correlated with complications were high BMI ($p<0.01$) and active smoking ($p<0.05$). Diabetes did not correlate with complications.

18 (35.3%) of IBR patients in *Study III* encountered a complication. One implant had to be removed due to infection, but no total loss of flaps occurred. Class IIIb complications in this group were skin necrosis, infection, and hematomas, which resulted in re-operations. One of them was an anastomosis check of the axillary artery after suspicion of insufficient arterial flow.

Anastomoses were re-done, and no further complications occurred. One expander implant was punctured while filling. This resulted in more frequent fillings before placing the permanent implant but no further problems.

13 (31.7%) of DR patients in *Study III* encountered a complication. Two total losses of flaps occurred: one LAP due to slowly fading circulation and one abdominal flap due to arterial thrombosis five days postoperatively. One patient had a hematoma at the operation site of the LD that led to removal of the implant, but the LD was saved. One patient presented a hernia at the donor site of the abdominal flap that resulted in revision and reconstructive surgery with a mesh. Table 6 presents the reconstruction patients' complications according to the Clavien-Dindo classification reconstruction methods.

32 of 1065 patients (3%) encountered a recurrence of the disease, and 22 patients (2.1%) encountered another cancer during follow-up. 16 patients (1.5%) died during follow-up. Two recurrences occurred -- one in the IBR and one in the DR group -- in the reconstruction groups. One IBR implant patient presented axillary metastases at 16 months that resulted in axillary clearance. The stage of her disease had been Grade 3 ductal carcinoma, T2 at baseline. One DR patient's recurrence was found at one year from baseline, resulting in DIEP-abdominal flap reconstruction.

Table 6. Complications according to Clavien-Dindo classification for reconstruction methods (Study III). Site of complication is indicated as "recipient" if the complication was at chest wall/mastectomy site and "donor" if the complication occurred at the site where the reconstruction tissue was raised. Clavien-Dindo I = less severe to class IIIb = most severe complication. No fatal complications occurred. Reproduced with permission from Springer Nature (Rautalin et al. 2022).

Immediate reconstruction	**Clavien-Dindo I**	**Clavien-Dindo II**	**Clavien-Dindo IIIa**	**Clavien-Dindo IIIb**
LD *recipient*	II		II	IIII
donor				
Abdominal flap *recipient*	I			III
donor				
Implant	II	II	I	I
TMG				
Delayed reconstruction	**Clavien-Dindo I**	**Clavien-Dindo II**	**Clavien-Dindo IIIa**	**Clavien-Dindo IIIb**
LD *recipient*				I
donor		I	I	
Abdominal flap *recipient*			I	III
donor	I			II
Implant				
Fat grafting				
Other		II		I

LD = latissimus dorsi flap, TMG = transverse musculocutaneus gracilis flap, Other = reduction, LAP.

7.4 Examination of Quality Indicators

Quality Indicators were examined for the prospective study population in applicable aspects. Re-operation rates, number of axillary surgery snb vs. axillary clearance and the proportion of patients having BCS and adjuvant radiation therapy were recorded. Table 7 presents the results.

Table 7. Percentages of surgical quality indicators achieved in study population of Studies II-IV. Underlined percentages indicate those QI's that were fulfilled according to EUSOMA guidelines.

	% achieved	Min % recommended
% of single operation for BCS or Mastectomy	86.2	80
% of single operation for DCIS	80.5	70
% snb for N0 state disease	91.7	90
% snb for DCIS	95.1	97
% BCS + radiation therapy	98.2	90

7.5 HRQoL

Differences between HRQoL measuring tools

Study I evaluated the differences between EORTC QLQ-30, EQ-5D, VAS and 15D in breast cancer patients with various states of the disease. With all the measuring tools, HRQoL deteriorated in patients with a higher disease burden or more advanced state. With the generic tools that provide HRQoL scores, VAS gave the lowest scores in all other groups than the palliative care group. EQ-5D presented high ceiling effects in all disease states. The ceiling effect with EQ-5D was 41.3%, with 15D 6.0%, and with VAS 5.6%.

HRQoL in different states of breast cancer

HRQoL deteriorated with a heavier disease burden or advanced state in *Study I*. Figure 1 presents mean HRQoL utility scores with generic measuring tools.

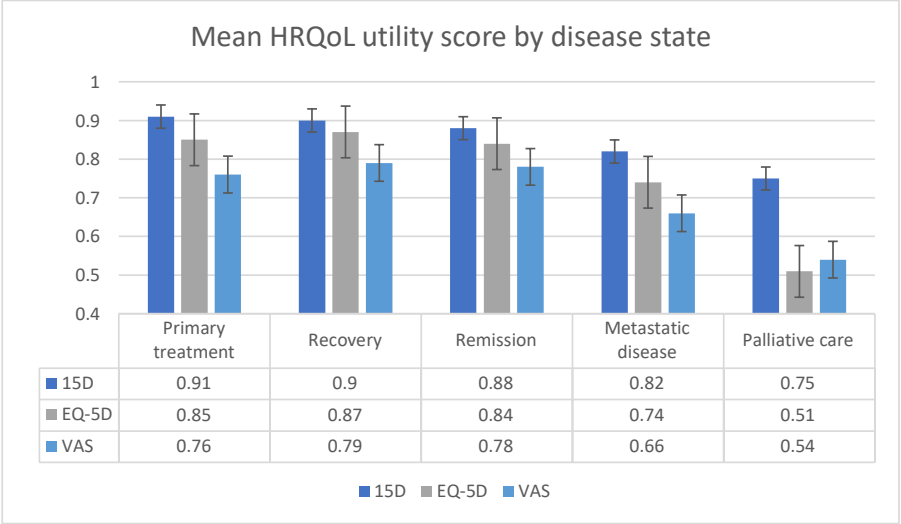

Figure 1. Mean HRQoL utility scores with different measuring tools by breast cancer disease state in *Study I*. Reproduced with permission from Taylor & Francis group (Rautalin et al. 2018).

All patient groups presented symptoms of fatigue, pain, and insomnia. Social, role and physical functioning were the most affected with EORTC. With 15D, sleeping and discomfort and symptoms were affected in all disease states. Usual activities, mobility, vitality, and sexuality were more affected at the metastatic disease and palliative care states than at earlier states.

Factors influencing HRQoL

The analysis of explanatory factors for HRQoL in *Study I* revealed in the *Phase I* analysis that age, financial difficulties, and belonging to the metastatic or palliative group were explanatory factors with all measuring tools with statistically significant P-values. 26–38% of the variance of HRQoL scores were explained by *Phase I* factors. Financial difficulties, pain and fatigue were found to be explanatory factors for diminishing HRQoL scores when EORTC symptom and functional scores were entered into the *Phase II* analysis. The explanatory power of the variance of scores rose with all measuring tools: with 15D up to 72.5%, with EQ-5D up to 63.1%, and with VAS up to 52.2%. Table 8 shows the results of the regression analyses.

Table 8. Statistically significant factors influencing HRQoL scores, Study *I*. Reproduced with permission from Taylor & Francis group (Rautalin et al. 2018). *p<0.05, **p<0.01, ***p<0.001

	15D		**EQ-5D**		**VAS**	
Variable	Std coefficient	*p*-value	Std coefficient	*p*-value	Std coefficient	*p*-value
Phase 1 Model	R^2=0.377		R^2=0.263		R^2=0.277	
Age	-0.158	<0.001***	-0.084	0.021*	-0.088	0.011*
Financial Difficulties	-0.490	<0.001***	-0.392	<0.001***	-0.401	<0.001***
Higher education	0.068	0.043*	0.093	0.011*	-	-
Local disease	-	-	-	-	-0.096	0.006**
Metastatic disease	-0.194	<0.001***	-0.161	<0.001***	-0.241	<0.001***
Palliative care	-0.169	<0.001***	-0.187	<0.001***	-0.157	<0.001***
Phase 2 model	R^2=0.725		R^2=0.631		R^2=0.522	
Age	-0.112	<0.001***	-0.069	0.002**	-	-
Appetite loss	-	-	-	-	-0.062	0.042*
Constipation	-0.094	<0.001***	-	-	-	-
Diarrhea	-0.050	0.012*	-	-	-	-
Dyspnea	-0.202	<0.001***	-	-	-0.074	0.009**
Fatigue	-0.345	<0.001***	-0.276	<0.001***	-0.342	<0.001***
Financial difficulties	-0.160	<0.001***	-0.107	<0.001***	-0.085	0.003**
Insomnia	-0.129	<0.001***	-	-	-	-
Metastatic disease	-0.040	0.044*	-	-	-0.071	0.006**
Pain	-0.187	<0.001***	-0.513	<0.001***	-0.302	<0.001***
Palliative care	-0.046	0.018*	-0.065	0.003**	-	-

Factors affecting HRQoL varied in *Study II* depending on the measuring tool. Higher age (p=0.008), comorbidity burden (p<0.000), and having to go through more than 10 times of seroma aspiration (p<0.04) correlated negatively with the 15D total score but not with the EORTC global score. High BMI (p<0.05) correlated negatively with HRQoL with both instruments. High disease burden correlated negatively with HRQoL: Grade, T-, N-, and M-class all affected the scores at some measuring point as listed in Table 9. Axillary clearance correlated negatively with HRQoL with both instruments from 3 to 12 months (p<0.01), and EORTC still at 24 months (p<0.002). Having to go through more than one surgical operation, encountering a recurrence, receiving radiation therapy or endocrine treatment, did not affect HRQoL. Encountering a complication did not correlate with HRQoL for IBR or DR with either of the measuring tools, p>0.05 (*Study III*).

Table 9: Regression analysis results in *Study II*. Statistical significance (*p*-values) and standard coefficients (Std Co) of nominated factors' effect on overall HRQoL at different measuring points: EORTC above, 15D below in box. Table presents those factors that affected HRQoL negatively, other tested factors did not have statistically significant effect on HRQoL with either measuring tool. Reproduced with permission from Elsevier Ltd. (Rautalin et al. 2021)

Variable		3 Months		6 Months		12 Months		24 Months	
		p-value	Std Co	*p*-value	Std Co	*p*-value	Std Co	*p*-value	Std Co
Grade	EORTC	0.015*	-0.094	ns		ns		ns	
	15D	0.000***	-0.150	ns		ns		ns	
T - class	EORTC	ns		ns		0.014*	-0,086	ns	
	15D	ns		ns		ns		ns	
N - class	EORTC	0.000***	-0.174	ns		ns		ns	
	15D	0.001***	-0.131	0.032*	-0.079	0.001***	-0,106	0.002**	-0.103
M - class	EORTC	ns		ns		ns		0.032*	-0.071
	15D	ns		ns		ns		ns	
BMI	EORTC	0.012*	-0.094	-		-		-	
	15D	0.002**	-0.113						
Chemo	EORTC	-		0.000***	-0.245	0.032*	-0,075	0.013*	-0.082
therapy	15D			0.000***	-0.158	ns		ns	

*p<0.05, **p<0.01, ***p<0.001

Differences in HRQoL results depending on surgical method

The EORTC symptom and functioning scores varied in *Study II* along with time, as did the global HRQoL score (Figure 2). The variance analysis showed at the end of the 24-month follow-up endpoint that there were only a few symptom and functional scores that differed between the groups in a statistically significant manner ($p<0.05$). Mastectomy patients reported the most financial difficulties and arm symptoms. BCS produced high body-image scores, and oncoplastic surgery had the highest. Breast reconstruction patients had the highest physical and sexual functioning scores at baseline and during the whole study period (Table 10). Pain, fatigue, and sleeping disturbances were reported in all groups and at all measurement points. Mastectomy patients reported more pain at baseline ($p<0.05$), but later the difference between the different study groups was not significant ($p>0.05$).

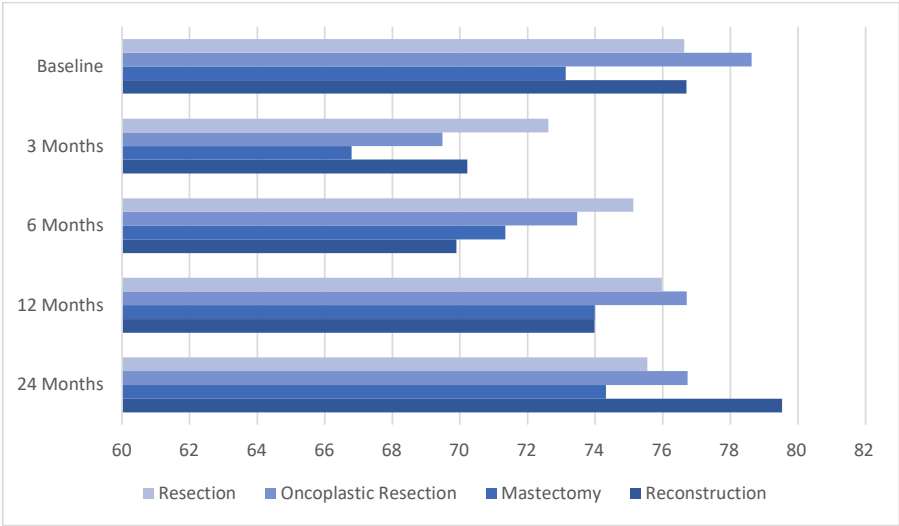

Figure 2: Mean EORTC HRQoL global scores for the study groups by time (*Study II*). High score indicates good health. Reproduced with permission from Elsevier Ltd. (Rautalin et al. 2021)

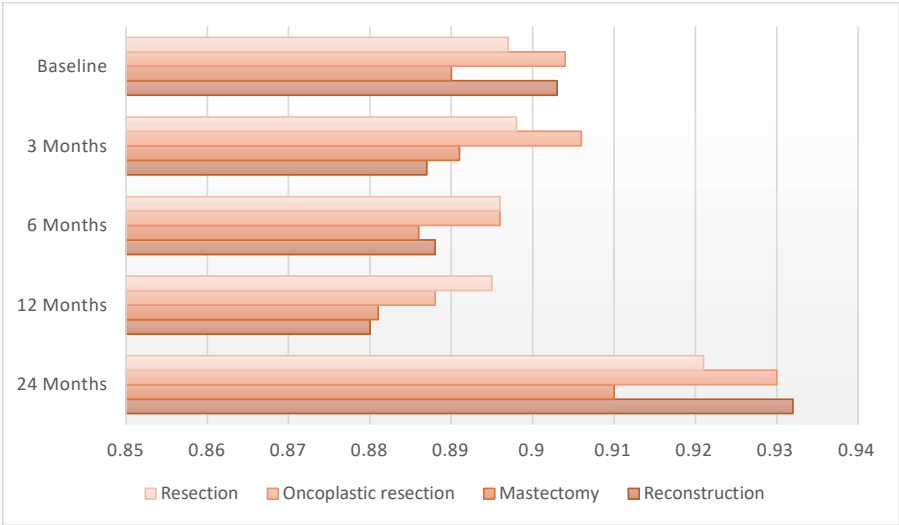

Figure 3. Mean 15D HRQoL total scores for the study groups by time (*Study II*). High score indicates good health.

Table 10. Means, Standard deviations and 95% Confidence intervals between groups regarding those EORTC Functional and Symptom scores that were statistically significantly different between the groups at 24 Months (*Study II*). High value represents good functional status for Physical functioning, Body Image and Sexual functioning. High value represents problems in this particular area for symptom scores of Financial difficulties and Arm symptoms. Reproduced with permission from Elsevier Ltd. (Rautalin et al. 2021)

24 Months		Resection			Oncoplastic Resection			Mastectomy			Reconstruction		
	P	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI	Mean	SD	95% CI
Financial difficulties	0.012*	7.123	20.022	5.062; 9.184	4.921	16.373	2.693; 7.148	9.29	19.988	7.037; 11.542	8.696	20.409	2.635; 14.756
Physical functioning	0.002**	82.511	17.506	80.714; 84.308	85.548	14.363	83.594; 87.502	81.832	17.654	79.836; 83.827	90.519	12.018	86.908; 94.129
Body Image	0.000***	85.808	19.623	83.794; 87.823	86.019	18.131	83.558; 88.48	70.500	27.367	67.391; 73.609	67.803	27.702	59.381; 76.225
Sexual functioning	0.046[B]	26.6	26.079	23.854; 29.345	25.248	25.714	21.680; 28.815	22.569	25.803	19.577; 25.562	32.576	26.646	24.475; 40.677
Arm symptoms	0.000***	11.929	17.141	10.169; 13.688	15.377	18.368	12.884; 17.869	19.616	19.377	17.440; 21.792	10.386	13.334	6.427; 14.347

[B] Bonferroni's test can't identify which groups differ, *p<0.05, **p<0.01, ***p<0.001. Highest mean underlined.

Total HRQoL scores varied between groups in time for the 15D (Figure 3). A statistically significant change was found from baseline to 3 months for all groups ($p<0.05$). The rise in the total HRQoL score from the lowest 3-month timepoint was clinically significant for oncoplastic resection patients already at 12 months, but for reconstruction patients later at 24 months (MID reaching equal or higher than 0.015 change, Table 11). The rise in the total 15D score did not reach clinically significant values for resection and mastectomy patients. Sleeping disturbances and Discomfort and symptoms were the most affected in all groups of the dimensions reported (Figure 4).

Table 11. 15D Mean score by groups (*Study II*). High value represents good health, 1.0 being the best possible. Even small changes in these numeric values are significant according to the MID marked with an asterix. Reproduced with permission from Elsevier Ltd. (Rautalin et al. 2021)

15D mean score	Resection	Oncoplastic resection	Mastectomy	Reconstruction
Baseline	0.921	0.930	0.910	0.932
3 Months	0.895*	0.888*	0.881*	0.88*
6 Months	0.896	0.896	0.886	0.888
12 Months	0.898	0.906**	0.891	0.887
24 Months	0.897	0.904**	0.890	0.903**

* MID ≥0.015 change from baseline ** MID ≥ 0.015 change from lowest measured timepoint within groups

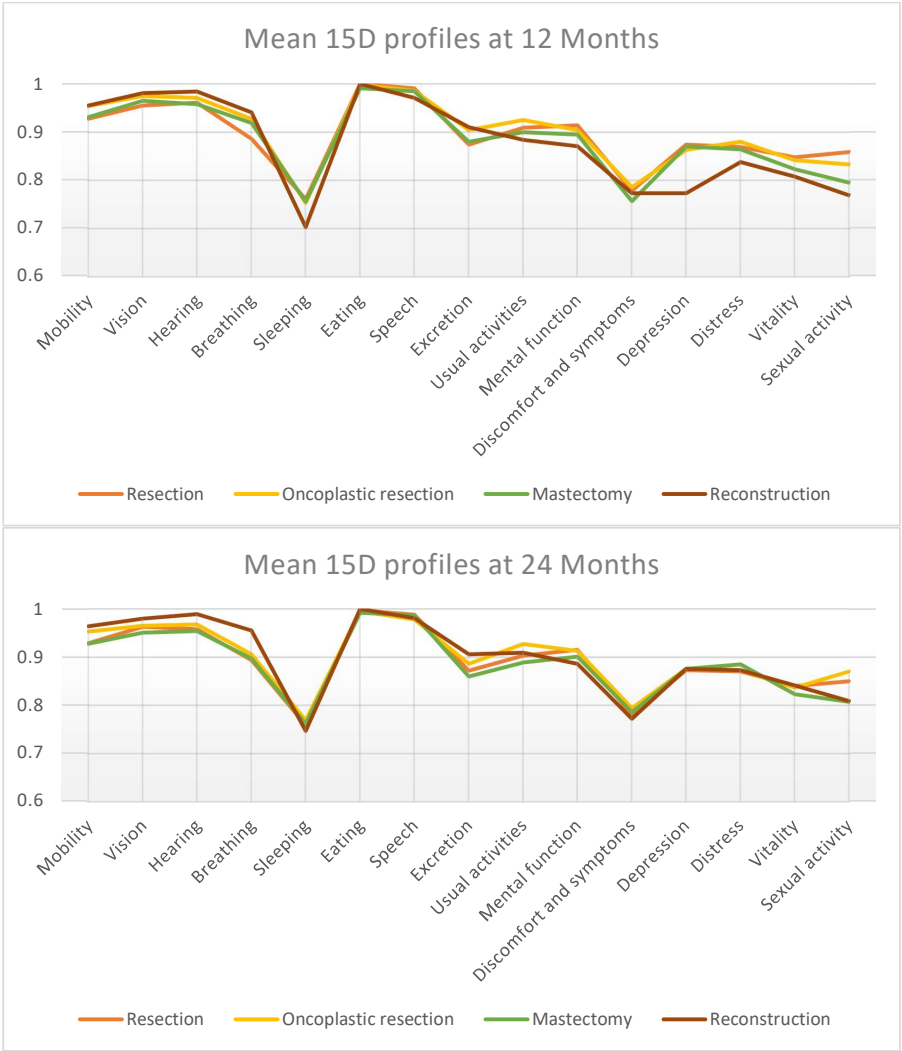

Figure 4. 15D health profiles of different groups (mean) at 12 and 24 months (*Study II*).

Differences in HRQoL results depending on the timing of breast reconstruction

EORTC showed a statistically significant difference in global score change from 12 to 24 months (p= 0.017) between the IBR and DR groups when comparing the change in HRQoL scores between breast reconstruction patients: HRQoL improved in the IBR group, whereas it deteriorated in the DR group. The change in overall score profile was different for 15D than that found with EORTC, but the change was not statistically significant (p>0.05). HRQoL improved with 15D in both group from 12 months to 24 months but remained lower at 24 months than at baseline (Figure 5).

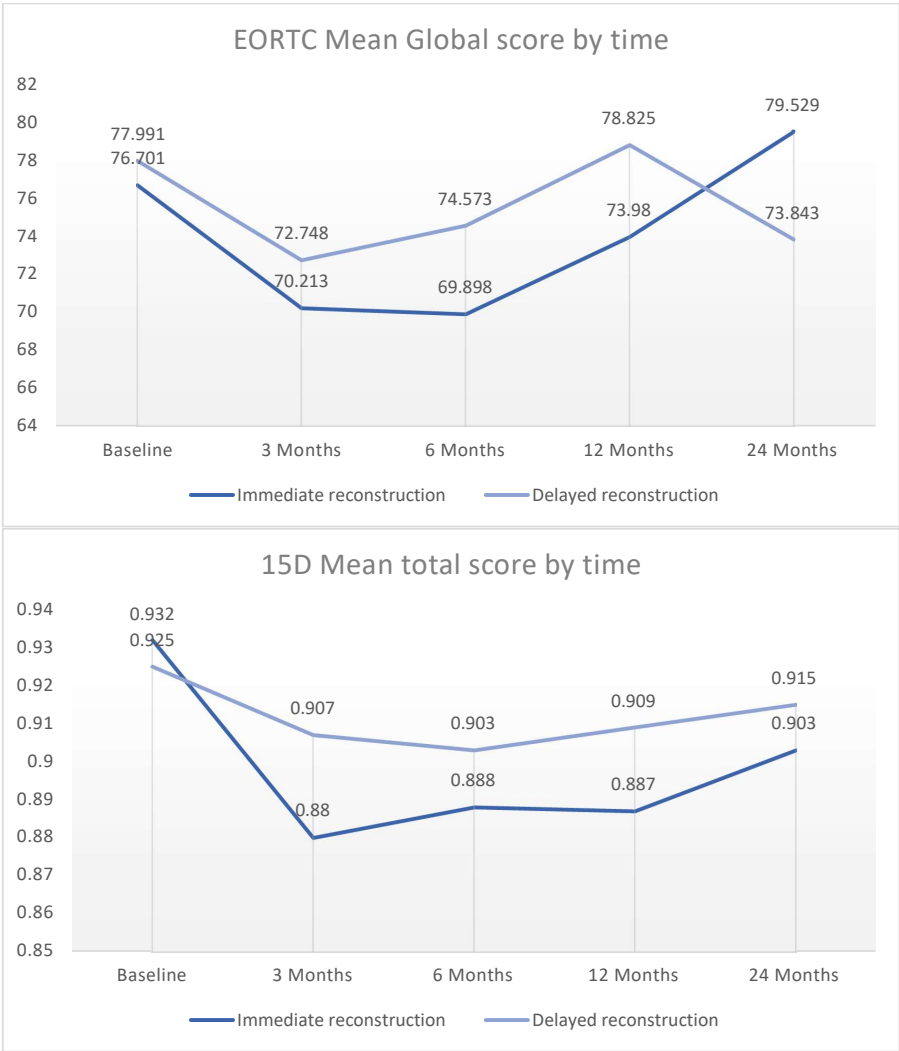

Figure 5. Mean total HRQoL scores for EORTC and 15D for IBR and DR groups in relation to time (*Study III*). Reproduced with permission from Springer Nature (Rautalin et al. 2022).

Regarding EORTC QLQ-30 BR 23-specific questions, Sexual functioning scores diminished in both the IBR and DR groups. The drop in the score was steeper for the DR group with a statistically significant difference ($p< 0.01$). IBR patient's arm symptoms diminished after 12 months, but they increased for DR ($p<0.001$).

Differences in HRQoL results depending on breast reconstruction method

The total 15D score and the Global EORTC score did not differ between surgical groups in IBR or DR patients at 12 or 24 months (p>0.05). All groups reported disturbances in Sleeping, Discomfort and Symptoms and Sexual functioning, but the differences between the groups was not statistically significant when measured with 15D (p>0.05) (Figure 6). There was only one difference in the symptom scores of the patient groups operated on with different methods: EORTC QLQ C-30 BR23 found a difference at 12 months in the IBR group -- abdominal flap patients reported more Systemic therapy side effects than implant patients (p= 0.034). Patients reported similar symptoms of Fatigue, Pain and Sleeping disturbances (all scores in both IBR and DR groups p>0.05) at 24 months, irrespective of the surgical method. The same was true for EORTC functional scores; no statistically significant differences were found between surgical methods (p>0.05) (Figure 7).

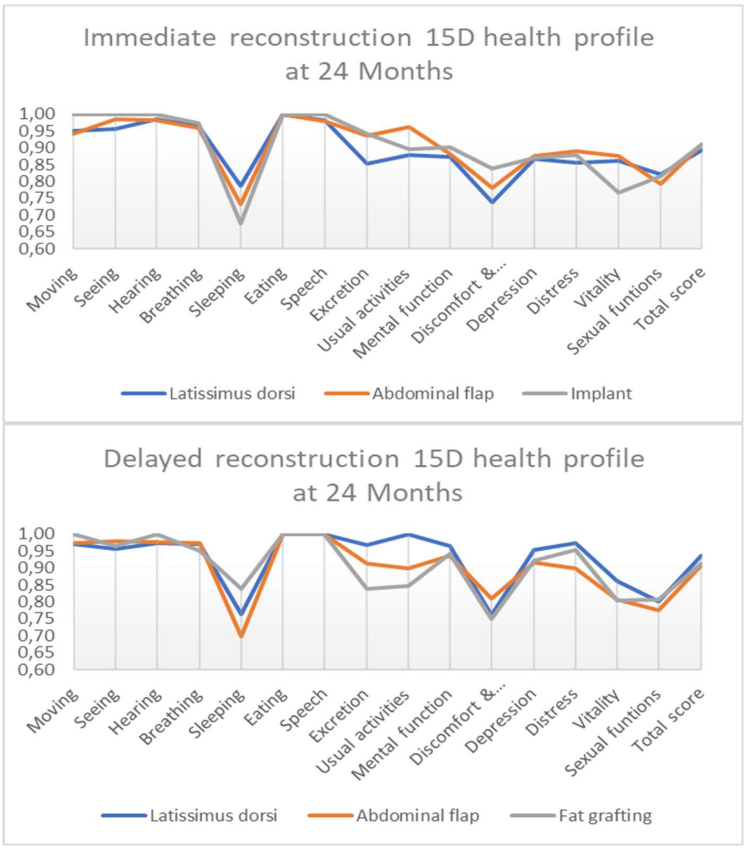

Figure 6. Mean health profiles at 24 months for patients operated on with different surgical methods (*Study III*). No statistically significant differences were found between groups for 15D (p>0.05). Reproduced with permission from Springer Nature (Rautalin et al. 2022).

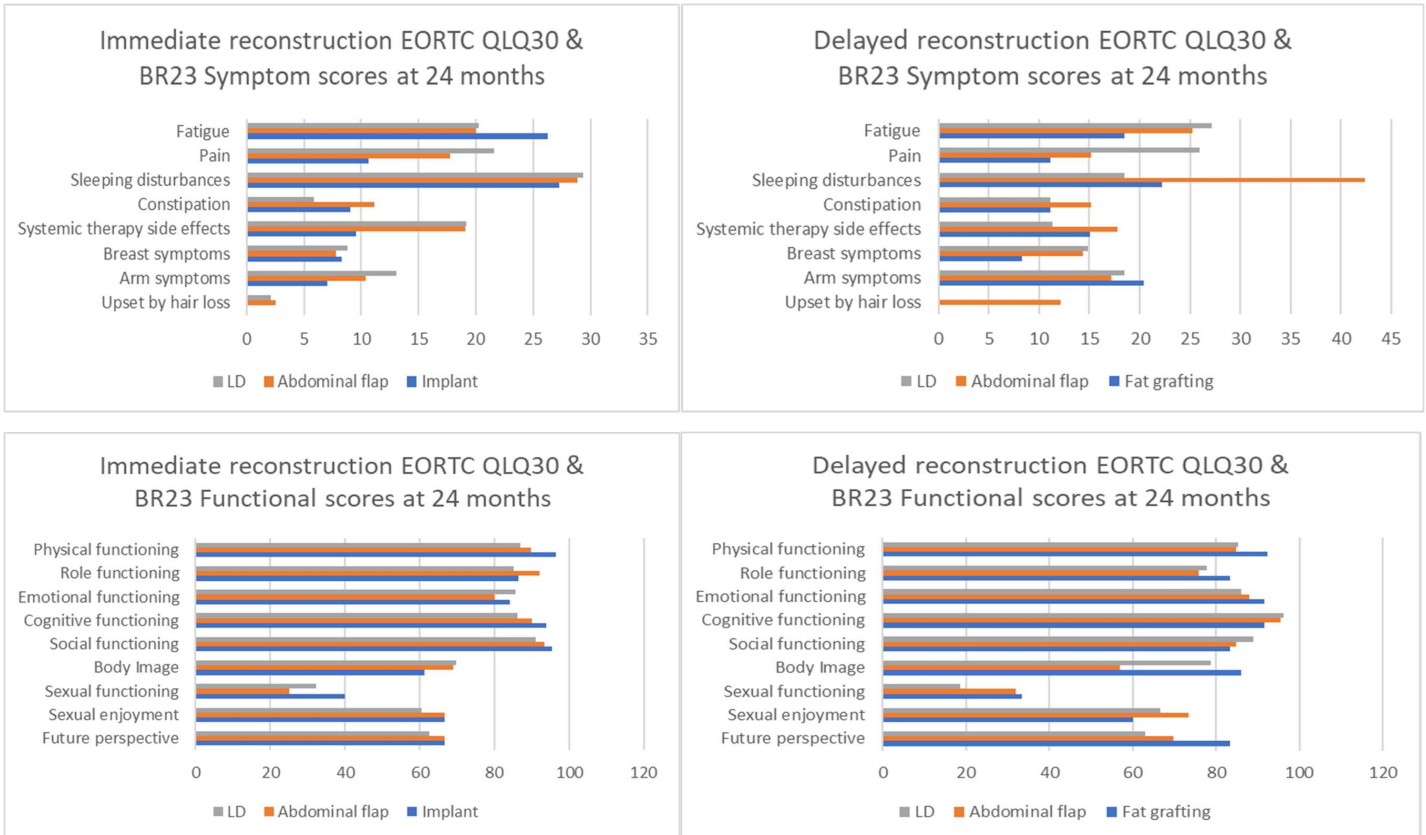

Figure 7. Mean EORTC Symptom and Functional scores for patients operated on with different surgical methods. No differences were found between groups (p>0.05). Reproduced with permission from Springer Nature (Rautalin et al. 2022).

7.6 Cost of care

The costs of oncological care

Data about costs of oncological care were found for 1 004 patients from the ECOMED database. Data were missing for 61 patients.

Mean total cost of care in the oncological department was 8 521 Euros per patient (SD 10 424) during the two-year follow-up. Patients rarely spent time at oncology wards, only a mean of 0.3 days, but they paid frequent visits to the outpatient departments: mean 31 visits per patient and mean 19 outpatient clinic procedures. Radiation therapy is given at the outpatient clinic. Patients received expensive medications (other than standard chemotherapy, for example, trastutsumab) a mean of 4.2 times per patient. Figure 8 presents a more detailed distribution of the costs of oncological care.

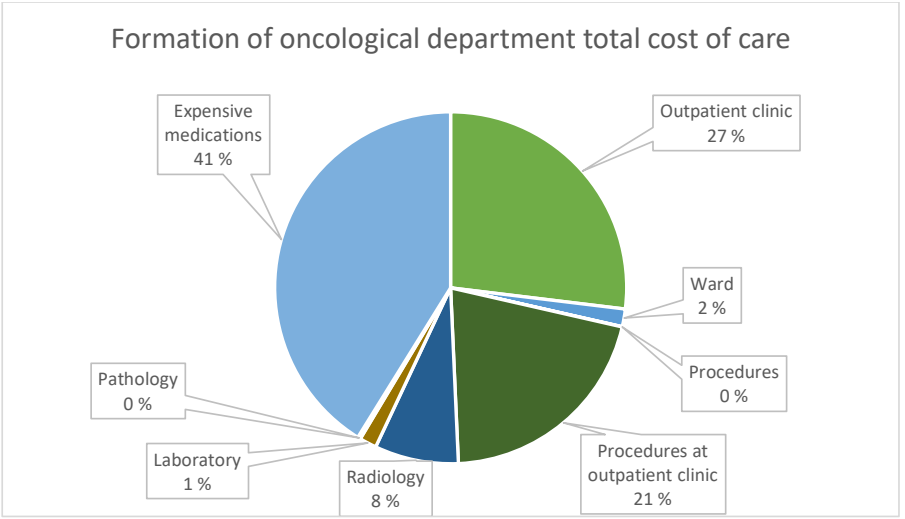

Figure 8. Oncological department cost distribution, mean (n = 1004). Reproduced with permission from International Institute of Anticancer Research (Rautalin et al. 2022).

Patients with distant metastases at baseline triggered an accumulation of oncological care costs up to a mean of 41 602 Euros during follow-up. Patients who died during follow-up incurred a mean cost of 18 014 Euros. Those encountering a recurrence but surviving through the follow-up incurred a mean oncological care cost of 14 690 Euros (Table 12).

Table 12. All patients' oncological treatment costs in Euros (mean) depending on disease status during follow-up. Highest costs are underlined. Reproduced with permission from International Institute of Anticancer Research (Rautalin et al. 2022).

	All Patients n = 1004	**Patients with M1 at baseline n = 11**	**Patients with recurrences n = 32**	**Patients who died during follow-up n = 15**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Total cost	8 521 (10 424)	41 602 (37 493)	14 690 (12 895)	18 014 (26 739)
Outpatient clinic	2 239 (1 658)	5 578 (3 949)	3 834 (2 693)	3 131 (3 330)
Ward costs	136 (807)	733 (1 335)	994 (2 817)	1 979 (3 880)
Procedures	1.8 (40)	0	32 (182)	69 (266)
Outpatient clinic procedures	1 723 (935)	1 515 (1 147)	2 185 (1 121)	1 725 (1 418)
Radiology	642 (749)	3 381 (1 895)	1 552 (1 228)	1 561 (1 761)
Laboratory	131 (165)	496 (279)	307 (252)	276 (279)
Pathology	21 (114)	109 (209)	151 (374)	176 (377)
Expensive treatments	3 423 (8 010)	28 809 (32 319)	5 179 (8 369)	8 555 (21 294)

The costs of surgical care

Data about surgical care cost were found for 946 patients from the ECOMED database. Data were missing for 119 patients: 70 BCS, 37 mastectomy, 9 IBR, and 3 DR patients.

The mean cost of surgery was 6 015 Euros in BCS patients; 8 114 Euros in mastectomy patients; 18 214 Euros in IBR patients; and 19 041 Euros in DR patients during the follow-up. IBR patients spent the most days on wards (mean 7.7 days), had the highest number of outpatient clinic visits and outpatient clinic procedures, and, consequently, the highest outpatient clinic costs. The total cost of treatment (operation and inpatient treatment costs) were the highest in DR patients of all groups. Mastectomy patients visited the outpatient clinic a mean of 13.1 times, BCS patients a mean of 6.4 times. Thus, the cost of mastectomy patients' outpatient treatment was almost double that of BCS patients (Table 13).

Table 13. Surgical costs, oncological total cost, and specifics of surgical cost formation for different groups in Euros, mean (SD), during follow-up. Highest underlined. Reproduced with permission from International Institute of Anticancer Research (Rautalin et al. 2022).

	BCS (n = 591)	**Mastectomy (n = 282)**	**IBR (n = 42)**	**DR (n = 31)**
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Total cost of surgery	6 015 (2 901)	8 114 (4 020)	18 217 (9 355)	19 041 (10 695)
Total cost of oncological treatments	7 460 (9 217)	10 746 (12 734)	8 102 (8 362)	9 504 (9 435)
Cost of operation theatre procedures	2 572 (1 428)	3 047 (1 593)	8 560 (5 069)	9 381 (4 996)
No. of surgical procedures	1.3 (0.8)	1.8 (1.5)	3.3 (2.7)	3.5 (3.4)
Ward costs	714 (1 072)	1 264 (886)	3 999 (2 682)	4 162 (3 968)
Days spent at wards	1.1 (1.8)	2.2 (3.3)	7.7 (4.9)	7.2 (6.2)
Outpatient clinic costs	656 (641)	1 235 (886)	1 894 (992)	1 747 (1 027)
No. of visits at outpatient clinic	6.4 (5.7)	13.1 (8.6)	19.7 (9.4)	18 (9.8)
Outpatient clinic procedure costs	117 (190)	38.6 (163)	540 (506)	345 (585)
No. of outpatient clinic procedures	4 (4.9)	11.2 (8.1)	16.9 (8.4)	15.5 (9.5)

8 DISCUSSION

8.1 Study population

The recruitment process for *Studies II-IV* was prolonged due to mandatory halting of the recruitment to allow other studies to recruit patient material at times. This was done to protect patients from experiencing too high a burden caused by studies in a difficult situation when they have just received a cancer diagnosis. This halting of the recruitment process hampered the data collection so that the exact number of patients recruited at baseline remained uncertain. Thus, the baseline response rate is unknown. The response rate of 59% in *Study I* is in line with previous studies, as a recent review has indicated (Meyer et al. 2022).

Patients who died were included in the response rate percentage calculations at all measuring points in *Studies II-IV*. There was a drop in the response rate at three months that is understandable, presumably because of tiredness caused by possible oncological treatments. However, the response rate increased again after three months. It was delightful to discover at later follow-up points how meticulous patients were in returning the questionnaires, and the response rate remained at an astonishingly high level of over 90 percent throughout the study period of two years.

The whole answer was marked as a non-response if the global score could not be computed due to missing answers. All groups presented similar numbers of missing answers: depending on the question, some data were missing for approximately 5% of responses at baseline, some data from 7% to 14% at 12 months, and from 14 to 20% at 24 months.

Finding a common factor for not answering is not easy; some patients did not answer at some timepoints but then answered at the next one. Some patients remained loyal to the research from baseline to the end and returned the questionnaires at all timepoints, even some of those who encountered a recurrence. The reasons for patients not answering the questionnaires are unclear. Most often the questions left unanswered were those concerning sexual wellbeing. The search for common factors for a non-response did not produce any obvious reasons; the mean age of the respondents did not differ from that of the non-respondents, and the number of complications was similar in both groups. The only difference found between responding and non-responding patients was observed in mastectomy patients, of whom 76% of non-respondents received chemotherapy compared to 66% of respondents.

8.2 Limitations and strengths of the study

A limitation in *Study I* is the small patient group of palliative care patients; it is the rather small patient group of breast reconstruction patients in *Studies II-IV*. Group comparisons between reconstruction methods had to rule out some methods due to group sizes (four TMG in IBR, and three implants and one LAP in DR). Bigger group sizes might reveal more differences between groups.

The unfortunate mandatory halting of the recruitment process resulted in not having a consecutive series of patients in *Studies II-IV* and prolonged the time of gathering the study group. The baseline response rate is unknown. The halting of recruitment presumably affected the number of reconstruction patients recruited and the long recruitment time in general might include some evolving trends in the choices that are made in patient care.

The economic aspect of breast cancer treatment costs is of a descriptive nature in *Study IV*. A cost-effectiveness analysis was not performed, nor were the productivity losses evaluated in this study.

The absolute strength of this study is evident in both the cross-sectional and prospective study: both study designs covered *all* different possible aspects that were under investigation. The cross-sectional study investigated the HRQoL of *all disease states* of breast cancer patients and found mutual explanatory factors for HRQoL that indicated the aspects on which health care should focus with patients at different states. The design is a strong strength in itself in the prospective study, but the study population of over 1000 patients is also respectable and, in the analysis, covering *all breast cancer surgery treatment options* is a strength and produces new data.

The very high commitment of patients in the prospective study is a strength: the 90 % response rate after baseline in repeated questionnaires is respectable and supports the high quality of the research.

The comparison of both generic and disease-specific measuring tools is valuable: *Study I* produced information about the weaknesses and strengths of different measuring tools. The research scene has not yet resolved the question of which HRQoL measuring tools should be used. The *Studies II-IV* method of investigating HRQoL with both generic and disease-specific tools gives weight to the interpretation of results. Different surgical methods and timings are evaluated critically, and factors influencing HRQoL are revealed in a study design covering all autologous and allogenous methods in a novel way.

The repeated measuring of HRQoL is a strength: this study design produces information about the recovery process of different study groups, and the 24-month follow-up is regarded as long-term follow-up.

The cost formation in *Study IV* over the whole two-year follow-up presents valuable information about how different treatment options generate costs. Reflecting the costs with HRQoL results might be usable information in future planning of treatments.

8.3 The choice of HRQoL measuring tools

There are many different HRQoL measuring tools available, but still no firm consensus exists concerning the most suitable tool. Recent recommendations have favored the disease-specific BREAST-Q in breast cancer studies, but it had not been validated in Finnish language at the onset of this thesis (Pusic et al. 2019). Consequently, although BREAST-Q is a promising tool, it was not an option in this thesis. Breast cancer outcome measurements of overall survival rates or relapse rates are not included in quality indicators as the EUSOMA Quality Indicator definitions state. HRQoL, however, is an outcome recommended to be measured in breast cancer patients' routine care, and the most reliable results are achieved when using validated tools (Biganzoli et al. 2017; Biganzoli et al. 2020). The use of both a generic and a disease-specific measuring tool as presented in this thesis is recommendable (Weber et al. 2020).

The EORTC QLQ30 –BR23 HRQoL measuring tool was chosen in this thesis because it is a well-established, breast cancer-specific questionnaire that produces both functional and symptom scores with a global health score. The idea was to use an instrument that can be used to study breast cancer-specific symptoms and treatment-related problems in addition to the functional effects of encountering breast cancer and going through the recovery process.

The generic 15D HRQoL measuring tool has been used in several previous breast cancer studies in Finland and is well established and validated (Färkkilä et al. 2014; Roine et al. 2021; Toija et al. 2019;). *Study I* strengthened the usability of 15D in breast cancer research compared to other generic HRQoL instruments, namely, the EORTC, EQ-5D and VAS. *Study I's* results revealed that the 15D is sensitive to breast cancer. It has little ceiling or floor effects compared to some other commonly used HRQoL instruments, like the EQ-5D, which showed a ceiling effect in 41% of the patients. 15D and EORTC both established acceptable results concerning breast cancer patients' HRQoL and thus appear to be valid measuring tools in breast cancer patients' HRQoL assessment.

Study II also tested the floor and ceiling effects for both instruments: the instrument's maximum score was reached at baseline by 8% of the patients with 15D and by 15% with EORTC, respectively. The ceiling effect was a little less pronounced at later measurement points. Consequently, it can be argued that the instruments used performed quite well in reflecting HRQoL, and patients rarely reported "perfect health" (ceiling effect) or "worst possible health" (floor effect, only 0.2% at 3 months and 0.1% at 24 months with EORTC).

8.4 Categorisation of procedures

The group "resection" in our study refers to the group of patients whose surgical procedure was a straightforward procedure in which the breast tumor was excised with/without the overlying skin and/or the underlying fascia. This procedure includes moderate glandular reshaping. The group "oncoplastic resection" depicts the need for potentially more excessive reshaping that includes, when necessary, the re-positioning of the nipple and/or wider glandular shaping to achieve the best possible cosmesis. The distinction between procedures was based on reading the operating reports and, most importantly, on checking which operating code was used for the procedure. The operation coding system (Nordic Classification of Surgical Procedures (NCSP)) gives different codes for these slightly different methods (HAB40 resection, HAB99 lumpectomy and HAB50 oncoplastic resection). The classification used in this thesis is somewhat different from those of other countries (as stated in oncoplastic surgery Level 2 techniques) (Clough et al. 2010).

The numbers of patients operated on with different methods might raise questions when evaluating the study population and the long recruitment time. The proportion of oncoplastic techniques and reconstruction patients seems low, but it can be seen that both operation techniques show a growing trend in numbers when looking at the years when patients were recruited. The data from our breast cancer unit show the evolution of oncoplastic techniques: in 2009, 8.8% of breast conserving procedures were classified as oncoplastic resection, whereas in 2011 the corresponding percentage was 53.7% (data collected by Dr. Voynov, Helsinki Breast Unit). The proportion of oncoplastic surgery has evolved in the Helsinki Unit similar to the proportion seen in other countries (Gilmour et a. 2021). The yearly proportions of recruited breast conserving patients in our study population were 13.8% in 2008; 0% in 2009; 3.6% in 2010; 44.3% in 2011; 31.9% in 2012; 45.5% in 2013; 42.3% in 2014; and 48.3% 2015, respectively. Thus, it is possible that patients recruited later in this study were more often offered surgical treatment with a better aesthetic outcome.

The number of immediate breast reconstructions has been around 100 patients per year from year 2008 to 2011, numbers that are showing a slight tendency to grow from after that (data from Dr Jahkola). The halting of our recruitment process at times in *Studies II-IV* had an unknown effect on the study population. The goal was to continue the recruitment of patients until the number reached 1000 patients, although the process took longer than anticipated. Breast cancer treatment evolves, so some effect on the operation trends might have had an influence on the study population in this way: patients recruited at the onset of the study might have had more simple resections than oncoplastic surgery. The patient material would have more accurately reflected the numbers our unit operates on if the study population had been a consecutive series as originally planned.

8.5 Statistical analyses

Clinical data and symptom scores were entered into the regression analyses in a two-phase analysis in *Study I*, a method to compare the validity of measuring tools as Blumenschein reported 1996. The regression analyses lifted up explanatory factors of pain, fatigue and financial difficulties as diminishing HRQoL.

The statistical analyses of *Studies II-IV* are based on the differences between differentially operated groups. The distribution of HRQoL results was skewed; therefore, the Box-cox transformation was performed to ensure the normal distribution of the data while bearing in mind the rather small size of the reconstruction group and the subgroups of reconstruction techniques. Variance analysis was performed with non-parametric Kruskal-Wallis One-way ANOVA to determine if there were differences between our study groups on any of the measuring points. The analyses were performed in cooperation with a statistical expert, as guidelines on research strategies suggest (Husereau et al. 2022; Tessler et al. 2014).

The EORTC scoring manual states that “the changes in scores over time and differences between groups may be more difficult to interpret than the absolute scores” (EORTC 2002). The *Study II* scores between groups at different timepoints were tested and reported. Table 9. represents EORTC Symptom and Function scores that presented statistically significant differences between study groups at the last measuring point of 24 months. All functional and symptom scores were tested at all measuring points in the analysis. There were more differences between groups at earlier measuring points, but the differences settled at 24 months to only a few statistically significant ones as stated in Table 9. *Study III* analysed both the change in scores and the comparison of score values at timepoints.

A small group of patients that suffered from excessive seroma formation after surgery was noticed in the data collection phase. Seroma formation led to numerous visits to the hospital for seroma aspiration (the line was drawn here at more than 10 aspirations; less frequent is considered quite normal after breast/axillary surgery). Based on clinical experience, the assumption was that patients suffer from these frequent visits substantially more than from other, more straightforward complications, such as wound infection or corrective surgery. Therefore, excessive seroma formation was included in the regression analyses. Indeed, this assumption appeared to be correct because frequent seroma aspirations had a negative effect on HRQoL, whereas having to go through more than one operation, encountering complications or a recurrence of the disease did not affect HRQoL.

8.6 Factors affecting the choice and timing of surgical method

Breast conserving surgery is considered the standard of care in breast cancer surgery (Biganzoli et al. 2017). Conserving the breast produces good HRQoL and content patients with superior aesthetic outcome compared to mastectomy (Pearce et al. 2019). However, patients are not all equal in the treatment choices they have, not even in Finland. Smaller breast cancer units might have limitations in their ability to offer oncoplastic knowledge or the possibility for breast reconstruction. The breast unit in Helsinki where this study was performed is the biggest breast cancer unit in Finland and has the resources to offer patients all treatment options.

Patients do not go through a preoperative meeting in Helsinki's unit unless there is a specific need for multidisciplinary evaluation of the treatment path. Patients' referrals are evaluated prior to their first visit to the hospital, and a preliminary surgery plan is decided upon based on referral notes to efficiently schedule operating times. The final decision on operation technique is made in collaboration between the surgeon and the patient at the first visit. The patient is guided to an appointment with a plastic surgeon in case the first surgeon was not a reconstructive plastic surgeon and there is a need for a second opinion, for example, concerning immediate reconstruction. A surgeon-dependent preference is a matter that can probably never be mapped thoroughly. Patient-dependent features naturally set boundaries on what kind of plastic surgery can be performed for each individual, yet it can be debated that surgeons might favour some techniques over others with reasons that are difficult to reveal (Mac Bride et al. 2013). This thesis did not record the number of operating surgeons, so surgeon-related preferences cannot be totally ruled out from the decision making. Even as surgeons strictly follow the national guidelines, there might be some deviation, especially between choices of simple resection and oncoplastic resections. This was probably apparent, especially at the onset of this study - as discussed earlier, the evolution of oncoplastic procedures was well underway during the recruitment process of

this study. The trend towards oncoplastic surgery was developing. Patients sometimes demand mastectomy, even when it would be possible to perform BCS. This creates a difficult situation and needs delicate conversation. National guidelines are to be followed, but in the end, the patient's wish must be respected after adequate patient information. The same question of timing with reconstructive surgery might be partially surgeon dependent. Opinions might vary on what the best reconstructive timing is, immediate or delayed. No data on surgeon-related preferences regarding reconstructive options or timing are available from the Helsinki unit. Surgeons are expected to follow national guidelines, and patients go through post-operative multidisciplinary meetings.

8.7 HRQoL in breast cancer

This thesis depicts the HRQoL in different states of breast cancer (*Study I*). As expected, patients with a heavier disease burden report poorer HRQoL. Belonging to metastatic or palliative care group were explanatory factors for poor HRQoL. Patients reported pain and fatigue, and all the measuring tools also revealed that experiencing financial difficulties were significant factors in explaining poor HRQoL. These results reveal what should be the focus in symptom handling and how to help the patients that most need help. Adequate pain control and focus on fatigue is imperative in the effort to enhance HRQoL, especially in patients with a heavy disease burden. The financial difficulties that patients encounter should also be accurately addressed. The social security system should be able to detect these patients and advise them with financial support. After all, Finland has been proud of the health-care system that is available for all patients without ruling out any treatment options. This is true on the big scale: patients do not pay for operations based on their extent of difficulty, they pay for outpatient clinic visits, day surgery and for the days spent in wards. Thus, undergoing whole-day microsurgery or a simple resection differs in costs for the patient only regarding the days they spent postoperatively in the hospital. Patients with a low income or financial difficulties due to other reasons should be recognised and offered support and counselling.

Studies II-III studied the HRQoL in relation to operation techniques. Oncoplastic procedures proved to produce the best body image, which is in line with previous studies. It is understandable that breast conserving surgery, when accompanied with shaping of the remaining breast tissue to achieve best possible cosmetic outcome, produces good HRQoL (Meretoja et al. 2010; Chand et al. 2017). The patient's own tissue that has sensation is bound to be more easily accepted after cancer treatments than having no breast at all. Additionally, having a breast reconstruction to replace something they have lost can easily be seen as an enhancement of HRQoL. How expectations and needs come together after heavy cancer treatments is a complex issue.

Reconstruction with autologous materials produced the best sexual and physical functioning. Autologous breast reconstruction in which patients receive corrective treatment with their own tissue is well accepted (Alderman et al. 2007; Pusic et al. 2017; Santosa et al. 2018). Implants are generally not very popular in Finland. The detection of BIA-ALCL and an increased awareness of that disease may have an influence against allogenous reconstruction. There is a strong tradition of autologous breast reconstruction at the Helsinki unit that might influence the choices made regarding breast reconstruction.

Some concerns have been presented on autologous methods regarding shoulder dysfunctions with LD. Blackburn's review stated that there are contradictory findings: some studies indicate dysfunction and others do not (Blackburn et al. 2018). In this thesis, patients with LD reconstruction, with or without an implant, and in an immediate or delayed setting, did not report statistically significantly more symptoms than those with other autologous or allogenous reconstruction methods. Palve discovered an association with complications in patients with LD (Palve et al. 2020). This thesis did not reveal statistically significant differences in the number or severity of complications between methods or different timings. LD patients had the smallest percentage of those receiving chemotherapy between IBR groups (42% as shown in Table 5. Patient characteristics) and more complications than those with abdominal flaps, but the difference was not statistically significant. The numbers were vice versa in the delayed setting: LD patients had slightly more chemotherapy than patients with abdominal flap (70 vs 50%) and encountered fewer complications (30 vs 50%), but again, there were no statistically significant differences between groups. What was found between groups was that abdominal flap patients experienced significantly more systemic therapy side effects than implant patients. Abdominal flap patients received less chemotherapy but more endocrine treatments than implant patients in both IBR and DR settings, which could explain the reporting of these symptoms.

The overall HRQoL diminished in both the IBR and DR groups from baseline to three months but then started to improve. This can be a result of oncological treatments in the beginning and, consequently, the fading influence of the treatments. With EORTC, the DR group showed a drop at 24 months, which seems natural: experiencing surgery after 12 months and recovering from it is still an ongoing process at 24 months. A later measuring point for DR patients probably would reveal an enhancement of HRQoL after a sufficient time had passed from their reconstructive surgery. 15D, in contrast, does not reveal this: HRQoL improves after 12 months in both groups with 15D. Neither group reached the baseline 15D sore with 15D, but the IBR group's HRQoL rose to a higher level than that at baseline with EORTC. Statistical significance was found for the change in overall HRQoL with EORTC in DR and IBR from 12 to 24 months, and a drop in sexual functioning scores was observed in both

groups. DR patients suffered from sexual functioning problems more extensively than IBR patients and reported more arm symptoms. These findings can be linked to the timing itself: recent surgery probably generates a higher symptom burden in DR patients. Otherwise, statistically significant differences were not found between different operation methods.

Both measuring tools detected disturbances in sleeping, fatigue, and sexual functioning. These findings in the differences between methods and timings support the previous findings: patients' experiences vary greatly irrespective of the timing or surgical methods. These noticeable symptoms that breast cancer patients report -- sleeping disturbances, pain, fatigue, and impaired sexual functioning -- need attention to enhance HRQoL.

The correlation between some patient characteristics and HRQoL indicates that some patient groups are at risk of poor HRQoL and need special attention. Higher age, comorbidity burden, and high BMI had a negative correlation with HRQoL. Active smoking and obesity were associated with complications that indicate the need for patient education and health promotion. High disease burden and axillary clearance correlated negatively with HRQoL, indicating that patients with a high disease burden are at risk of poor HRQoL and might benefit from extra follow-up. Mastectomy patients are most often those with a heavy disease burden. Axillary clearance was performed for patients in all groups, so those with these diminishing HRQoL factors should be under scope. Treatment strategies towards axillary clearance have been changing after the AMAROS and ACOSOG studies towards less invasive surgery, surely benefitting patients as this study also indicates. Patients might experience less pain and other symptoms if avoiding axillary clearance is possible.

8.8 The fulfilment of Quality Indicators in breast cancer surgery

This thesis proves that most of the Quality Indicators (QIs) concerning breast cancer surgery that EUSOMA has presented are well fulfilled in the Helsinki Breast Unit (*Studies II-IV*). This study does not evaluate reaching the QIs of oncological treatment or diagnostics but focuses mainly on breast cancer surgery. The QI of surgery and loco-regional treatment states that for patients with invasive cancer, a minimum of 80% (target 90%) should go through one operation to reduce re-operation rates (reconstruction patients are not included in this QI). The re-operation rate for BCS and mastectomy patients in this thesis was 13.8% – the QI was well met with 86.2% of patients having single surgery. The single operation minimum QI is 70% (target 90%) for patients with DCIS. 80.5% of patients with DCIS were operated on with a single surgery in this thesis. Tumour size was not recorded at the data collection phase, so the QI of BCS proportion in relation to tumour size cannot be evaluated. In an attempt to provide good HRQoL, the EUSOMA stated that a minimum 90% (target 95%) of all breast cancer patients with preoperative

clinically negative axilla (N0) should have snb (no axillary clearance). This number was 91.7% in this thesis, indicating yet another QI well fulfilled. The number of snb nodes collected was not recorded, so the evaluation of snb number QI is not applicable. The QI of not having axillary clearance is a minimum 97% (target 99%) for DCIS. 4.9% did have axillary clearance with DCIS only in this study population, meaning that the percentage of 95.1% of patients with snb is just a little behind the minimum of 97%. The QI of breast reconstruction offered to mastectomy patients is 40% of patients. The number of patients in this study is small, and the patient recruitment was not a consecutive series, so the QI in offering breast reconstruction cannot be evaluated in this thesis.

What can be said about diagnostics QI? No patient in the Helsinki Breast Unit is operated on without triple diagnostics being fulfilled. The pathology reports meticulously follow the guidelines of reporting histological type, Grading, ER, PR and HER2/neu parameters, which are listed as the minimum QI of diagnostics. The pathological staging, the size of the invasive component, peritumoral vascular invasion, and distance to nearest radial margin are all reported and discussed after surgery in postoperative multidisciplinary meetings. The report follows the same scheme with all patients. These data were recorded at the data collection phase except for the size of the tumour and the distance to the margins; thus, the percentage of QI fulfilment cannot be stated with 100% accuracy but it can be argued that this QI is undoubtably fulfilled. The proportion of BCS patients that received radiation therapy for oncological treatment QIs was 98.2% in the study population. QI for radiation therapy minimum is 90% (target 95%), indicating clear fulfilment of QI.

8.9 Factors on economic evaluations concerning breast cancer treatment

The timeframe for data collection in *Study IV* covered time from baseline minus one month to 26 months to ensure that all relevant costs were included.

The comparison of economic aspects is difficult between countries. The structure of health-care system financing varies greatly, and the patients do not all have similar access to treatments. This thesis does not address cost-effectiveness because the randomisation of breast cancer treatments is unethical. Neyt suggested that it is tempting to think that IBR is the best choice from an economic viewpoint because the disease is treated and reconstruction is finished within one operation, hospital stay and sick leave (Neyt et al. 2005). The mean total cost of breast reconstruction differed only by 1000 Euros between IBR and DR in our study. The total cost of breast reconstruction of about 18 000 to 19 000 in this study indicates that 1000 euros difference in costs is small. This might be due to the inclusion of all surgical methods in the comparison; for example, microsurgical breast reconstruction costs more than

fat crafting. Fat crafting is not performed at the IBR phase, so all IBR reconstructions were of the kind of generating higher costs. There were also unexplained data missing for reconstruction patients: data were missing for 9 IBR and for three DR patients. Missing data might skew the results, especially when study group sizes were so small. The cost comparisons did not take into account the costs of complications, for example, revisional surgery. That is, the sum of reconstruction can include corrective operations or just the reconstruction itself if there were no need for further operations. The costs are presented as means. However, the number of complications patients encountered were similar in both reconstruction groups and, as stated earlier, encountering a complication or having to go through more than one operation did not affect HRQoL. Thus, these deviations did not diminish the patient-experienced HRQoL even if the patient had deviations in the recovery after breast reconstruction. It is also important to notice that the 24-month study period is not a limit when all patients' breast reconstructions are ready. Some patients need later corrective surgery, fat grafting, or other balancing procedures, so the total cost of breast reconstruction might build up longer than this study period reveals. Longer follow-up might reveal more operations and more costs, and surely more patients of the mastectomy group seek DR later than at this thesis endpoint at 24 months.

HRQoL should be included in the consideration and evaluation of what kind of effect different procedures have on HRQoL when looking at the big picture and considering what is the best way to approach surgery and its relation to money. The health-economic calculations were not performed here in terms of quality-adjusted life years or productivity loss because of the non-randomisation of procedures problem. The aim was to describe what kind of factors are important in a patient's perspective and what kind of costs our treatments produce. Then again, looking merely at the costs of surgery is not advisable when discussing the choice each patient should make on their individual situation of encountering breast cancer.

8.10 Recommendations and future perspectives

According to this thesis, it is recommendable to use both disease-specific and generic HRQoL measuring tools in breast cancer research. Care must be taken when choosing the tool. Tools that produce high ceiling or floor effects are not advisable. The EORTC QLQ C-30 BR23 and 15D are both valid and reliable in studies of breast cancer patients. The BREAST-Q was unavailable in the Finnish language at the onset of this thesis, but it might bring value to future studies because it seems to be a promising measuring tool and has achieved recommendations for use.

Patients with a high disease burden are at risk of poor HRQoL, and resources should be allocated to find these at-risk patients. Pain, fatigue, sleeping

disturbances, and financial difficulties are factors that patients suffer the most and care providers should allocate resources to handle these symptoms and provide guidance to help solve financial problems. Surgeons should actively inquire if the patients have symptoms, especially pain and sleeping disorders, and treat those symptoms accordingly. Patients should be appointed to physiotherapists in case the regular meetings seem to be insufficient and the patient's rehabilitation is jeopardised. Health promotion should be focused on patients with obesity, several comorbidities, and active smoking to lighten the pressure of encountering complications and poor HRQoL.

BCS is an advisable surgical approach in all applicable breast cancer patients. Oncoplastic techniques should be preferred because these techniques provide the best body image and rapid recovery. Breast reconstruction should be offered to patients requiring mastectomy because breast reconstruction produces the best sexual and physical functioning, and mastectomy patients present the lowest HRQoL scores. The breast reconstruction method should be chosen in collaboration with the patient after the patient is informed of the different aspects of different methods. Autologous methods are to be favored because they seem to outperform allogenous methods in HRQoL outcomes. Patients should be informed of the long recovery time after breast reconstruction, but the timing of either an immediate or a delayed setting can be chosen according to patients' preferences.

The incidence of breast cancer is rising and pressure on health budgets is rising with it. Thus, economic studies of different breast cancer surgical approaches are recommended in the future to shed more light on the economic effects different treatments produce and to gain data on how these treatments impact the health-care systems.

EUSOMA suggested that prospective HRQoL studies of patients with different surgical approaches in the treatment of breast cancer are in demand. Multicenter and international studies should preferably be designed in the future to obtain data for wide use globally to help plan effective and safe breast cancer treatment in a sustainable way that societies can endure.

The overall prognosis of breast cancer is good in industrialised countries. The use of neoadjuvant treatments probably enhance the prognosis even further. Multidisciplinary treatment of breast cancer is imperative – early detection of the disease and an adequate treatment plan for patients raises the prognosis even higher and secures high quality breast cancer care.

9 CONCLUSIONS

I. Different HRQoL measuring tools produce variable results. EQ5D-3L produces a high ceiling effect, whereas 15D and EORTC QLQ C-30 do not have this problem. 15D and EORTC QLQ C-30 are valid and reliable for use in breast cancer patient studies. Breast cancer patients' HRQoL diminishes as the disease progresses. Patients suffer from insomnia, pain and fatigue.

II. Patients operated on with oncoplastic techniques have good HRQoL and body image. BCS patients recover from treatments within a year from diagnosis. Mastectomy patients' HRQoL is low from baseline to two years, and they suffer the most symptoms. Breast reconstruction produces good HRQoL as a slower process, with patients reaching close to the baseline HRQoL level at 24 months. Breast reconstruction produces the highest physical and sexual functioning scores at 24 months.

III. IBR and DR both produce good HRQoL. No difference exists between the incidence of complications regarding reconstruction timing nor between different surgical methods. Different autologous breast reconstruction methods produce similar HRQoL. The timing of breast reconstruction depends on patient characteristics and should be tailored individually.

IV. DR is most costly from the care providers' perspective with only a small difference from IBR in the two-year timeframe. Reflecting the cost on HRQoL proves that the most important determinants of which methods to use and in which timeframe are the patient's characteristics and the patient's own wish.

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Breast cancer survivors. Live long and prosper.

Mervi Rautalin
Helsinki, October 2022

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Appendix 1 : patient information and questionnaires for Study I

SUOSTUMUS
JA
KYSELYLOMAKKEET

HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRI

SUOSTUMUS TUTKIMUKSEEN OSALLISTUMISEEN JA SIINÄ KERÄTTÄVIEN HENKILÖTIETOJEN KÄSITTELYYN

Elämänlaatu ja kustannukset rinta-, eturauhas- ja kolorektaalisyöpäpotilailla

Minua on pyydetty osallistumaan yllä mainittuun tutkimukseen, jossa selvitetään kyselyn avulla syöpäpotilaiden elämänlaatua, kustannuksia ja oirekuvaa. Olen saanut tätä tutkimusta ja sen yhteydessä suoritettavaa tietojen keruuta ja käsittelyä kuvaavan tutkimustiedotteen.

Suostun vapaaehtoisesti osallistumaan yllämainittuun tutkimukseen ja annan suostumukseni tutkimuksen yhteydessä tapahtuvaan tietojen keräämiseen ja niiden käsittelyyn. Voin myöhemmin peruuttaa suostumukseni sen vaikuttamatta mitenkään saamaani hoitoon.

Annan tällä suostumuksella luvan siihen, että oheisilla kyselylomakkeilla kerätyt tiedot saadaan yhdistää muihin minua koskeviin Helsingin ja Uudenmaan sairaanhoitopiirissä oleviin hoitotietoihin sekä Tilastokeskuksen, Terveyden ja hyvinvoinnin laitoksen (THL) ja Kansaneläkelaitoksen (KELA) sekä kotikuntani sairauteni hoitoa koskeviin tietoihin. Ymmärrän, että henkilötunnuksella varustettu tieto tulee vain tutkimusryhmän tietoon ja, että tiedot tallennetaan erityistä salattua potilastunnusta käyttäen, jolloin niistä ei voi päätellä henkilöllisyyttäni.

Suostumuksen antaja täyttää

Paikka ja aika	Allekirjoitus
Henkilötunnus (xxxxxx-xxx)	Sukunimi, Etunimi
Osoite	

Olkaa ystävällinen ja palauttakaa tämä suostumuslomake yhdessä täytetyn kyselylomakkeen kanssa.

Täytetään HUS:ssa

Paikka ja aika	*Suostumuksen vastaanottajan allekirjoitus*
Nimenselvennys	

TERVEYTEEN LIITTYVÄN ELÄMÄNLAADUN KYSELYLOMAKE (15D©)

Lukekaa ensin läpi huolellisesti kunkin kysymyksen kaikki vastausvaihtoehdot. Merkitkää sitten rasti (x) sen vaihtoehdon kohdalle, joka parhaiten kuvaa nykyistä terveydentilaanne. On tärkeää, että vastaatte kaikkiin 15 kysymykseen rastittamalla kustakin yhden vaihtoehdon.

1. Liikuntakyky

1 ☐ Pystyn kävelemään normaalisti (vaikeuksitta) sisällä, ulkona ja portaissa.
2 ☐ Pystyn kävelemään vaikeuksitta sisällä, mutta ulkona ja/tai portaissa on pieniä vaikeuksia.
3 ☐ Pystyn kävelemään ilman apua sisällä (apuvälinein tai ilman), mutta ulkona ja/tai portaissa melkoisin vaikeuksin tai toisen avustamana.
4 ☐ Pystyn kävelemään sisälläkin vain toisen avustamana.
5 ☐ Olen täysin liikuntakyvytön ja vuoteenoma.

2. Näkö

1 ☐ Näen normaalisti eli näen lukea lehteä ja TV:n tekstejä vaikeuksitta (silmälaseilla tai ilman).
2 ☐ Näen lukea lehteä ja/tai TV:n tekstejä pienin vaikeuksin (silmälaseilla tai ilman).
3 ☐ Näen lukea lehteä ja/tai TV:n tekstejä huomattavin vaikeuksin (silmälaseilla tai ilman).
4 ☐ En näe lukea lehteä enkä TV:n tekstejä ilman silmälaseja tai niiden kanssa, mutta näen kulkea ilman opasta.
5 ☐ En näe kulkea oppaatta eli olen lähes tai täysin sokea.

3. Kuulo

1 ☐ Kuulen normaalisti eli kuulen hyvin normaalia puheääntä (kuulokojeella tai ilman).
2 ☐ Kuulen normaalia puheääntä pienin vaikeuksin.
3 ☐ Minun on melko vaikea kuulla normaalia puheääntä, keskustelussa on käytettävä normaalia kovempaa puheääntä.
4 ☐ Kuulen kovaakin puheääntä heikosti; olen melkein kuuro.
5 ☐ Olen täysin kuuro.

4. Hengitys

1 ☐ Pystyn hengittämään normaalisti eli minulla ei ole hengenahdistusta eikä muita hengitysvaikeuksia.
2 ☐ Minulla on hengenahdistusta raskaassa työssä tai urheillessa, reippaassa kävelyssä tasamaalla tai lievässä ylämäessä.
3 ☐ Minulla on hengenahdistusta, kun kävelen tasamaalla samaa vauhtia kuin muut ikäiseni.
4 ☐ Minulla on hengenahdistusta pienenkin rasituksen jälkeen, esim. peseytyessä tai pukeutuessa.
5 ☐ Minulla on hengenahdistusta lähes koko ajan, myös levossa.

5. Nukkuminen

1 ☐ Nukun normaalisti eli minulla ei ole mitään ongelmia unen suhteen.

2 ☐ Minulla on lieviä uniongelmia, esim. nukahtamisvaikeuksia tai satunnaista yöheräilyä.

3 ☐ Minulla on melkoisia uniongelmia, esim. nukun levottomasti tai uni ei tunnu riittävältä.

4 ☐ Minulla on suuria uniongelmia, esim. joudun käyttämään usein tai säännöllisesti unilääkettä, herään säännöllisesti yöllä ja/tai aamuisin liian varhain.

5 ☐ Kärsin vaikeasta unettomuudesta, esim. unilääkkeiden runsaasta käytöstä huolimatta nukkuminen on lähes mahdotonta, valvon suurimman osan yöstä.

6. Syöminen

1 ☐ Pystyn syömään normaalisti eli itse ilman mitään vaikeuksia.

2 ☐ Pystyn syömään itse pienin vaikeuksin (esim. hitaasti, kömpelösti, vavisten tai erityisapuneuvoin).

3 ☐ Tarvitsen hieman toisen apua syömisessä.

4 ☐ En pysty syömään itse lainkaan, vaan minua pitää syöttää.

5 ☐ En pysty syömään itse lainkaan, vaan minulle pitää antaa ravintoa letkun avulla tai suonensisäisesti.

7. Puhuminen

1 ☐ Pystyn puhumaan normaalisti eli selvästi, kuuluvasti ja sujuvasti.

2 ☐ Puhuminen tuottaa minulle pieniä vaikeuksia, esim. sanoja on etsittävä tai ääni ei ole riittävän kuuluva tai se vaihtaa korkeutta.

3 ☐ Pystyn puhumaan ymmärrettävästi, mutta katkonaisesti, ääni vavisten, sammaltaen tai änkyttäen.

4 ☐ Muilla on vaikeuksia ymmärtää puhettani.

5 ☐ Pystyn ilmaisemaan itseäni vain elein.

8. Eritystoiminta

1 ☐ Virtsarakkoni ja suolistoni toimivat normaalisti ja ongelmitta.

2 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on lieviä ongelmia, esim. minulla on virtsaamisvaikeuksia tai kova tai löysä vatsa.

3 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on melkoisia ongelmia, esim. minulla on satunnaisia virtsanpidätysvaikeuksia tai vaikea ummetus tai ripuli.

4 ☐ Virtsarakkoni ja/tai suolistoni toiminnassa on suuria ongelmia, esim. minulla on säännöllisesti "vahinkoja" tai peräruiskeiden tai katetroinnin tarvetta.

5 ☐ En hallitse lainkaan virtsaamista ja/tai ulostamista.

9. Tavanomaiset toiminnot

1 ☐ Pystyn suoriutumaan normaalisti tavanomaisista toiminnoista (esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot).

2 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista hieman alentuneella teholla tai pienin vaikeuksin.

3 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista huomattavasti alentuneella teholla tai huomattavin vaikeuksin tai vain osaksi.

4 ☐ Pystyn suoriutumaan tavanomaisista toiminnoista vain pieneltä osin.

5 ☐ En pysty suoriutumaan lainkaan tavanomaisista toiminnoista.

10. Henkinen toiminta

1 ☐ Pystyn ajattelemaan selkeästi ja johdonmukaisesti ja muistini toimii täysin moitteettomasti.

2 ☐ Minulla on lieviä vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai muistini ei toimi täysin moitteettomasti.

3 ☐ Minulla on melkoisia vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on jonkin verran muistinmenetystä.

4 ☐ Minulla on suuria vaikeuksia ajatella selkeästi ja johdonmukaisesti, tai minulla on huomattavaa muistinmenetystä.

5 ☐ Olen koko ajan sekaisin ja vailla ajan tai paikan tajua.

11. Vaivat ja oireet

1 ☐ Minulla ei ole mitään vaivoja tai oireita, esim. kipua, särkyä, pahoinvointia, kutinaa jne.

2 ☐ Minulla on lieviä vaivoja tai oireita, esim. lievää kipua, särkyä, pahoinvointia, kutinaa jne.

3 ☐ Minulla on melkoisia vaivoja tai oireita, esim. melkoista kipua, särkyä, pahoinvointia, kutinaa jne.

4 ☐ Minulla on voimakkaita vaivoja tai oireita, esim. voimakasta kipua, särkyä, pahoinvointia, kutinaa jne.

5 ☐ Minulla on sietämättömiä vaivoja ja oireita, esim. sietämätöntä kipua, särkyä, pahoinvointia, kutinaa jne.

12. Masentuneisuus

1 ☐ En tunne itseäni lainkaan surulliseksi, alakuloiseksi tai masentuneeksi.

2 ☐ Tunnen itseni hieman surulliseksi, alakuloiseksi tai masentuneeksi.

3 ☐ Tunnen itseni melko surulliseksi, alakuloiseksi tai masentuneeksi.

4 ☐ Tunnen itseni erittäin surulliseksi, alakuloiseksi tai masentuneeksi.

5 ☐ Tunnen itseni äärimmäisen surulliseksi, alakuloiseksi tai masentuneeksi.

13. Ahdistuneisuus

1 ☐ En tunne itseäni lainkaan ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

2 ☐ Tunnen itseni hieman ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

3 ☐ Tunnen itseni melko ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

4 ☐ Tunnen itseni erittäin ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

5 ☐ Tunnen itseni äärimmäisen ahdistuneeksi, jännittyneeksi tai hermostuneeksi.

14. Energisyys

1 ☐ Tunnen itseni terveeksi ja elinvoimaiseksi.

2 ☐ Tunnen itseni hieman uupuneeksi, väsyneeksi tai voimattomaksi.

3 ☐ Tunnen itseni melko uupuneeksi, väsyneeksi tai voimattomaksi.

4 ☐ Tunnen itseni erittäin uupuneeksi, väsyneeksi tai voimattomaksi, lähes "loppuun palaneeksi".

5 ☐ Tunnen itseni äärimmäisen uupuneeksi, väsyneeksi tai voimattomaksi, täysin "loppuun palaneeksi".

15. Sukupuolielämä

1 ☐ Terveydentilani ei vaikeuta mitenkään sukupuolielämääni.

2 ☐ Terveydentilani vaikeuttaa hieman sukupuolielämääni.

3 ☐ Terveydentilani vaikeuttaa huomattavasti sukupuolielämääni.

4 ☐ Terveydentilani tekee sukupuolielämäni lähes mahdottomaksi.

5 ☐ Terveydentilani tekee sukupuolielämäni mahdottomaksi.

EORTC QLQ-C30 (VERSION 3.0.)

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopiva numero. Tässä kyselyssä ei ole "oikeita" eikä "vääriä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
1. Tuntuvatko rasittavat työt kuten painavan ostoskassin tai matkalaukun kantaminen teistä työläältä?	1	2	3	4
2. Tuntuvatko pitkät kävelymatkat työläiltä?	1	2	3	4
3. Tuntuvatko lyhyet kävelymatkat kotinne ulkopuolella työläiltä?	1	2	3	4
4. Pitääkö teidän pysytellä levolla tai istumassa päivän mittaan?	1	2	3	4
5. Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä?	1	2	3	4

Kuluneella viikolla:	Ei lainkaan	Vähän	Melko paljon	Hyvin paljon
6. Oliko teillä vaikeuksia suoriutua työstänne tai muista päivittäisistä toimistanne?	1	2	3	4
7. Oliko teillä rajoituksia harrastus- tai muissa vapaa-ajan toiminnoissanne?	1	2	3	4
8. Oliko teillä hengenahdistusta?	1	2	3	4
9. Oliko kipuja?	1	2	3	4
10. Tunsitteko levontarvetta?	1	2	3	4
11. Oliko unettomuutta?	1	2	3	4
12. Tunsitteko heikotusta?	1	2	3	4
13. Oliko ruokahaluttomuutta?	1	2	3	4
14. Oliko pahoinvointia?	1	2	3	4
15. Oksensitteko?	1	2	3	4

Kuluneella viikolla:	**Ei lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
16. Oliko ummetusta?	1	2	3	4
17. Oliko ripulia?	1	2	3	4
18. Olitteko väsynyt?	1	2	3	4
19. Häiritsikö kipu päivittäisiä toimianne?	1	2	3	4
20. Oliko teillä keskittymisvaikeuksia esim. sanomalehteä lukiessanne tai televisiota katsellessanne?	1	2	3	4
21. Olitteko jännittynyt?	1	2	3	4
22. Olitteko huolestunut?	1	2	3	4
23. Olitteko ärtynyt?	1	2	3	4
24. Olitteko masentunut?	1	2	3	4
25. Oliko teidän vaikea muistaa asioita?	1	2	3	4
26. Häiritsikö hoito tai fyysinen kuntonne perhe-elämäänne?	1	2	3	4
27. Häiritsikö hoito tai fyysinen kuntonne sosiaalista kanssakäymistä?	1	2	3	4
28. Aiheuttaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia?	1	2	3	4

Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto

29. Millainen yleinen terveydentilanne oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono						Erinomainen

30. Millainen yleinen elämänne laatu oli kuluneella viikolla?

1	2	3	4	5	6	7
Erittäin huono						Erinomainen

TERVEYSKYSELY EQ-5D

Olkaa hyvä ja merkitkää rastilla (x), yksi rasti kunkin alla olevan ryhmän kohdalle, mikä väitteistä kuvaa parhaiten terveydentilaanne tänään:

Liikkuminen

- ☐ Minulla ei ole vaikeuksia kävelemisessä
- ☐ Minulla on jonkin verran vaikeuksia kävelemisessä
- ☐ Olen vuoteenomana

Itsestään huolehtiminen

- ☐ Minulla ei ole vaikeuksia huolehtia itsestäni
- ☐ Minulla on jonkin verran vaikeuksia peseytyä tai pukeutua itse
- ☐ En kykene peseytymään tai pukeutumaan itse

Tavanomaiset toiminnot *(esim. ansiotyö, opiskelu, kotityö, vapaa-ajan toiminnot)*

- ☐ Minulla ei ole vaikeuksia suorittaa tavanomaisia toimintojani
- ☐ Minulla on jonkin verran vaikeuksia suorittaa tavanomaisia toimintojani
- ☐ En kykene suorittamaan tavanomaisia toimintojani

Kivut/vaivat

- ☐ Minulla ei ole kipuja tai vaivoja
- ☐ Minulla on kohtalaisia kipuja tai vaivoja
- ☐ Minulla on ankaria kipuja tai vaivoja

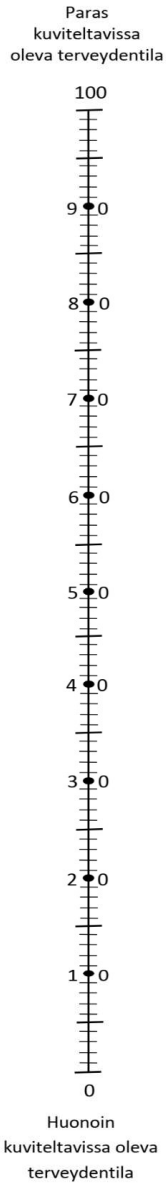
Ahdistuneisuus/Masennus

- ☐ En ole ahdistunut tai masentunut
- ☐ Olen melko ahdistunut tai masentunut
- ☐ Olen erittäin ahdistunut tai masentunut

Auttaaksemme ihmisiä sanomaan, kuinka hyvä tai huono jokin terveydentila on, olemme piirtäneet lämpömittaria muistuttavan asteikon. Parasta terveydentilaa, jonka voitte kuvitella, merkitään siinä 100:lla ja huonointa 0:lla.

Haluaisimme Teidän osoittavan tällä asteikolla, miten hyvä tai huono Teidän terveytenne on mielestänne tänään. Olkaa hyvä ja tehkää tämä vetämällä alla olevasta laatikosta viiva siihen kohtaan asteikolle, joka osoittaa, miten hyvä tai huono terveydentilanne on tänään.

Terveydentilani tänään



TAUSTAKYSYMYKSET JA RESURSSIEN KÄYTTÖ

On tärkeää, että vastaatte **kaikkiin** 25 kysymykseen rastittamalla tai numeroin.

TAUSTATIEDOT

1. Sukupuoli
- ☐ Nainen
- ☐ Mies

2. Siviilisääty
- ☐ Naimaton
- ☐ Naimisissa
- ☐ Avoliitossa
- ☐ Leski

3. Mikä on koulutuksenne (korkein loppuun suoritettu koulutus)?
- ☐ Kansakoulu tai vähemmän
- ☐ Keskikoulu tai peruskoulu
- ☐ Ammattikoulu
- ☐ Lukio
- ☐ Opisto- tai ammattikorkeakoulutasoinen koulutus
- ☐ Yliopisto tai korkeakoulu

4. Mikä kuvaa parhaiten tämänhetkistä toimintaanne. Oletteko?
- ☐ Kokopäivätöissä
- ☐ Osapäivätöissä
- ☐ Vanhuuseläkkeellä
- ☐ Työkyvyttömyyseläkkeellä syövän takia
- ☐ Työkyvyttömyyseläkkeellä tai varhaiseläkkeellä muun syyn vuoksi
- ☐ Työtön
- ☐ Olen poissa työelämästä muun syyn takia

5. Missä ammattiasemassa olette tai olette viimeksi ollut työelämässä?
- ☐ Työntekijä
- ☐ Alempi toimihenkilö
- ☐ Ylempi toimihenkilö
- ☐ Yrittäjä
- ☐ Muu
- ☐ En ole ollut työelämässä

6. Mikäli olette töissä, miten arvioisitte nykyisen työkykynne?
- ☐ Täysin työkykyinen
- ☐ Osittain työkyvytön
- ☐ Täysin työkyvytön

7. Mikäli olette työelämässä, kuinka monta päivää olette olleet poissa töistä viimeisen kolmen kuukauden (3 kk) aikana syövästänne johtuen?

____ päivää viimeisen 3 kk aikana

TERVEYSPALVELUIDEN KÄYTTÖ

Kuinka usein olette käynyt viimeisen kolmen kuukauden aikana seuraavissa terveydenhoidon yksiköissä syöpänne vuoksi?

8. Lääkärillä terveyskeskuksessa

____ kertaa viimeisen 3 kk aikana

9. Terveydenhoitajan/sairaanhoitajan vastaanotolla terveyskeskuksessa

____ kertaa viimeisen 3 kk aikana

10. Työpaikan työterveyslääkärillä

____ kertaa viimeisen 3 kk aikana

11. Työpaikan työterveyshoitajalla

____ kertaa viimeisen 3 kk aikana

12. Yksityisellä erikoislääkärillä

____ kertaa viimeisen 3 kk aikana

13. Erikoislääkärillä sairaalan poliklinikalla

____ kertaa viimeisen 3 kk aikana

14. Erilliskäynti laboratoriossa tai röntgentutkimuksissa

____ kertaa viimeisen 3 kk aikana

15. Kuinka monta kertaa olette viimeisen kolmen kuukauden aikana ollut syöpänne vuoksi yhteydessä puhelimitse sairaanhoitajaan tai lääkäriin?

____ kertaa viimeisen 3 kk aikana

16. Kuinka monta kertaa olette viimeisen kolmen kuukauden aikana tavannut kotonanne syöpänne vuoksi kotisairaanhoitajan tai terveydenhoitajan?

____ kertaa viimeisen 3 kk aikana

17. Kuinka monta kertaa viimeisen kolmen kuukauden aikana luonanne kotona on käynyt teitä hoitamassa/auttamassa kodinhoitaja tai kotiavustaja syöpänne vuoksi?

____ kertaa viimeisen 3 kk aikana

18. Miten paljon olette saanut hoitoa ja apua perheeltänne tai ystäviltänne syöpänne vuoksi keskimäärin viikossa viimeisen kolmen kuukauden aikana?

Keskimäärin ____ tuntia/viikossa viimeisen 3 kk aikana

Kuinka monta kertaa ja vuorokautta (vrk) olette ollut viimeisen kolmen kuukauden aikana syöpänne vuoksi hoidossa seuraavissa paikoissa?

19. Terveyskeskuksen vuodeosastolla

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

20. Keskus- tai yliopistosairaalassa

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

21. Muussa yleissairaalassa (aluesairaalassa)

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

22. Yksityisessä sairaalassa

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

23. Kuntoutuslaitoksessa

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

24. Kunnallis-/vanhainkodissa,

____ kertaa yhteensä ____ vrk viimeisen 3 kk aikana

LÄÄKEMENOT

25. Arvio, kuinka paljon olette käyttäneet rahaa lääkkeisiin viimeisen kolmen kuukauden (3 kk) aikana?

_____ € viimeisen 3 kk aikana

Kiitos vaivannäöstänne.

Appendix 2 : patient information and EORTC QLQ BR-23 questionnaire for Studies II-IV

HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRI
HELSINGFORS OCH NYLANDS SJUKVÅRDSDISTRIKT

Arvoisa vastaanottaja,

Teidät on valittu Helsingin ja Uudenmaan sairaanhoitopiirissä tehtävään selvitykseen, jonka tarkoituksena on mitata hoidon vaikuttavuutta. Pyrimme arvioimaan miten terveyteen liittyvä elämänlaatunne muuttuu saamanne hoidon vuoksi. Tällä tavoin haluamme aiempaa tarkemmin seurata, miten potilaamme hoidon jälkeen voivat. Selvitys tehdään yhteistyössä Terveyden ja hyvinvoinnin laitoksen (THL) kanssa.

Selvityksen onnistumisen kannalta vastauksenne on ensiarvoisen tärkeä ja pyydämme, että täyttäisitte oheiset tutkimuslomakkeet mahdollisimman huolellisesti vastaamalla kaikkiin lomakkeiden kysymyksiin. Lomakkeet voitte palauttaa valmiiksi maksetussa vastauskuoressa postitse. Kaikki antamanne tiedot käsitellään **luottamuksellisesti** ja siten, ettei yksittäistä vastaajaa voida tunnistaa. Tutkimuksesta ei aiheudu Teille ylimääräisiä poliklinikkakäyntejä tai kuluja.

Kysely tehdään **viisi kertaa**: nyt sekä noin 3, 6, 12 ja 24 kuukautta hoidon aloittamisen jälkeen. Pyrimme uusimaan kyselyn myös 5 ja 10 vuoden kuluttua hoidon alkamisesta. Lisäksi selvitämme Tilastokeskuksen, STAKES:n, ja Kansaneläkelaitoksen (KELA) rekistereistä ja kotikunnastanne tämän sairautenne hoitoa koskevia tietoja. Osallistuminen tutkimukseen on tietysti täysin vapaaehtoista, eikä päätöksenne osallistua tai olla osallistumatta mitenkään vaikuta saamaanne hoitoon. Toivomme kuitenkin, että haluatte olla mukana kehittämässä ja parantamassa sairaanhoitomme vaikuttavuutta.

Mikäli päätätte osallistua, täyttäkää **kyselylomakkeiden** lisäksi myös oheinen **suostumuslomake** ja varmistakaa **allekirjoituksellanne**, että sallitte antamienne tietojen käyttämisen tämän tutkimuksen tutkimustarkoituksiin.

Tutkimusta koskevissa kysymyksissä annamme mielellämme lisätietoja.

Avustanne etukäteen kiittäen,

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HELSINGIN JA UUDENMAAN SAIRAANHOITOPIIRI
HELSINGFORS OCH NYLANDS SJUKVÅRDSDISTRIKT

Suostumus

Olen saanut tietoa tutkimuksesta, jonka tarkoituksena on mitata hoidon vaikuttavuutta terveyteen liittyvällä elämänlaadulla, ja annan tällä suostumuksella luvan siihen, että oheisilla kyselylomakkeilla kerätyt tiedot saadaan yhdistää muihin minua koskeviin Helsingin ja Uudenmaan sairaanhoitopiirissä oleviin hoitotietoihin sekä Tilastokeskuksen, Terveyden- ja hyvinvoinnin laitoksen (THL) ja Kansaneläkelaitoksen (KELA) sekä kotikuntani sairauteni hoitoa koskeviin tietoihin. Ymmärrän, että henkilötunnuksella varustettu tieto tulee vain tutkimusryhmän tietoon ja, että tiedot muuten tallennetaan erityistä salattua potilastunnusta käyttäen, jolloin niistä ei voi päätellä henkilöllisyyttäni.

Paikka ja aika _____

Allekirjoitus _____

Nimenselvennys _____

Henkilötunnus _____

Olkaa ystävällinen ja palauttakaa tämä suostumuslomake yhdessä täytetyn kyselylomakkeen kanssa.

Täytetään HUS:ssa

*Paikka ja aika*_____
Suostumuksen vastaanottaja HUS:ssa _____
*Nimenselvennys*_____

EORTC QLQ - BR23

Potilaat kertovat joskus, että heillä on seuraavia oireita tai ongelmia. Olkaa hyvä ja ilmoittakaa, missä määrin teillä on ollut näitä oireita tai ongelmia viimeksi kuluneen viikon aikana.

Kuluneella viikolla:	**Ei/en lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
31. Oliko suunne kuiva?	1	2	3	4
32. Maistuiko ruoka ja juoma erilaiselta kuin ennen?	1	2	3	4
33. Vuotivatko silmänne tai olivatko ne kipeät tai ärtyneet?	1	2	3	4
34. Lähtikö teiltä hiuksia?	1	2	3	4
35. Vastaa viimeiseen kysymykseen vain, jos sinulla on ollut hiustenlähtöä: Oletko ollut järkyttynyt hiustenlähdön vuoksi?	1	2	3	4
36. Tunsitteko olevanne sairas tai huonovointinen?	1	2	3	4
37. Oliko teillä kuumia aaltoja?	1	2	3	4
38. Oliko teillä päänsärkyä?	1	2	3	4
39. Oletteko tuntenut itsenne ruumiillisesti vähemmän viehättäväksi sairautenne tai saamanne hoidon takia?	1	2	3	4
40. Oletteko tuntenut itsenne vähemmän naiselliseksi sairautenne tai saamanne hoidon takia?	1	2	3	4
41. Oliko teistä vaikea katsoa itseänne alasti?	1	2	3	4
42. Olitteko tyytymätön vartaloonne?	1	2	3	4
43. Olitteko huolissanne tulevasta terveydentilastanne?	1	2	3	4

Kuluneen <u>neljän</u> viikon aikana:	**Ei/en lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
44. Missä määrin seksi oli teistä kiinnostavaa?	1	2	3	4
45. Missä määrin olitte seksuaalisesti aktiivinen? (yhdynnässä tai ilman)	1	2	3	4
46. Täyttäkää vain jos olitte seksuaalisesti aktiivinen: Missä määrin nautitte seksistä?	1	2	3	4

Jatkuu seuraavalle sivulle

Kuluneella viikolla:	**Ei/en lainkaan**	**Vähän**	**Melko paljon**	**Hyvin paljon**
47. Oliko teillä kipua käsivarressa tai olkapäässä?	1	2	3	4
48. Oliko käsivartenne tai kätenne turvonnut?	1	2	3	4
49. Oliko teillä vaikeaa nostaa käsivarttanne tai liikuttaa sitä sivuille?	1	2	3	4
50. Tuntuiko sairastuneen rinnan alueella kipua?	1	2	3	4
51. Oliko sairastuneen rinnan alue turvoksissa?	1	2	3	4
52. Oliko sairastuneen rinnan alue yliherkkä?	1	2	3	4
53. Oliko sairastuneen rinnan alueella iho-ongelmia (esim. kutinaa, kuivumista hilseilyä)?	1	2	3	4