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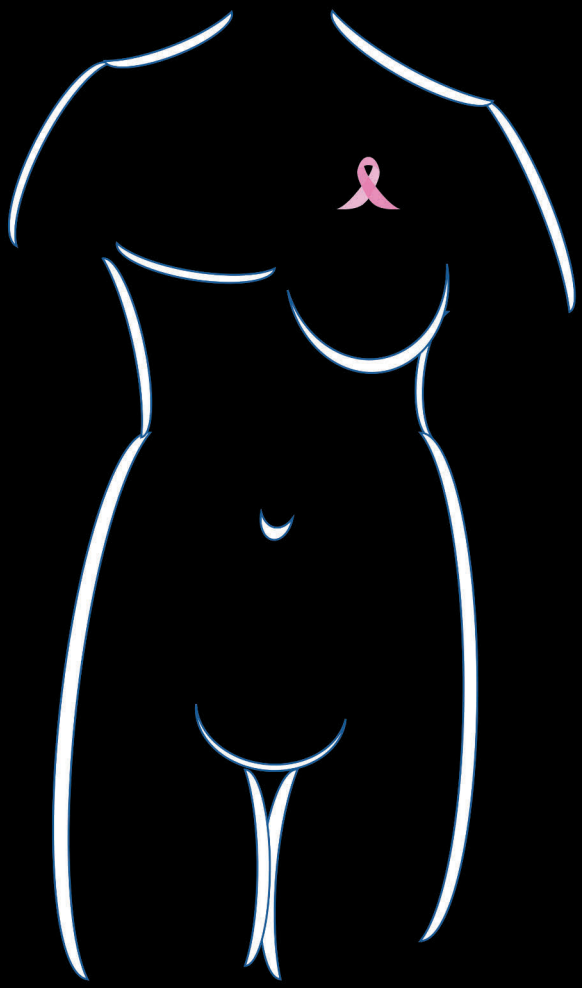

SAFETY OF MASTECTOMY IN BREAST CANCER

Anselm Tamminen

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SARJA – SER. D OSA – TOM. 1690 | MEDICA – ODONTOLOGICA | TURKU 2023

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To my wife, Jenni, and my children Aku, Taavi, Seela and Isla.

UNIVERSITY OF TURKU
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ANSELM TAMMINEN: Safety of Mastectomy in Breast Cancer
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ABSTRACT

BACKGROUND: Breast cancer is the most common cancer in women worldwide. Mastectomy is performed when the patient is not eligible or willing to undergo breast conserving surgery. Surgical complications add morbidity and anxiety for the patient, consume limited healthcare resources, and delay the initiation of adjuvant therapy. Thus, improving the safety of mastectomy is of utter importance.

METHODS: Information of all patients undergoing mastectomy for breast cancer in the Turku University Hospital in the years 2010–2019 was retrieved from the Auria Clinical Informatics Register. The information was verified and supplemented from patient records. Patient characteristics, details of the performed surgery, and complications during the 30 postoperative days were evaluated. The data was used in each study (I-IV). In study II, an additional oncological follow-up information was gathered from electronic patient records and in study III, the results were compared with corresponding data from the Helsinki University Hospital.

RESULTS: In study I, the safety of same-day mastectomy was evaluated by comparing postoperative complications in 259 patients operated in same day regime to 654 patients staying overnight in the hospital. It was detected that the rate of returning to care after the operation was similar in both patient groups (odds ratio: 0.79, p=0.26). In study II, oncological follow-up information of 71 patients undergoing a skin-sparing mastectomy with immediate breast reconstruction for extensive ductal carcinoma in situ (DCIS) was evaluated to assess the oncological safety of the procedure. No local or distant metastasis was detected during a follow-up of 71 months. In study III, the efficacy of antibiotic prophylaxis in mastectomy was studied by comparing 335 patients not receiving to 1078 patients receiving antibiotic prophylaxis. The rate of surgical site infections was similar in both patient groups (6.9 % vs. 6.3 %, p=0.70). In study IV, the rate of bleeding complications was compared between 364 patients operated in the Turku University Hospital using ultrasonic instrument in mastectomy and matched cohort of 364 patients operated in the Helsinki University Hospital using electrocautery. The rate of complications was lower in patients operated with ultrasonic instrument (0.3 % vs 11.5 %, p<0.001)

CONCLUSIONS: The study indicates that day surgery is safe in mastectomy, and that prophylactic antibiotics are usually not needed in the procedure. The risk of postoperative bleeding complications may be diminished by using an ultrasound instrument. A skin-sparing mastectomy is oncologically safe in extensive DCIS.

KEYWORDS: mastectomy, complications, safety

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Lääketieteellinen tiedekunta
Kliininen laitos
Kirurgia
ANSELM TAMMINEN: Rinnan poistoleikkauksen turvallisuus rintasyöpäpotilailla
Väitöskirja, 152 s.
Turun Kliininen tohtoriohjelma
Helmikuu 2023

TIIVISTELMÄ

TAUSTA: Rintasyöpä on maailmanlaajuisesti naisten yleisin syöpä. Kun säästävä leikkaus ei ole mahdollinen tai kun potilas toivoo sitä, on kasvaimen poistamiseksi tehtävä rinnan poistoleikkaus. Leikkausturvallisuuden parantaminen on keskeisen tärkeää, sillä leikkauskomplikaatiot aiheuttavat potilaalle vaivaa ja ahdistusta, kuluttavat terveydenhuollon resursseja ja viivästyttävät liitännäishoidon aloittamista.

MENETELMÄT: Auria-tietopalvelun kautta kerättiin tiedot potilaista, joille tehtiin rintasyövän vuoksi rinnan poistoleikkaus Turun yliopistollisessa keskussairaalassa vuosina 2010–2019. Tietoja potilaiden ominaisuuksista, tehdystä leikkauksesta sekä komplikaatioista verrattiin toisiinsa. Osatyössä II kerättiin lisäksi tiedot syöpäseurannoista ja osatyössä III kerättyjä tietoja verrattiin Helsingin Yliopistollisen keskussairaalan vastaavaan potilasaineistoon.

TULOKSET: Osatyössä I arvioitiin päiväkirurgisen rinnanpoistoleikkauksen turvallisuutta vertaamalla komplikaatioita 259 päiväkirurgisesti leikatun potilaan ja 654 sairaalaseurannassa olleen potilaan välillä. Hoitoon palaamisessa leikkauksen jälkeen ei ollut eroa (kerroinsuhde: 0,79, p=0,26). Osatyössä II kerättiin seurantatiedot 71 potilaalta, joille tehtiin rinnan poistoleikkaus yhdistettynä välittömään rinnan korjausleikkaukseen rintasyövän esiasteen (DCIS) takia. Yhdelläkään potilaalla ei todettu tautiuusiutumaa keskimäärin 71 kuukauden seurannan aikana. Osatyössä III selvitettiin leikkauksen yhteydessä annettavan antibioottiannoksen tehoa leikkausinfektioiden estossa vertaamalla 335 potilasta, jotka eivät saaneet antibioottia 1078 potilaaseen, jotka saivat antibiootin. Leikkausinfektion riskissä ei ollut eroa ryhmien välillä (6,9 % vs. 6,3 %, p=0,70). Osatyössä IV verrattiin leikkauksen jälkeisen verenvuodon riskiä Turun yliopistollisessa keskussairaalassa käytössä olevan ultraääni-instrumentin ja Helsingin yliopistollisessa keskussairaalassa käytössä olevan sähköisen diatermiainstrumentin välillä. Vertaistetuissa 364 potilaan ryhmissä verenvuotoriski oli selvästi alempi ultraääni-instrumenttiryhmässä (0,3 % vs. 11,5 %, p<0,001).

JOHTOPÄÄTÖS: Tutkimuskokonaisuus osoittaa, että päiväkirurginen rinnan poistoleikkaus on turvallinen ja että leikkausta edeltävästä antibiootista ei ole hyötyä infektioiden estämisessä. Vuotokomplikaatioita voidaan vähentää käyttämällä ultraääni-instrumenttia leikkauksessa. Ihoa säästävä rinnanpoisto on onkologisesti turvallinen laajan DCIS:n hoidossa.

AVAINSANAT: Rinnan poistoleikkaus, komplikaatiot, turvallisuus

Table of Contents

Abbreviations

ALND	axillary lymph node dissection
ASA	American Society of Anaesthesiologists
BCS	breast conserving surgery
BCSS	breast cancer-specific survival
BMI	body mass index
CDC	Centers for Disease Control
CRP	C-reactive protein
DCIS	ductal carcinoma in situ
ER	estrogen receptor
HER2	human epidermal growth factor receptor 2
HR	hazard ratio
HUS	Helsinki University Hospital
IQR	interquartile range
ITC	isolated tumour cells
LD	latissimus dorsi -musculocutaneous flap
MRI	magnetic resonance imaging
NACT	neoadjuvant chemotherapy
NSAID	non-steroidal anti-inflammatory drug
NSQIP	National Surgical Quality Improvement Program
OS	overnight stay in hospital
OR	odds ratio
pCR	pathological complete response
PR	progesterone receptor
RR	risk ratio
RCT	randomized controlled trial
SAP	surgical antibiotic prophylaxis
SDS	same-day surgery
SFN	skin-flap necrosis
SNB	sentinel lymph node biopsy
SSI	surgical site infection
SSRI	selective serotonin reuptake inhibitors
TNBC	triple-negative breast cancer

List of Original Publications

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

I Tamminen A, Meretoja T, Koskivuo I. Same-day mastectomy and axillary lymph node dissection is safe for most patients with breast cancer. *Journal of Surgical Oncology.* 2022, Vol. 125, 831–838.

II Tamminen A, Meretoja T, Koskivuo I. Oncological Safety of Skin-Sparing Mastectomy and Immediate Breast Reconstruction in Extensive Ductal Carcinoma In Situ, *Journal of Surgical Research*. 2022, Vol. 279, 25–32.

III Tamminen A, Koskivuo I. Preoperative antibiotic prophylaxis in mastectomy: A retrospective comparative analysis of 1413 patients with breast cancer. *Scandinavian Journal of Surgery*. 2022, Vol. 111(3), 56–64.

IV Tamminen A, Huttunen T, Niinikoski L, Meretoja T, Koskivuo I. Ultrasonic scissors decrease postoperative bleeding complications in mastectomy: A retrospective multicenter cohort study on 728 patients, *European Journal of Surgical Oncology*. 2023, Vol. 49(1), 68–75.

1 Introduction

Breast cancer is the most common cancer among women worldwide, and it is estimated that one in eight women in Western countries develop breast cancer during their lifetime (Sung et al. 2021). The basic paradigm of the treatment has remained the same for decades: surgery is the most effective and principally imperative treatment to enable full recovery (Downs-Canner and Iii 2022).

The treatment of breast cancer has evolved constantly for almost fifty years. Considering breast cancer, knowing the history and the development of the treatment is essential to understand why we treat breast cancer as we do today. The still ongoing de-escalation in surgical treatment of breast cancer started in the 1970s. First, breast conserving surgery was introduced and perceived to produce equal survival to mastectomy. When breast conserving surgery was accepted as the standard treatment, the discussion went on to the surgical margins. The long debate came finally to its end in the 2010s when "no ink on tumour" was accepted as standard-of-care (Moran et al. 2014).

De-escalation of surgery expanded to axillary surgery in the 1990s, when it was discovered that a routine axillary clearance could be substituted with sentinel node biopsy in patients with no clinically detected metastasis. Later, the axillary clearance was substituted with radiotherapy in patients with only one or two axillary metastases. Currently, several trials are examining the possibility to resume the de-escalation process even further.

Simultaneously with the de-escalation of the surgical approach, the adjuvant treatment of breast cancer has developed considerably, and the treatment has expanded to be given before the surgery as neoadjuvant therapy, which has allowed an increasing number of patients to be treated with breast conserving surgery techniques.

The development has respectively affected the surgical approach and added demand for surgeons' profound understanding of the entire treatment pathway (MacNeill et al. 2018). The survival rate after the treatment has improved remarkably, which together with the general aging of the people has led us to the situation, where patients are more often fragile and at the same time are expected to live longer after the treatment (Biganzoli et al. 2012). Thus, the patient's quality of

life has become increasingly important aim to consider, underlining the need for more tolerable breast cancer surgery (Curran et al. 1998).

Breast conserving surgery is associated with a lower risk of complications and less morbidity when compared to mastectomy, but mastectomy is still obligated in some patients, and preferred by others. Thus, the number of women undergoing mastectomy is still large, and the interest in advancing the tolerability of surgery extends to the mastectomy procedure (Dalberg et al. 2004; Al-Hilli et al. 2015; Chatterjee et al. 2015; Jagsi et al. 2016). A large portion of the research on the surgical complications is oldish and has methodological deficits, and the amount of research on subject is very limited (de Blacam et al. 2012). Therefore, on many parts the treatment practice is based on reasoning and assumptions, rather than on research and true knowledge of the subject.

In Turku University Hospital, several changes have been made to the treatment practice. Ultrasonic instrumentation was introduced as a primary instrument in mastectomy in the early 2000's, same-day mastectomy was introduced in 2013 and regular preoperative antibiotic prophylaxis in 2016. Until now, the influence of these changes had not been studied. Additionally, there has been no guideline on treatment of extensive ductal carcinoma in situ (DCIS) and narrow surgical margins when an immediate breast reconstruction has been made. The dilemma is encountered frequently in clinical practice, but there has been no treatment guideline in which to refer. The interest to improve understanding of these subjects led to the initiation of this study entity.

In study I, the safety of mastectomy in same-day surgery protocol was investigated by comparing the number of complications in patients discharged on the day of the surgery to those who were admitted to the ward for the first postoperative night and discharged the following day. In study II, the oncological safety of the immediate breast reconstruction in case of extensive DCIS was evaluated by examining the follow-up information of such patients from the electronic patient records. In study III, the number of surgical site infections was investigated in relation to the preoperatively administrated antibiotic prophylaxis. In study IV, the efficacy of ultrasonic instrument was evaluated by comparing the data to the corresponding data from the Helsinki University Hospital, where traditional electrocautery was used as a primary instrument in mastectomy.

2 Review of the Literature

2.1 Breast cancer

2.1.1 Invasive breast cancer

Breast cancer is the most common cancer among women worldwide. According to the GLOBOCAN 2020 statistics, approximately one in eight women (13 %) in the Western world will develop breast cancer during their lifetime (Sung et al. 2021). The incidence of the disease has increased gradually over the years, approximately doubling in Finland since the year 1980. Despite this, the number of breast cancer deaths has remained essentially the same for decades. This is related to the comprehensive screening program which has enabled diagnosis at an earlier stage and to the considerable development of adjuvant treatment during the last thirty years. The five-year overall survival in patients diagnosed with breast cancer in Finland in 2011-2013 was 91 % and the 15-year relative survival ratio was 80 % (Finnish Cancer Registry 2020).

The most common type of breast cancer is ductal carcinoma (70–80 %), also referred to as carcinoma of no special type, followed by lobular carcinoma (10–15 %). Other types of invasive cancer (papillary, micropapillary, tubular, mucinous, cribriform, metaplastic, and apocrine cancer) are infrequent, each consisting of less than 3 % of breast cancer cases (Li et al. 2005).

Breast cancer is often categorized to five intrinsic subtypes according to molecular classification and gene expression profile (**Table 1**). Gene expression profiling is not practical in clinical use, and thus biological surrogates defined by immunohistochemistry of estrogen receptor status, progesterone receptor status, human epidermal growth factor 2 receptor and Ki-67 index are used (Sørlie et al. 2001; Perou 2011; Boyle 2012). However, the Finnish treatment guidelines do not comply with this categorization as such but uses a simplified classification for clinical use (Finnish Breast Cancer Group 2019).

Table 1. Breast cancer subtypes used in diagnostics and treatment.

INTRINSIC SUBTYPES	BIOLOGICAL SURROGATE SUBTYPES	CLASSIFICATION USED IN FINNISH TREATMENT GUIDELINES
LUMINAL A	Luminal A-like • ER and/or PR positive • HER2-negative • Ki-67 < 14 %	ER/PR-positive
LUMINAL B	Luminal B-like (HER2-negative) • ER and/or PR positive • HER2-negative and Ki-67 ≥ 14 %	ER/PR-positive
LUMINAL B	Luminal B-like (HER2-positive) • ER and/or PR positive • HER2-positive with any Ki-67	HER2-positive
NORMAL BREAST LIKE	Luminal A-like • ER and/or PR positive • HER2-negative Ki-67 < 14 %	ER/PR-positive
HER2-ENRICHED	HER2-positive • ER and PR negative • HER2 positive	HER2-positive
BASAL-LIKE	Triple-negative • ER and PR negative • HER2-negative	Triple-negative

ER = estrogen receptor, PR = progesterone receptor, HER2 = human epidermal growth factor receptor 2

Although the breast cancer surgery is principally the same regardless of the breast cancer subtype, the adjuvant treatment of the subtypes differs. Similarly, the subtypes have different characteristics in how they react to neoadjuvant chemotherapy (NACT), which guides the decision whether the treatment is began with surgery or NACT (Houssami et al. 2012). The subtype also has a strong correlation to the clinical outcome of the patient (EBCTCG, 1998b).

The pathological TNM Classification is used for staging breast cancer (Brierley et al. 2016). The presentation is modified from the original source to correspond to the extent used in this dissertation.

Tx	Primary tumour cannot be assessed
Tis	Carcinoma in situ.
T1	Tumour 2 cm or less in greatest dimension
T1mi	the tumour is 0.1cm across or less
T1a	the tumour is more than 0.1 cm but not more than 0.5 cm
T1b	the tumour is more than 0.5 cm but not more than 1 cm
T1c	the tumour is more than 1 cm but not more than 2 cm
T2	the tumour is more than 2 cm but not more than 5 cm
T3	the tumour is bigger than 5 cm in greatest dimension.
T4	Tumour of any size with direct extension to chest wall and/or skin
N0	No regional lymph node metastasis o including isolated tumour cells (ITC)
N1	Micrometastasis (metastasis sized 0.2–2.0 mm); or metastasis in 1–3 axillary ipsilateral lymph nodes
N2	Metastasis in 4–9 ipsilateral axillary lymph nodes
N3	Metastasis in 10 or more axillary lymph nodes or metastasis in infraclavicular or supraclavicular lymph nodes
M0	No distant metastasis
M1	Distant metastasis

The traditional rationale has been, that at first the breast cancer develops as a local, curable surgical disease, but as the tumour grows and eventually spreads through the lymphatic system, breast cancer develops to systemic, incurable disease. (Fisher et al. 2002; Veronesi et al. 2002). Currently, the progression is not considered such a simple binary phenomenon, but rather a spectrum with multiple stages. It has long been known that the metastases may develop years or even decades after the primary tumour has been treated. The conclusion is that the tumour must be able to release circulating cancer cells in early stage of the disease, and these cells may develop to overt metastases over a long period of time (Hellman and Weichselbaum 1995). The interval from the surgery to the manifestation of distant metastasis is the potential time frame for adjuvant treatment. Although the optimal timing of initiating adjuvant therapy is not precisely defined, it may be presumed, that the treatment is most effective when the circulating cancer cells have not yet developed to overt metastasis and that the optimal timing for adjuvant therapy is imminently after the surgical treatment of the primary tumour (Chavez-MacGregor et al. 2016; Gagliato et al. 2014).

When the distant metastases have already developed, the complete recovery is generally not considered possible. The median survival time after the diagnosis of

metastasized breast cancer is three years, which has not changed substantially during the last years (Chia et al. 2007; Caswell-Jin et al. 2018). However, there is some evidence, that if the treatment is given at a limited "oligometastatic" stage, often defined as at maximum of five detectable metastases, the prognosis may be improved with radiation treatment or targeted therapy (Hellman and Weichselbaum 1995; Mahklin and Fox 2020; van Ommen et al. 2022)

2.1.2 Diagnostics of breast cancer

Historically, breast cancer presented as a palpable, slowly growing lump in the breast. At early stage, the benign and malignant lesions could not be distinguished from each other, but based on a text in an Egyptian papyrus, the disease was considered incurable if it was "cool to touch, bulging and spread all over the breast" (The translation of Edwin Smith surgical papyrus, 1930). The diagnostic accuracy did not evolve much until the 1900s.

In 1913, a German surgeon Albert Salomon investigated mastectomy specimen with x-rays, which had been discovered by a fellow German, physicist Wilhelm Röntgen in 1895. Salomon realized that the clinically detected breast cancer could be correlated to the microcalcifications in the radiographs (Salomon 1913). Unfortunately, it took half a century before the discovery was exploited in breast cancer screening programs (Kalaf 2014). In Finland, the first pilot study on mammography screening began in 1982 (Hakama et al. 1995). The nationwide screening program was started five years later, in 1987. The effectiveness of the program was evaluated by using randomized birth cohorts, showing a 24 % reduction in breast cancer mortality (Hakama et al. 1997). The result is highly similar to the several randomized trials, showing typically 25 % reduction in breast cancer mortality in women aged 50–69 years at the time of the randomization (Smith 2003).

At present, Finnish women aged 50–69 years are invited to biannual screening mammography. Half of the breast cancer cases occur in this age group, and more than half of these cancers are detected in screening mammography. One quarter of breast cancers in this age group are interval cancers, and one out of six cancers occur in patients not attending the screening program, reflecting the fact that five out of six women participate the screening program in Finland (Sarkeala et al. 2014).

The interval cancers and cancers detected outside the screening program present most often as a palpable lump, but various other signs and symptoms are also possible, such as nipple discharge, skin or nipple retraction, erythema and mastitis (Finnish Breast Cancer Group 2019).

The breast cancer diagnosis is confirmed by core needle biopsy, completing the triple diagnostic approach of breast cancer, in addition to clinical examination and imaging studies. The imaging studies usually consist of mammography and

ultrasound study with biopsies, and magnetic resonance imaging (MRI) may be used to provide additional information. The core needle biopsy enables histological assessment of the tumour and preoperative planning of the most favorable treatment for each patient (Kaufman et al. 1994).

2.1.3 Ductal carcinoma in situ

Ductal carcinoma in situ (DCIS) is a stage of breast cancer when the cancer cells have not yet penetrated the ductal basement membrane. Thus, the cancer should not be able to metastasize, regardless of how large the DCIS lesion is (Lakhani, 2012; Punglia et al.2013; Barnes et al. 2012). If no tumour exists, even an extensive DCIS lesion may stay asymptomatic, and it is often detected only in screening mammography. When the DCIS lesion grows and becomes symptomatic, the associated symptoms are similar to those in invasive breast cancer (chapter 2.1.2.)

Before the utilization of widespread mammography screening programs, where DCIS often presents as microcalcifications in otherwise asymptomatic breasts, DCIS was only rarely encountered (Ernster et al. 2002; Punglia et al. 2013). For example, in the well-known prospective trial confirming the safety of BCS by Fisher et al (Fisher et al. 1985), the proportion of DCIS was only 1.5 % of all breast cancer cases, whereas nowadays percentages of 20 to 25 % are presented (Ernster et al. 2002; Brinton et al. 2008). The differential diagnostics between benign and malignant microcalcifications is often challenging, and DCIS cannot be reliably distinguished from invasive breast cancer by any imaging study (Sanders et al. 2005). The diagnosis is confirmed by core needle biopsy. However, the biopsy only represents a limited part of the lesion. Thus, on some occasions the biopsy may reveal only DCIS, even if the lesion would contain an invasive component, and the diagnosis of the invasive cancer is confirmed in postoperative histopathological assessment (Brennan et al. 2011). DCIS frequently presents with separate foci away from the primary lesion, which is interpreted to underline the importance of meticulous removal of the diseased breast tissue and all the suspicious microcalcifications (Holland et al. 1990).

Furthermore, it is presumed that a significant proportion of DCIS lesions never progress to invasive cancer. In such cases, any surgery is overtreatment. Currently, we have no method of predicting which patients have progressive DCIS and which do not (Cowell et al. 2013).

2.2 Surgical treatment of breast cancer

2.2.1 Long-term de-escalation and current trends in breast cancer surgery

Before the era of anesthesia, only few women were willing and/or able to undergo surgery, even though the disease was known to be lethal. There were some experiments to cure the patient by early surgical removal of the tumor. The operation was harrowing, frequently led to the death of the patient and the risk for recurrence was high. After the introduction of general anesthesia in the early 1800s, options for surgical treatment expanded, and multiple surgical techniques were introduced. However, the results remained poor for the first decades of surgical treatment (Kaartinen 2013; Brown 2017).

In the year 1880, William Halsted presented the radical mastectomy, including *en bloc* removal of entire breast with axillary lymph nodes and pectoralis muscles. Halsted was also the first to report the survival dependence on nodal status. He reported the 3-year survival to be 85 % in patients with negative nodes, 31 % in patients with positive axillary nodes, and 10 % when supraclavicular nodes were positive. Overall, Halsted's patient had a 51 % chance of being disease-free in three years from surgery (Halsted 1907). For the first time, the patients were given any proper hope of being cured of the disease (Zurrida and Veronesi 2015).

Although there were experiments with other surgical techniques than Halsted's radical mastectomy, none gained popularity and the paradigm of the surgical approach remained the same for almost a century, until the 1970s (Madden et al. 1972). In Finland, the modified radical mastectomy sparing the pectoral muscles, described by Madden et al. in 1972, replaced the Halsted's radical mastectomy as a standard surgical treatment for breast cancer.

It was likewise in the 1970s when the Milan and NSABP-B06 trials investigating the safety of breast conserving surgery (BCS) were initiated. The pivotal results from these trials were published by Umberto Veronesi and Bernard Fisher in the early 1980s, showing no difference in overall survival (OS) or risk of distant metastases when BCS was compared to mastectomy (Fisher et al. 1985; Veronesi et al. 1986). However, the lack of long-term results kept the surgical community cautious, and the acceptance of the results was slow. Finally, in 1990 the National Institutes of Health Consensus Conference endorsed BCS as the preferred treatment for early-stage breast cancer, after which the procedure was gradually accepted worldwide (Treatment of Early-Stage Breast Cancer, 1991). The long-term results of the Milan and NSABP-B06 trials were eventually verified after 20 years of follow-up, adding reliability to the results (Veronesi et al. 2002; Fisher et al. 2002).

As the experience with BCS grew, more was learned of its upsides. It was shown that patients treated with BCS experienced superior psychological and physical well-being compared to mastectomy, improving patients' quality of life. BCS became the standard treatment for breast cancer and the rate of BCS gradually increased (Arndt et al. 2008).

After the wide acceptance of BCS, the discussion moved to the debate of accepted surgical resection margins, as the trials of that time were performed with wide variation. The Milan trial defined the resection margin as “grossly negative at surgery”, NSABP-B06 as “no ink on tumour”, and many retrospective studies used 1 cm margins (Macdonald et al. 2006). This understandably led to huge variation in the re-operation rates. As the research produced increasing amounts of data, the resection margin narrowed over the years, until the principle “no ink on tumour” was finally accepted in the 2010s, seemingly concluding the de-escalation of breast surgery in breast cancer (Moran et al. 2014).

However, the proportion of mastectomies began to increase again in the early 2000s (McGuire et al. 2009; Mahmood et al. 2013). The two most evident reasons for the change appeared to be the patients’ increasing fear of recurrent cancer and the assumption that more radical surgery would offer superior control over the disease, and the increasing use of preoperative magnetic resonance imaging (MRI). The very same factors do still increase the rates of mastectomy (Katipamula et al. 2009; Itakura et al. 2011; Covelli et al. 2015). Currently, most published data indicates, that 20–40 % of breast cancer patients in western countries undergo mastectomy (Cardoso et al. 2019).

In the early 2000s, another innovation changed the landscape of breast cancer surgery significantly. Previously, mastectomy was the only option in case of large tumors, but the introduction of oncoplastic techniques enabled wider and wider tumors to be operated with breast conserving techniques (Clough et al. 2010; Macmillan and McCulley 2016). In breast conserving oncoplastic surgery, plastic surgery techniques are applied to preserve the breast shape and symmetry, even though the breast volume is decreased by the tumor removal. At first, the oncological safety of the procedure was questioned, but several trials have subsequently proved the procedure to yield results similar to conventional BCS (Petit et al. 1998; Spear et al. 2003). The number of oncoplastic techniques has grown to abundant numbers, enabling the surgeon to choose the best suitable for each patient. Contemporarily a major portion of patients ineligible for traditional BCS can be operated conservatively with these oncoplastic techniques, as up to 50 % of a breast volume may be excised, still producing an esthetically acceptable shape of the breast (Clough et al. 2010). However, in some countries with insurance-based health care system, the health insurance may still not cover the oncoplastic procedures but only mastectomy, which increases the mastectomy rates (Kijima et al. 2016).

2.2.2 De-escalation of axillary surgery

Until the 1990s, axillary lymph node dissection (ALND) was the cornerstone of axillary surgery for two main reasons. First, many patients presented with advanced disease and overt axillary involvement, and the removal of the metastatic lymph nodes has been considered to improve the prognosis of the patient. Second, axillary staging provided essential information on the prognosis of the patient (Veronesi et al. 1990). However, permanent upper limb lymphedema is a common consequence of ALND, and other side effects, such as pain, arm weakness, and loss of movement were also frequent (Kuehn et al. 2000; Mandelblatt et al. 2002). As the incidence of these consequences depends largely on the definition and the published data, it is challenging to estimate the clinical significance of these matters. The incidence for lymphedema is reported to be 17 % in a meta-analysis published in 2013, but the incidence reported in individual studies varies from 2 % to 83 % (DiSipio et al. 2013). The risk for postoperative persisting pain also varies depending on the data and follow-up time. In a study by Veronesi et al (Veronesi et al, 2003), 91 % of patients reported pain six months after the surgery, and 39 % in 24 months, respectively.

The scenery changed when the results of the NSABP B04 -trial were published suggesting, that the patients undergoing mastectomy with or without ALND had an equal risk of distant metastasis or death, and that the rate of false-negative clinical axillary exam was 39 % (Fisher et al. 1977). The results obliged to consider, whether the ALND should not be performed on all patients. The means to substitute the ALND by procedure with less morbidity were examined. In the early 1990s, a procedure called sentinel node biopsy (SNB) was shown to reliably assess the axillary status (Krag et al. 1993; Giuliano et al. 1995). The finding enabled omitting ALND in patients with negative SNB, decreasing the morbidity of the patients considerably. In Turku University Hospital, ALND was the standard axillary procedure until the year 2002, when SNB was introduced.

The first RCT investigating the long-term safety of SNB was published in 2003, presenting 516 patients randomized in two groups, one undergoing SNB+ALND and the other SNB and ALND only in the patients with positive SNB. After more than five years of surveillance, there was no difference between groups in terms of recurrence or survival, but the patients undergoing only SNB had less pain and superior arm mobility when compared to the patients undergoing ALND (Veronesi et al. 2003). SNB with intraoperative frozen section analysis, followed by ALND only in patients with positive SNB was rapidly adopted as the standard approach for the patients with clinically negative axilla (Lyman et al. 2014).

Soon after, the Z0011 trial indicated that ALND could be omitted in T1–T2 breast cancer patients without clinically palpable adenopathy and only one or two positive SNBs, as the patients without ALND presented similar overall survival to

the patients undergoing ALND (Giuliano et al. 2011). Based on the results, the Saint Gallen consensus panel suggested omitting ALND in patients with clinically negative axilla and only 1–2 positive sentinel nodes, when the patient was to receive radiation therapy (Giuliano et al. 2012). In the year 2014, the AMAROS trial investigated T1–T2 primary breast cancer and no palpable lymphadenopathy and one or two positive SNs. The patients with positive SNB were randomized to either undergo ALND or to receive axillary RT. The rate of axillary recurrence was low in both groups, as the recurrence occurred in four of 744 patients (0.43 %) in ALND group and in eleven of 681 patients (1.19 %) in the axillary radiation therapy group. Expectedly, the patients undergoing radiation therapy suffered significantly less side effect compared to ALND group. The recommendation of substituting the ALND with radiation therapy in patients fulfilling the inclusion criteria of the AMAROS study was soon adapted to the Finnish treatment guidelines (Finnish Breast Cancer Group 2019).

These trials seemed to question the benefit of ALND in patients with low metastatic burden in the axilla. Thus, it was logical to dispute the use of SNB in patients who had no clinically suspected lymph nodes. In the Cancer and Leukemia Group B 9343 -trial, women with cT1N0 ER-positive breast cancer and over 70 years of age were randomized into two groups. One underwent only BCS and the other received radiation therapy as adjuvant therapy for BCS. Although 62 % of patients did not undergo axillary surgery, only 3 % of patients developed axillary recurrence, and in 10 years there was no difference in distant metastasis or overall survival between the groups (Hughes et al. 2013). Based on the results, The Society of Surgical Oncology recommends against performing SNB in patients fulfilling inclusion criteria for Cancer and Leukemia Group B 9343 -trial (Calderon et al. 2019).

Furthermore, it seems that the de-escalation of the axillary surgery has not yet come to an end. The results of past trials evoke a question, whether the SNB is necessary at all in patients with clinically negative axilla. At present, the ongoing SOUND trial aims to provide an answer, comparing SNB to omitting the axillary operation in clinically negative, <2 cm breast cancer. The results of the trial may provide the next step in the de-escalation of axillary surgery in the near future (Gentilini and Veronesi 2012). Additionally, the increasing use of NACT and its effect on axillary surgery is under investigation. There is evidence, that the rate of false-negative SNB is elevated after NACT, but the treatment guidelines are still evolving, and it is too early to predict how increasing use of NACT will change the future axillary surgery (Cavalcante et al. 2020).

2.2.3 Surgical treatment of ductal carcinoma in situ

As DCIS is a local disease by definition, its treatment differs from invasive cancer. However, DCIS involves a risk of postoperative upgrading, designating invasive cancer detected in postoperative histopathological assessment without prior knowledge. The estimated risk of upgrading varies widely in previous literature, being 8–59 % (Sauer et al. 2005; Rutstein et al. 2007; Sheaffer et al. 2019; Lamb et al. 2020; Venkatesh et al. 2021). In a meta-analysis, the risk was estimated to be 26 % for all patients, and as high as 46 % in patients presenting with symptomatic DCIS (Brennan et al. 2011).

As DCIS should not have metastatic potential, performing SNB is principally not recommended in DCIS surgery (EBCTCG 2010; Lyman et al. 2014). However, most guidelines recommend performing SNB, if it would be technically challenging to be done in a reoperation, as in mastectomy (Si et al. 2019). The risk of finding an axillary metastasis in DCIS surgery is 3–15 % (Intra et al. 2003; Leikola et al. 2007; Si et al. 2019; van Leeuwen et al. 2020).

Recommended resection margin for DCIS is two millimeters. This is related to the tendency of DCIS to occur as dispersed foci inside the ducts (Holland et al. 1990; Kaufmann et al. 2010; van Zee et al. 2015: Finnish Breast Cancer Group 2019). There is some evidence, that the risk of LR would be the same in cases of under and over the 2 mm RM, as long as it is negative, and the patient receives radiation therapy postoperatively (Matsen et al. 2016; Wapnir et al. 2011). Thus, the need for reoperation on such occasion should be considered individually (van Zee et al. 2015; Tadros et al. 2019).

There have been no clear guidelines on how to treat an extensive DCIS (Kaidar-Person et al. 2021). The extent of DCIS cannot be accurately estimated in imaging studies, as mammography has shown to underestimate and MRI to overestimate the extent (Kneeshaw et al. 2006; Kuhl et al. 2007). In several trials, preoperative MRI has doubled the rate of mastectomies without reducing the rate of reoperations or mortality. The guidelines recommend against the use of MRI in DCIS and if MRI is used, the findings affecting the extent of the surgery should be confirmed with biopsy (Fancellu et al. 2015; Keymeulen et al. 2019).

The survival benefit of treatment for DCIS is much smaller than it is for invasive breast cancer, and therefore the quality of life is emphasized in the decision-making of the treatment (King et al. 2017). Skin-sparing mastectomy or nipple-sparing mastectomy combined with immediate breast reconstruction is a one-stage procedure, recommended for patients with pure large DCIS and opting for a breast reconstruction (Barnes et al. 2012).

Due to the challenges in defining the extent of the DCIS preoperatively, positive or close resection margin is often encountered in postoperative assessment. In the case of nipple or skin sparing mastectomy and extensive DCIS, the resection margin

towards the spared skin is often compromised. In operation, the surgeon must evaluate the flap thickness carefully, as a thin flap compromises blood circulation, and a thick flap compromises the complete removal of the breast tissue. When skin sparing mastectomy has been performed, reoperation for insufficient resection margin is technically difficult, as the exact location of close margins is challenging to define, and the options to remove additional tissue from the breast are limited. For such cases, there is currently no proper treatment guideline (Larson et al. 2011; Robertson et al. 2014).

2.2.4 Breast reconstruction

Patients who undergo a mastectomy are candidates for breast reconstruction. According to the Finnish treatment guidelines, possibility to undergo breast reconstruction should always be discussed with the patient when mastectomy is performed (Finnish Breast Cancer Group 2019). The reconstruction can be performed as an immediate reconstruction with mastectomy or as a delayed reconstruction, usually one year after the adjuvant treatment when the patient and the tissues have recovered from the primary treatment (Yoon et al. 2018). An immediate breast reconstruction is not recommended for the patients with four of more metastatic axillary lymph nodes, in presence of distant metastasis, or when the patient is diagnosed with inflammatory breast cancer (Finnish Breast Cancer Group 2019). The rate of immediate breast reconstruction performed in patients undergoing mastectomy varies widely from one country to another and regionally within countries. A review in 2013 reported the rate of immediate reconstructions to be 3.9–29.2 % in different countries (Howard-McNatt 2013).

There are several different techniques to perform the reconstruction. The decision of the reconstruction technique should be made individually based on the suitability of the patient, rather than the surgeon's preference (Yoon et al. 2018). Implant-based reconstruction is the most used method worldwide (Albornoz et al. 2013; Mennie et al. 2017), but in Finland, autologous breast reconstruction methdos have been more popular (Jahkola et al. 2021). The deep inferior epigastric perforator flap is the most used autologous flap, but numerous alternative flaps may be used as well (Toyserkani et al. 2020). In Turku University Hospital, the latissimus dorsi musculocutaneous flap (LD) has been traditionally the most used reconstruction method.

When compared to delayed breast reconstruction, the immediate breast reconstruction has shown to yield psychosocial and financial advantages, as only a single operation is required, and to improve the patient's quality of life. Thus, the procedure is preferred by several guidelines (Medina-Franco et al. 2002; Agrawal, et al. 2013). When comparing implant-based breast reconstruction to the autologous

breast reconstruction, the latter has shown to yield superior patient satisfaction (Toyserkani et al. 2020)

The immediate breast reconstruction bears an elevated risk of postoperative complications when compared to simple mastectomy, especially in regards of the mastectomy flaps (Huttunen et al. 2022). Complications may delay the initiation of adjuvant therapy, compromising the oncologic treatment and the optimal outcome (Li et al. 2020). Furthermore, the immediate reconstruction methods bear a risk of other long-term complications, such as developing a ventral hernia or bulging after utilizing abdominal flaps and pain or impaired function of the shoulder after latissimus dorsi flap reconstruction (Mortada et al. 2022). Although immediate reconstruction has shown not to compromise the oncological safety, delayed reconstruction may be chosen when the patient is expected to undergo adjuvant treatment (Petit et al. 2008). Conversely, when the patient is not expected to receive adjuvant therapy, immediate reconstruction is the optimal treatment. This is the case especially in pure DCIS, if mastectomy is for some reason preferred over BCS (Mokbel 2003).

2.3 Adjuvant and neoadjuvant therapy

The adjuvant therapy is given to the patient to reduce the risk of recurrence, both local and distant, and thus to minimize long-term morbidity and mortality. The choice of surgical technique may be affected by the planned adjuvant therapy. For example, some patients wish to avoid radiation therapy and thus mastectomy is preferred. Due to the multiplicity of sophisticated treatment chains, most starting with the surgery, the surgeon responsible for surgical decisions must be familiar with the principles of adjuvant treatment protocols.

2.3.1 Radiotherapy

Already when the BCS was introduced, it was understood, that there would be some risk of leaving cancer in retained breast tissue. At that time – before the screening programs were introduced – the rate of cancer multifocality, based on the studies made on the mastectomy specimens, was estimated to be 40–60 % (Holland et al. 1985).

Holland et al. collected in the years 1980–1982 mastectomy specimens of 399 consecutive women undergoing breast cancer surgery. The patients who were estimated to be ineligible for BCS were excluded from the study. All mastectomy specimens were sliced to 5 mm thickness and radiographed. A histological study was performed, and the histological results were compared to the x-rays. It was detected, that only 37 % of the patients had unifocal cancer and 43 % had additional tumour

foci at least 2 cm away from the primary tumour, suggesting that these foci would have been left to the patient if mastectomy was not performed (Holland et al. 1985).

In that context, the first trials comparing BCS, and mastectomy were daring. The understanding was, however, that not all patients required deforming radical mastectomy. The rationale was to experiment with BCS in small tumors, with the least probability of leaving cancer behind.

In NSABP B04 -trial (Fisher et al. 1977), the patients undergoing BCS were randomized into two groups, one with and another without RT. The risk of LR was 14.3 % in patients receiving radiation therapy and 39.2 % in patients without RT. Interestingly, the risk of LR in patients without radiation therapy was relatively close to Holland et al's evaluation of the risk of a having residual tumour in the breast after BCS. The biological significance of the small cancer foci left behind was soon questioned, and the importance of radiation therapy was recognized, emphasizing the crucial significance of adjuvant treatment in breast cancer.

Contemporarily, radiation therapy is considered an essential adjuvant treatment when BCS is performed. A meta-analysis published in 2011 (EBCTCG 2011) concluded a major reduction in local recurrence (35.0 % to 19.3 %) in ten years when radiation therapy was given after BCS. Furthermore, the radiation therapy seemed to be associated also with superior breast cancer-specific survival (BCSS, 25.2 % to 21.4 %) in 15 years.

Radiation therapy is also recommended in patients undergoing mastectomy if axillary lymph node metastases are detected, as it has been shown to reduce the overall risk of recurrence and breast cancer mortality (EBCTCG 2014). This has an important consequence, as some patients have chosen to undergo mastectomy to avoid RT. Based on the recommendation, the patients cannot be promised to receive optimal treatment by choosing to undergo mastectomy without radiation therapy.

2.3.2 Systemic adjuvant therapy

The connection between hormones and breast cancer has been long known. Already in 1896, Beatson reported that when premenopausal women suffering from advanced breast cancer underwent oophorectomy, the tumour shrank dramatically and improved the patient's prognosis. The effect, however, was not present in all patients, which at the time was not fully understood (Beatson 1896). When the estrogen and estrogen receptors (ER) were discovered, the effect of oophorectomy was finally understood, and why some of the patients (those with ER negative cancer) did not seem to benefit from the operation (Jensen and Jordan 2003).

Tamoxifen was the first medicine to be used in the systemic treatment of breast cancer. It was first synthesized in 1962, originally to be used as a contraceptive pill, but it failed in that purpose (Quirke 2017). As an anti-estrogen, it was experimented

in a clinical trial for breast cancer already in 1971. It was shown to induce temporary remission in late breast cancer expressing ER, as did the oophorectomy (Cole et al. 1971). The benefit of the drug also in the adjuvant setting was soon discovered and the use of tamoxifen expanded (Baum et al. 1983). A meta-analysis published in 1998 showed that tamoxifen yielded a 47 % reduction in recurrence and a 26 % reduction in mortality when compared to patients not receiving tamoxifen (EBCTCG, 1998a).

Chemotherapy was introduced first in advanced breast cancer in the 1960s, and the first trials in the adjuvant setting were started in the early 1970s (Rossi et al. 1981). Already the first trials showed significant improvement in overall survival and the rate of distant metastasis. A meta-analysis from the trials that were started before the year 1990, showed an absolute improvement of 7–11 % in the patients diagnosed before the age of 50 and 2–3 % in the patients diagnosed after the age of 50 years. According to the meta-analysis, the 10-year survival was then 77.6 % at ten years, even when the patient was node-negative (EBCTCG, 1998a).

Subsequently, the spectrum of available options for systemic treatment expanded as the studies proceeded. The anthracyclines and taxanes were introduced (Albain et al. 2012) and different combinations of endocrine and chemotherapy were experimented (EBCTCG, 2005). In the 1990s, the HER2-targeted agents and aromatase inhibitors were introduced (EBCTCG 2021). Most recently, cell cycle inhibitors and immune checkpoint inhibitors have been introduced (Johnston et al. 2020; Tarantino et al. 2022).

From a surgical point of view, this propitious development has two important consequences. First, the high survival and long life-expectancy after the treatment emphasize the patient's quality of life after treatment. Secondly, and perhaps more significantly from the surgeons' point of view, the treatments used in an adjuvant setting may also be used as a neoadjuvant treatment to downstage the tumor, with major advantages by expanding options in surgical treatment (Mols et al. 2005).

Adjuvant chemotherapy is most often initiated within 30–40 days of surgery, and it has been suggested that delaying the administration of chemotherapy beyond this time can decrease the benefit of the treatment (Chavez-MacGregor et al. 2016). It has been shown that the patients whose adjuvant treatment has been initiated within 30 days of surgery do have better prognosis than those whose treatment is started more than 61 days from the surgery (Gagliato et al. 2014). Postoperative complications may delay the initiation of the adjuvant treatment, which underlines the importance of high-quality surgery with as low number of complications as possible (Harmeling et al. 2015).

2.3.3 Neoadjuvant therapy

Neoadjuvant chemotherapy (NACT) was invented already in the 1970s, when patients with inoperable breast cancer were prescribed chemotherapy, in order to downstage the disease to enable surgical treatment (Rubens et al. 1980). With the increasing use of BCS, the use of NACT was extended to operable breast cancer to downstage the tumour, allowing BCS instead of mastectomy. A major advantage of NACT is, that it produces direct information on the chemosensitivity of the tumour *in vivo*, guiding the selection of the treatment. In addition, it has been presumed, that micrometastatic disease may be eradicated more efficiently with NACT than with adjuvant chemotherapy, due to the delay in initiation of the treatment (Mougalian et al. 2015; Clough et al. 2015; Vugts et al. 2016). Conversely, if the tumour proves to be resistant to chemotherapy, NACT may increase the risk of metastatic spread by delaying the surgical removal of the tumour (Cortazar et al. 2014; von Minckwitz et al. 2013). The risk of such progression does seem rather low, as a meta-analysis considering NACT showed the rate of progression to be 3 % during the treatment (Caudle et al. 2010). Additionally, if a pathological complete response (pCR) is not achieved, the adjuvant therapy after surgery may be directed by the analysis of the residual tumour. This is an advantage, which is lost if the surgery is performed before chemotherapy (Pusztai et al. 2019)

Multiple trials have compared the same chemotherapy in NACT and adjuvant setting (EBCTCG 2018). A recent meta-analysis concluded that the patients responding to NACT had a lower risk of distant recurrence and breast cancer death than the non-responders. However, when the patients responding and not responding to the NACT are evaluated altogether, the results are equal in patients undergoing NACT and adjuvant chemotherapy. It must be noted that the patients included in the analysis were treated in the years 1983–2002 and the advances of the 21st century neoadjuvant treatment are mostly not detected in the results. Especially, none of the included patients received cancer biology-targeted therapy such as trastuzumab or pertuzumab (EBCTCG 2018). The risk of breast cancer death in 15 years of follow-up was relatively high in the included trials (34.4 % in NACT and 33.7 % in adjuvant chemotherapy), suggesting that the patients do not represent the patients treated in the present say.

Neoadjuvant therapy has been shown to be most effective in HER2-positive and TNBC. Recent meta-analyses have showed pCR in 43–53 % of the cT1–2 HER2-positive patients (Buzdar et al. 2019; An et al. 2022) and 31.1 % in TNBC (Houssami et al. 2012). In the latter analysis, 42 % of the patient's ineligible for BCS were converted to BCS-eligible by using NACT.

Two recent studies have investigated adjuvant therapy after surgery in patients who have undergone NACT but present residual cancer. In CREATE-X trial, investigating HER2-negative breast cancer patients, adding capecitabine to the

standard postsurgical treatment was shown to improve survival in 5 years. In that trial, the HR for recurrence, second cancer, or death was 0.70 in all patients receiving capecitabine and the HR for death was 0.52 in patients with TNBC (Masuda et al. 2017) In KATHERINE trial, patients with HER2-positive breast cancer and residual cancer after NACT were randomized to receive either trastuzumab emtansine or trastuzumab as adjuvant treatment. The risk of death or recurrent invasive cancer was halved in patients receiving trastuzumab emtansine (HR 0.50) (von Minckwitz et al. 2019). These trials have proved the survival benefit of residual-guided therapy after NACT, also rationalizing the benefit of NACT in all patients with TNBC or HER2-positive breast cancer.

2.4 Recurrence after breast conserving surgery and mastectomy

2.4.1 Invasive breast cancer and local recurrence

Along with the progression of modern adjuvant therapy, the risk for LR and distant metastases has decreased dramatically. Thus, the research of contemporary data produces different results than those in the early days of BCS, and the results are not comparable. Currently, the acceptable rate of local recurrence (LR) is considered a fundamental quality indicator of care. A limit of 5 % for LR in five years has been suggested as an acceptable upper limit for both BCS and mastectomy (van der Heiden et al. 2015). Unintuitively, most studies published during the last decade, have shown no difference in the rate of LR between BCS and mastectomy, or that the risk of LR is even lower in patients undergoing BCS.

Merino et al reported the risk of LR to be 4.9 % in 61-months after BCS+RT or mastectomy for stage I–II breast cancer. There was no difference in the risk of LR between patients treated with BCS+RT or mastectomy (HR 0.85, p=0.43; Merino et al. 2018). Corradini et al reported a risk for LR to be 4.6 % in five years and 9.4 % in ten years, respectively. After multivariate analysis, the authors concluded, that BCS+RT was an independent predictor for improved local control (HR 1.517, p=0.013). Ten-year cumulative incidence for lymph node recurrence was 2.0 % in the BCS+RT group and 5.8 % in the mastectomy group, respectively (Corradini et al. 2019). van der Heiden et al reported superior local control in BCS+RT (risk of LR 2.38 % vs 3.45 % in mastectomy) in a data of 40 892 patients (van der Heiden et al. 2015). Wang et al reported a risk of 3.2 % for new ipsilateral breast cancer after BCS during 13 years of follow-up. The authors concluded that more than half of the cancers (54.1 %) were new primary tumors, and the true rate of LR was only 1.5 % (Wang et al. 2021).

In Finnish data of patients treated in the years 2000–2003, the rate of LR was 2.9 % (22/755) in a median follow-up of 89 months after mastectomy (Siponen, Joensuu, and Leidenius 2013). Six of the twenty-two patients (27 %) had a distant metastasis diagnosed simultaneously or before the LR was detected.

2.4.2 Invasive breast cancer and survival

The overall survival in breast cancer has improved rapidly during the last decades. The five-year overall survival was 91 % in patients diagnosed with breast cancer in 2011–2013 in Finland and the latest 15-year relative survival ratio was 80 % (Finnish Cancer Registry 2020).

The long-time paradigm has been, that BCS and mastectomy have an equal long-term prognosis. This has been supported by several analyses of the patients treated in the 1970s and 1980s (Veronesi et al. 2002; Fisher et al. 2002; Litière et al. 2012). Since the days of the first trials confirming the non-inferiority of BCS+RT to mastectomy, the breast cancer adjuvant treatment has changed substantially. Screening programs have enabled early treatment and the rate of node-positive patients has decreased, at the same time when adjuvant therapy has evolved drastically (Poortmans et al. 2012). Thus, it must be pondered, to what extent the results of the 1980s may be applied to contemporary circumstances (Tan 2016).

Several large contemporary retrospective analyses have concluded that BCS+RT is superior to mastectomy in different populations and stage-adjusted breast cancer, offering increasing evidence of the superiority of BCS+RT over mastectomy.

First, Hwang et al published retrospective data of more than 112 000 patients from the USA in 2013 (Hwang et al. 2013). The study showed the patients to have undergone BCS+RT to have both improved overall survival and disease-free survival when compared to patients undergoing mastectomy (adjusted HR 0.81). Soon after Agarwal et al (Agarwal et al. 2014) presented data from more than 132 000 patients with corresponding results (HR 1.31 for survival in BCS, $p<0.001$). During the last decade following these findings, several large trials have presented corresponding results (**Table 2**).

In addition to the retrospective analysis, de Boniface et al published Swedish data of 2767 prospectively included patients with under 30 mm tumour and clinically node-negative axilla, who underwent breast surgery between 2000 and 2004 (de Boniface et al. 2018). This study with a 13-year follow-up had the benefit of being collected prospectively and the patients being followed up regularly, adding reliability to the results. According to the data, BCS+RT was superior to mastectomy without radiation therapy in terms of overall survival (79.5 % vs 64.3 %) and recurrence-free survival (90.5 % vs. 84.0 %)

Table 2. Several large retrospective analyses comparing overall survival in breast conserving surgery and radiotherapy vs. mastectomy have been published since 2013.

Study	Number of patients	Adjusted HR for BCSS in BCS+RT	Adjusted HR for overall survival in mastectomy
Hwang et al. 2013	112 154		0.81 (0.80–0.83)
Agarwal et al. 2014	132 149	1.31 (1.25–1.39)	
Hartmann–Johnsen et al. 2015	13 015	1.64 (1.43–1.88)	
Hofvind et al. 2015	9 547	1.7 (1.3–2.4)	
van Maaren et al. 2016	37 207		0.51 (0.49–0.53)
Yu et al. 2022	180 495		0.764 (0.734–0.787)
de la Cruz Ku et al. 2022 (meta-analysis)	>1.5M		0.64 (0.55–0.74)

BCS = breast conserving surgery, RT = radiation therapy, HR = hazard ratio, BCSS = breast cancer specific survival.

These studies have included all subtypes of breast cancer. There has been criticism, that the behavior of different breast cancer subtypes cannot be presumably the same, and thus addressed in a similar manner. The eligibility of BCS has been questioned especially in the case of TNBC, as it is known to have an increased risk of developing both local and distant recurrence and to do it earlier than other subtypes of breast cancer, and it has the worst prognosis (Dent et al. 2007; Gangi et al. 2014). This subject has been examined in a recent meta-analysis, showing a lower risk of LRR (pooled OR 0.64, $p<0.002$) and distant metastasis (pooled OR 0.70, $p<0.02$) in favor of BCS compared to mastectomy (Fancellu et al. 2021).

It is possible that women treated with BCS may have had more favorable prognostic tumour characteristics and/or better health in general, when compared to those treated with mastectomy (Hofvind et al. 2015). However, the amount of retrospective data to support the BCS is excessive. Stage-adjusted data with more than 450 000 patients treated in the 2000s have produced concordant results, independent of the patient group investigated (Tan and Silva 2018). Although the existence of an explaining confounder cannot be excluded, the difference seems to be too large and universal to be explained by such a factor. It has been proposed that screening-detected cancer would have a better prognosis compared to symptom-detected cancer, but the difference in survival appears to be similar also in patients who have not been screened (Kalager et al. 2009; Hofvind et al. 2015). Another proposed explanation is, that radiation therapy may activate the patient's immune system and contribute to the spared tumour cell elimination (Kroemer and Zitvogel 2012; Chen et al. 2016).

2.4.3 Recurrence and survival in ductal carcinoma in situ

The prognosis in pure DCIS is excellent. In a cohort of more than 140 000 patients with DCIS, the 15-year breast cancer mortality was 2.33 % in patients treated with BCS only, 1.74 % in BCS+RT, and 2.26 % in mastectomy (Giannakeas et al. 2018). In another large analysis of more than 100 000 patients with pure DCIS, (Narod et al. 2015) the 20-year breast cancer mortality was 3.3 %. Patients undergoing BCS+RT with no other adjuvant therapy had an LR risk of 2.5 % and breast cancer mortality of 0.8 % in 10 years. Thus, the risk of breast cancer death in patients with a diagnosis of DCIS is 1.8 times higher than the risk in women without the diagnosis of DCIS.

The reported risk of recurrence after skin sparing mastectomy is highly variable (0–24 %) and depends mostly on the extent of the disease which has been treated (Slavin et al. 1994; Newman et al. 1998; Meretoja et al. 2007; Petit et al. 2008). A meta-analysis of skin sparing mastectomy in patients including both invasive cancer and DCIS presents an LR rate of 6.2 % (Lanitis et al. 2010). Three studies have considered only skin sparing mastectomy in pure DCIS, two of them presenting risks of 1.0 % and 3.3 % for LR and one presenting a risk of 5.9 % for LRR (Carlson et al. 2007; Timbrell et al. 2017; Lhenaff et al. 2019). The numbers are comparative with the ones in a meta-analysis of mastectomy in pure DCIS, presenting an LR risk of 5.3 % in patients with close or positive margins and 1.6 % when margins were negative. The analysis included twelve studies, of which four studies defined the resection margin to be close or positive when it was less than one millimeter and eight when the resection margin was less than two millimeters (Kim et al. 2020). When scrutinizing only the studies in which the close resection margin was defined to be less than one millimeter, the risk of recurrence is reported to be higher at 5.3–10.5 % (Carlson et al. 2007; Chadha et al. 2012; Fitzsullivan et al. 2013). In addition, it has been detected that upgrading to invasive disease is associated with a higher risk of recurrence (Romics et al. 2012).

The median time from the surgery to the recurrence is reported to be 36 to 57 months, but with a great variation as some recurrences happen soon after the surgery but it is possible to have a recurrence even decades later (Meretoja et al. 2007; Lanitis et al. 2010; Romics et al. 2012; Lhenaff et al. 2019).

2.5 Defining the optimal surgical treatment

2.5.1 Multidisciplinary meeting

The treatment of early breast cancer involves several medical specialties, and multiple approaches may be chosen when the treatment is began. Although surgery is the primary treatment for the majority of the patients, increasing number of patients receive neoadjuvant therapy. In Turku University Hospital, neoadjuvant therapy is

recommended most often for patients with inflammatory breast cancer or locally advanced cancer to enable surgery. In many other Western hospitals, the NACT is much more frequently used. For example, 57.7 % of patients treated in Germany received NACT already in 2017, irrespective of tumor subtype (Riedel et al. 2020).

The decision of the primary treatment is most often discussed in multidisciplinary meeting, comprising of breast surgeon, pathologist, oncologist, radiologist and in some cases plastic surgeons. Concordantly, the decision regarding adjuvant treatment and/or possible reoperations are also discussed in multidisciplinary meeting postoperatively. The use of multidisciplinary meeting is expected to improve the clinical decision making and the quality of treatment and it is suggested to be a quality indicator of breast cancer treatment (Biganzoli et al. 2017).

2.5.2 Comparison of breast conserving surgery and mastectomy

The current treatment protocols mostly lean on the paradigm, that the BCS+RT and mastectomy are equivalent options, although many guidelines suggest primarily for the BCS+RT. Thus, the decision of the surgical technique is made individually. The oncological results should be emphasized, but especially in the elderly people secondary objectives, such as quality of life and psychosocial factors should also be considered (Curran et al. 1998; Finnish Breast Cancer Group 2019).

Perhaps the two most significant drawbacks of BCS are the need to undergo RT, and the risk of reoperation for lack of sufficient surgical margins. The risk of reoperation for such reason is reported to be 20–24 % (McCahill et al. 2012; Jeevan et al. 2012; Wilke et al. 2014). Conversely, BCS is associated with substantially lower risk of postoperative complications (Dalberg et al. 2004; Chatterjee et al. 2015; Jagsi et al. 2016) and superior quality of life after the treatment (Engel et al. 2004; Arndt et al. 2008; Bhat et al. 2019).

Mastectomy is performed for the patients not suitable for BCS or when the patient prefers mastectomy. Mastectomy indications include (Heymann et al. 2010; Faermann et al. 2014; Cardoso et al. 2019)

- excessive tumour-to-breast volume ratio
- genetic alteration associated with a high risk of second primary breast cancer
- contraindications for radiotherapy, such as Li-Fraumeni syndrome
- inflammatory breast cancer
- a wish to avoid radiation treatment for BCS due to distance despite the new protocol for axillary treatment with RT instead of ALND

The patient preference has a decisive impact on the surgical treatment. Therefore, it is essential to understand, what are the factors influencing the patient's comprehension of the treatment. Fisher et al observed that majority of the patients choose mastectomy on basis of "a feeling of relief because of their belief that their risk of recurrence was minimized after mastectomy'' and concluded, that many patients make the decision on fallacious basis (Fisher et al. 2012). Furthermore, it has been shown, that the patients' fear of recurrence and death is often exaggerated (King et al. 2017). In Fisher et al's study, the surgeon's recommendation was listed as the primary influencing factor for treatment choice (Fisher et al. 2012). This should imply, that the surgeons also shared the assumption of superiority of the mastectomy. It is concluded that the patient preference is largely based on the information they are given, and the surgeon's opinion on the treatment may be decisive. A quantitative estimation of the surgeon's effect on the patient decision was retrieved from a study by Jagsi et al, who reported that only 1.9 % of average-risk breast cancer patients opted for contralateral prophylactic mastectomy when surgeon did not recommend it, but 19 % when the surgeon was ambivalent (Jagsi et al. 2017). Concordant results have since been repeated in multiple trials, underlining the importance of appropriate information provided for the patients by the treating physicians (Rosenberg et al. 2019; Lee et al. 2018; Dicks et al. 2019; Tan and Silva 2018).

2.6 Day surgery

Surgery with same-day discharge (SDS), also referred to as outpatient surgery, has been increasingly utilized in various surgical procedures (Bailey et al. 2019). In past years, patients were frequently monitored in the hospital after the surgery (overnight-stay surgery, OS). Gradually the length of the hospitalization has shortened, as it has been observed that lengthy hospitalization is not needed for all patients, and in fact, may be harmful to some patients (Wang et al. 2017). The general improvement in surgical techniques, reduced risk for complications, and improved communication systems have also made SDS more acceptable for patients, whose experience of the safety of SDS is essential (Shahbazi and Woods 2016).

Finnish treatment recommendations considering SDS state that the same day discharge should be the primary discharge setting and that advanced age, obesity, or underlying diseases in good control should not be considered an obstacle for SDS (Preoperative evaluation, Current Care Guidelines, 2014).

There are at least two viewpoints on the SDS. First, the feasibility of the procedure, meaning that the patient is potentially physically and mentally fit to be discharged after the operation. This must be evaluated in relation to the surgery, and to the patient's general health and domestic circumstances. It is not the same to

discharge a young patient with good general health and with the support of family members as it is to discharge an old and fragile solitaire patient. SDS is feasible if the patient is able to recover from the surgery in a time span of a limited number of hours to the level, in which she/he is able to cope at home on the evening of the surgery, with the help of her/his family or friends if needed (Bailey et al. 2019).

In addition to the feasibility of SDS, also the safety of the procedure must be considered regarding possible complications. It may be argued that SDS is safe when the risk for major complications is low, and that the treatment of complications is not endangered by discharging the patient. To evaluate the safety of day surgery in a specific surgical procedure, the possible complications need to be identified and the urgency of required treatment measures evaluated. Furthermore, there are some complications related to surgery in general, such as deep venous thromboembolism and pneumonia (Lovely et al. 2012; Bailey et al. 2019).

Previous research has identified several advantages in SDS for women undergoing breast cancer surgery. Marchal et al. stated that patients undergoing SDS instead of hospitalization tend to experience less side effects and to be more satisfied with the procedure (Marchal et al. 2005). Dooley reported that women undergoing an SDS felt having more control over the treatment and recovery and that the procedure might be associated with faster recovery and more effective psychological adjustment (Dooley 2000). McManus et al. stated that SDS patients were more satisfied and reported faster healing and recovery after the surgery (McManus et al. 1994). Margolese and Lasry reported patients to manifest a better emotional adjustment and less distress symptoms after surgery (Margolese and Lasry 2000).

The SDS in breast surgery, including mastectomy, has been first reported in the USA in the 1980s. Some of the first studies on the matter suggested an increased risk of rehospitalization after the procedure (Warren et al. 1998; Ferrante et al. 2000). The procedure was first criticized for being implemented to save on costs and in expense of treatment safety (Ferrante et al. 2000; W. C. Dooley 2000; Case, et al. 2001). Nevertheless, SDS was progressively utilized in the USA during the 1990s (Warren et al. 1998; Case et al. 2001). At the time, BCS was already performed in the SDS protocol in Europe, but mastectomy was still considered unfeasible for same-day discharge (Marla and Stallard 2009; de Kok et al. 2010; Ballardini et al. 2016). The research conducted in the early 2000s presented evidence of the feasibility of SDS in mastectomy, adding that SDS offered improved psychosocial satisfaction compared to the inpatient procedure (Margolese and Lasry 2000; Dooley 2002; Rovera et al. 2008; Keehn et al. 2019). A major weakness in these studies was, that patients with co-morbidities, extensive axillary surgery, and advanced age were usually excluded from the study, and there is little evidence on the safety of SDS in these specific patient groups. Thus, it is stated that the patient selection for SDS is based more on tradition than research on the subject (Lermitte and Chung 2005;

Rovera et al. 2008). Most of the studies support SDS in young patients with good general health.

SDS in elderly patients was studied by Warren et al, who presented an equal rate of complications and reoperations in patients treated in SDS and OS groups (Warren et al. 1998) ALND patients are suggested to often have intractable pain preventing discharge after the operation (Marchal et al. 2005).

There are several limitations regarding the present literature on the subject. First, most of the study on the subject is published in the 1990s and early 2000s. Since then, there has been a major development in surgical approach, anesthesiology, and SDS practice in general, questioning the applicability of the results to contemporary practice. Second, no RCT on the subject has been published. Regarding the rarity of the complications and the minor difference in the rate of complications in published retrospective studies, it is not expected to have RCTs with an adequate number of patients to confirm the findings.

Third, the variation in patient demographics between the SDS and OS groups has usually been wide. Although the difference can be handled with statistical analysis to some extent, the unrecognized confounding factors cannot be eliminated.

2.7 Complications of mastectomy

Complications after breast cancer surgery are detrimental in many respects. Complications add morbidity to the patient, increase the cost of the treatment, and may delay the initiation of the adjuvant treatment (Kirkland et al. 1999; de Lissovoy et al. 2009; Recht et al. 2009). The delay in adjuvant therapy is shown to worsen the oncologic outcome of the treatment (Recht et al. 2009). Considering the significance of the complications, surprisingly little amount of data has been published on the subject (de Blacam et al. 2012).

The most frequent complications of mastectomy are surgical site infection (SSI), postoperative bleeding, and skin flap necrosis (SFN). Seroma formation occurs often after the mastectomy, and some authors consider it as a complication, whereas some others as an inevitable nuisance with few possibilities to be prevented. However, if the seroma is left untreated, it may lead to wound problems and even SFN. Most complications have common risk factors, and one complication may cause another. Thus, one patient may suffer multiple complications, leading to exponentially increasing morbidity, and emphasizing the need for effective ways to prevent all complications (Hoefer et al. 1990; Gonzalez et al. 2003; Pogson et al. 2003; Gallagher et al. 2019).

In addition to these mastectomy-specific complications, the patients may also suffer general complications associated to any major surgery, such as urinary tract infections, pneumonia, deep venous thrombosis, pulmonary embolism, and stroke (Dencker et al. 2021).

2.7.1 Surgical site infections

Despite the fact that breast surgery is considered to be "clean" surgery, surgical site infection (SSI) is the most common complication after the operation (De Blacam et al. 2012). In most clean surgery, the risk of SSI is 1.5–3.4 % (Vazquez-Aragon et al. 2003; Cruse and Foord 1980), but in breast cancer surgery, the reported rates of SSI are higher, 1–15 % (Witt et al. 2003; Vilar-Compte et al. 2004; Angarita et al. 2011; de Blacam et al. 2012; Gallagher et al. 2019). Most RCT's investigating surgical antibiotic prophylaxis report the rate of SSI to be 6–19 % in mastectomy (Wagman et al. 1990; Platt et al. 1990; Amland et al. 1995; Olsen et al. 2008), but percentages up to 41 % (16/39) have been published (Witt et al. 2003). Retrospective data from large cohorts usually present lower rates of SSI. According to the National Surgical Quality Improvement Program (NSQIP) data, the rate of SSI is 2.3 – 4.34 % (El-Tamer et al. 2007; de Blacam et al. 2012; Davis et al. 2013). Large retrospective database analyses have presented SSI rates of 2.3 %, 3.2 %, 3.3 % and 5.3 % in patients undergoing mastectomy (de Blacam et al. 2012; Eck et al. 2012; Davis et al. 2013; Palubicka et al. 2019).

To evaluate how the risk for SSI could be reduced, one should first be able to identify risk factors for SSI. Multiple risk factors have been suggested in the literature, such as smoking, diabetes, obesity, prior RT, old age, reoperations, prolonged duration of surgery, high amount of intraoperative bleeding, and preceding neoadjuvant therapy (Amland et al. 1995; El-Tamer et al. 2007; Olsen et al. 2008; Al-Hilli et al. 2015). Only a little can be done to reduce the effect of these factors.

Surgical antibiotic prophylaxis (SAP) is suggested to be the most effective method of reducing the risk of SSI, and it is widely used and recommended by multiple guidelines (Mangram et al. 1999; Bağhaki et al. 2014; Gallagher et al. 2019). The rationale of SAP is, that intraoperative bacterial contamination of the wound can be diminished by dosing an antibiotic before the surgical incision (Nichols 2004). SAP has been shown to be effective in several procedures involving wound contamination, but in most clean procedures, and especially in breast surgery, the trials have produced controversial results (Bratzler et al. 2005). Antibiotic usage adds the cost of the treatment and exposes the patients to side effects, such as allergic reactions and gastrointestinal infections, for example, *Clostridium Difficile* infection, and promotes the development and spread of antimicrobial resistance (Throckmorton et al. 2009). Thus, using SAP should be based on proven benefit, and unnecessary use of SAP should be abdicated. At present, the use of SAP seems to be more frequent than indicated (Tourmousoglou et al. 2008; Giordano et al. 2017).

Several RCTs have evaluated the efficacy of SAP in breast cancer surgery, but the studies have been highly heterogenous and the results conflicting. Some studies

have shown no benefit in using SAP (Gupta et al. 2000; Cabaluna et al. 2013), whereas some have yielded results highly in favor of SAP (Gulluoglu et al. 2013; Edwards et al. 2014). However, most studies have included various types of breast surgery and a very limited number of patients, narrowing the generalizability of the results. Additionally, a major portion of the RCTs on the subject have been published in the 1990s. After that, the whole treatment protocol has developed substantially. Thus, the results of these trials may not be directly applicable to the present day. As Amland et al state (Amland et al. 1995), at the time of the study, there was no proper definition for SSI, potentially leading to variation in diagnostic criteria and results in the trials of the time. The Centers for Disease Control (CDC) introduced the term "surgical site infection" and suggested criteria for diagnosis only in 1992 (Horan et al. 1992).

A Cochrane review published in 2019 (Gallagher et al. 2019) evaluated 10 RCTs investigating SAP in breast cancer surgery. It must be noticed that the review also included patients undergoing BCS, and probably lower risk of SSI than patients undergoing mastectomy (Platt et al. 1990; Witt et al. 2003). Of the ten trials included in the Cochrane review, only one concluded that SAP is effective in preventing SSI. Despite that, the overall risk of SSI in the trials included in the review was 7.1 % in patients with SAP and 10.5 % in patients without SAP (RR 0.67, 95 % CI 0.53–0.85), and the review concluded that SAP is probably effective and should be commenced in breast cancer surgery (Gallagher et al. 2019).

Detailed analysis of the trials seems to unveil factors decreasing the applicability of the results to the present-day Finnish environment. In a study by Gupta et al, 334 patients underwent mastectomy or BCS. Half of the patients received SAP (Augmentin 1.2 g) and the other half received placebo. Even though the rate of SSI was reasonably high in this study, there was no difference in the rate of SSI (SAP group 17.7 % vs. placebo 18.8 %, p=0.79). As a result, the authors concluded, that SAP is probably not beneficial in clean, elective breast surgery. In this study, less than half of the patients underwent a mastectomy (82/174 in the SAP group and 90/177 in the control group) and the results were not given for mastectomy patients separately (Gupta et al. 2000).

Cabaluna et al reported an SSI rate of 13.4 % (17/126) in mastectomy patients receiving SAP and 15 % (19/127) in patients receiving placebo (p=0.719; Cabaluna et al. 2013). Hall et al demonstrated similar rates of moderate or severe cellulitis between breast surgery patients with and without SAP. The rate of SSI was 3.2 % (10/311) in the SAP group and 4.6 % (14/307) in the control group (p=0.387). Only a minority of the patients underwent mastectomy (57 patients in the SAP group and 50 patients in the control group), and the rate of SSI is not given for mastectomy patients separately. Mastectomy is not mentioned as a risk factor for SSI in this

study, so it may be presumed that it was not associated with an elevated risk of SSI (Hall et al. 2006).

In the Bold et al's study, there was a trend toward fewer infections in the SAP group (placebo 13 % (10/72) versus cefonicid 6 % (3/69); p=0.080) in 200 patients undergoing ALND. The study was to investigate the ALND in particular, and therefore the study also included 35 patients with melanoma. Approximately half of the patients underwent mastectomy (49 in the SAP group and 43 in the control group). Eight patients (16 %) suffered an SSI in the placebo group and two (4.7 %) in the SAP group (Bold et al. 1998).

In Platt et al's study in 1990, the infection rate was 6.6 % in the SAP group and 12.2 % in the placebo group. The trial has been criticized for the broad definition of postoperative infections, as it included e.g., patients with pneumonia and urinary tract infections. The number of only definite SSIs was far smaller, 3.6 % in the SAP group (11/303) and 5.9 % (18/303) in the control group (Platt et al. 1990).

Amland et al's study considering plastic surgery operations apparently includes only breast cancer patients operated with BCS, although it is not explicitly expressed in the article. The rate of SSI in breast surgery seems to be very high (25 %, 22/88) without antibiotics and moderate (7.1 %, 6/85) with prophylaxis, especially considering the contemporary risk of SSI in BCS. The authors state, at the time there was no proper definition for SSI and the definition of SSI does not meet the criteria of the present day (Amland et al. 1995).

In a study by Paajanen and Hermunen the aim was to evaluate whether a preceding core needle biopsy would be a risk factor for SSI. The authors randomized patients into a group receiving SAP (1.0 g of dicloxacillin) and a control group receiving saline infusion. The overall rate of SSI was 7.2 % (21/292) with no difference between the SAP (5.6 %) and control (8.8 %) groups. The authors concluded that SAP did not prevent SSIs. The rate of SSIs was 6.8 % (12/177) in patients undergoing mastectomy, but the distribution of patients receiving SAP or saline is not given for mastectomy patients separately (Paajanen and Hermunen 2009).

Wagman et al conducted a prospective study of 59 patients undergoing mastectomy in both SAP and control groups. There were three SSIs (5.1 %) in the SAP group and five (8.5 %) in the control group (p=0.72) (Wagman et al. 1990). Chow et al investigated the effect of clarithromycin on acute inflammatory response rather than the rate of SSI. In this study, no SSIs were detected in 52 patients. (Chow et al. 2000). Additionally, Wagman et al. and Chow et al. both administered antibiotics before and after the surgery.

Gulluoglu et al. were the only ones to show a difference of statistical significance when using SAP in breast cancer surgery. The research was conducted to show

whether SAP would be effective in obese patients. Thus, only patients with a BMI of 25 kg/m^2 or higher were included in the randomization process. The rate of SSI was 4.8 % (9/189) in the SAP group and 13.1 % (25/183) in the control group. All SSIs in the study were detected in patients with a BMI of 30 kg/m^2 or higher. Interestingly, patients with BMI under 25 kg/m^2 were included in the study as a normal-weight control group having no SAP. In this group, the rate of SSI was 3.5 % (5/149). More than half of the patients underwent a mastectomy, mostly on patient preference, but the rate of SSI was not given for the mastectomy patients separately. Curiously, no patients had to be hospitalized for SSI management despite the high number of SSIs. As the authors state, the results of this study cannot be reflected in all breast cancer patients since the protocol only included patients with a BMI of 25 kg/m^2 or higher. The authors conclude that the results should be interpreted to support no SAP in patients having BMI less than 25 kg/m^2 and indirectly indicating a similar interpretation for the patients having a BMI of 25–30 kg/m^2 (Gulluoglu et al. 2013). This limitation is noted in the Cochrane review, but it is not taken into account in the analysis (Gallagher et al. 2019).

After the latest update on the Cochrane review, one RCT trial has been published. Prudencio et al, investigated 124 patients in an SAP vs. placebo setting and showed no benefit on SAP, as only one patient in the SAP group suffered SSI. In this study, only 13 patients underwent mastectomy (Prudencio et al. 2020).

In conclusion, the heterogeneity of the studies is conspicuous. There is major variation in hospitalization time (from a median of 1 day (Edwards et al. 2014) to 14 days (Yang et al. 2017)), patient characteristics (from the patient median weight of 57.5 kg (Yang et al. 2017) to mean BMI of 30 kg/m^2 (Edwards et al. 2014), operation time (from 50 minutes (Gupta et al. 2000) to 163 minutes (Edwards et al. 2014)), and the duration which the drains are kept in situ (from 5.7 days (Prudencio et al. 2020) to 14 days (Vilar-Compte et al. 2004)). Gulluoglu et al. used skin clips in wound closure for all patients, while absorbable sutures are used by default in many other institutes. Gulluoglu et al. also report the majority of SSIs (65 %) in the first week after the operation (Gulluoglu et al. 2013), whereas most other studies report the mean time from operation to the diagnosis of SSI to be 10–17 days (Wagman et al. 1990; Platt et al. 1990; Gupta et al. 2000). Thus, it seems obvious that these studies cannot merely be summarized to reach reliable conclusions and that the available data does not answer the question of whether the SAP may truly decrease the rate of SSI in breast surgery.

2.7.2 Postoperative bleeding

In a mastectomy, postoperative bleeding is a potentially serious but avoidable complication. Bleeding and thrombovenous complications are complications related to each other, especially in patients consuming medications affecting hemostasis. Although the risk of thromboembolism is studied on several occasions, the studies considering postoperative bleeding are rare (Lovely et al. 2012; Nwaogu et al. 2015).

The risk of postoperative bleeding complications is reported to be 2–11.6 % (Hoefer et al. 1990; Nwaogu et al. 2015; Al-Hilli et al. 2015). The risk factors identified to predispose to bleeding complications are medications affecting blood hemostasis, specifically anticoagulants, antiplatelets, and non-steroidal anti-inflammatory drugs (NSAIDs). Selective serotonin reuptake inhibitors (SSRIs) and glucocorticoids have been shown to have similar but lesser effect (Gärtner et al. 2010; Winther Lietzen et al. 2012). Also, patients with multiple co-morbidities have been shown to be at increased risk of bleeding complications, but old age itself has produced conflicting results (Nwaogu et al. 2015; Winther Lietzen et al. 2012; Friis et al. 2004).

It has been suggested, that as the bleeding activates platelets, with the capability of binding tumour cells, the postoperative bleeding might promote the metastatic spreading in patients with breast cancer. Pedersen et al performed a cohort analysis of more than 30 000 patients and 4769 cancer recurrences but found no evidence of such association and it seems unlikely that bleeding has such an adverse effect on cancer recurrence (Pedersen et al. 2017).

The risk of postoperative bleeding complications by the selection of surgical instrument has not been studied in RCTs, but Huang et al performed a meta-analysis of instrument used in surgery and the amount of intraoperative bleeding. The meta-analysis consisted of 11 RCT's including 702 patients in total. The mean blood loss in that analysis was 300 ml for the ultrasonic instrument (Harmonic Scalpel®) and 399 ml for electrocautery (Huang et al. 2015).

2.7.3 Wound dehiscence and skin flap necrosis

Minor wound problems are common after mastectomy, as the wound is long and the skin flaps lengthy. Both wound dehiscence and SFN are related to the impaired blood supply of the skin flaps (Palmer and Taylor 1986; Robertson, Rusby, and Cutress 2014). The rate of the complication is highly dependent on the data and how it is collected. According to the NSQIP data, 0.3 % of patients undergoing mastectomy required reoperation for SFN or any other wound issues, but prospective studies reporting percentages up to 30 %. have been published (Al-Hilli et al. 2015; Palmer and Taylor 1986) Several patient related factors are known to increase the risk of compromising the skin flap viability, such as patient smoking, previous scars and/or RT, diabetes, and obesity (Paige et al. 1998; Padubidri et al. 2001; Alderman et al.

2002). Unfortunately, except from smoking which may be ceased, the risk factors are not modifiable in the time scale from breast cancer diagnosis to surgery.

The risks of skin flap necrosis and wound dehiscence are understandably higher in patients undergoing nipple or skin sparing mastectomy, as the flaps are longer than in simple mastectomy. The risk of SFN is reported to be on average 5–6 % (range 0–17 %) after these operations (Chang et al. 2002; Kim et al. 2012; Du et al. 2018). It has been shown that a flap thickness under five millimeters increases the risk of SFN (Verheyden 1998). However, leaving the flap too thick increases the risk of leaving residual breast tissue (Torresan et al. 2005). Tumescence has been tried for decreasing the rate of SNF with the rationale, that it would enable a thicker flap with decreased risk of leaving breast tissue behind, but the technique proved to be a major risk factor for SNF (Chun et al. 2011).

In a study by Hoefer et al from 1990 (Hoefer et al. 1990), patients operated with electrocautery suffered more wound complications than those operated with a scalpel, but the newer study by Davies et al did not find difference between the instruments (Davies et al. 2011).

Negative Pressure Wound Therapy (NPWT) has been experimented to reduce wound complications in mastectomy, but so far, the studies have produced conflicting results and routine use may not be recommended (Kim et al. 2016; De Rooij et al. 2021).

2.7.4 Seroma

Seroma formation often occurs after mastectomy. Some surgeons consider the seroma formation as a complication, others as an inevitable nuisance and side effect as the majority of the patients require some intervention for seroma, and there is no known method to prevent the seroma formation (Talbot and Magarey 2002; Gonzalez et al. 2003; Pogson et al. 2003). The surgical instrument used in the mastectomy procedure has been shown to affect the rate of seroma formation (Srivastava et al. 2012). One study showed ultrasound instrument to decrease the rate of seroma formation (Lumachi et al. 2004). Using a scalpel induces less seroma formation than electrocautery but is associated with more intraoperative bleeding and longer operating time (Keogh et al. 1998).

Excessive formation of seroma may lead to subsequent complications, such as wound problems and SSIs (Hoefer et al. 1990). Drains are usually inserted in mastectomy and/or ALND procedures to remove the excessive seroma. The seroma formation usually decreases gradually over time until it eventually is absent (Somers et al. 1992; Cameron et al. 1988). Until the seroma formation ceases, repeated punctures are used to relieve the symptoms. Surgical interventions seem to be only rarely beneficial in treating persistent seroma (Srivastava et al. 2012).

Several methods have been tried to prevent seroma formation, with limited benefit. The duration of how long the drain is kept in situ has not been decisive on the rate of seroma formation and prolonged use of drainage increases the risk of SSI (Talbot 2002). Using sclerosants (Catsman et al 2016) of fibrin glue (Sajid et al. 2012) have been experimented. Skin flap fixation has been tried in several different techniques and conflicting methods, but the procedure prolongs the operation time and may increase the pain experienced by the patient (Almond et al. 2010; van Bastelaar et al. 2016).

Shoulder immobilization has proven to have efficacy in decreasing seroma formation, but it carries a risk of long-term range-of-motion limitation and may increase the risk of lymphedema, so it is not recommended (Flew 1979). The use of a pressure garment is not effective in reducing postoperative drainage and has low tolerance and a higher complication rate (Chen and Hoe 1998; O'Hea et al. 1999).

At present, the only successful treatment strategy for postoperative seroma formation seems to be repeated punctures (Gonzalez et al. 2003; Pogson et al. 2003).

2.7.5 Lymphedema

Lymphedema is a chronic condition, in which the lymph is not able to flow freely, causing lymph retention and swelling of the tissue. The lymphedema occurs most often in the upper limb, having the most detrimental effect on the patient, but it may be present in any tissue surrounding the operated breast. Lymphedema in the upper limb develops most often after ALND (17–21 %) but may also occur after SNB (3–7 %) or mere radiation therapy (Francis et al. 2006; A. G. Warren et al. 2007, DiSipio et al. 2013, Warren et al. 2014). The most prevalent symptoms of lymphedema are upper limb swelling, pain, limitations of motion, depression, and anxiety, having a substantial effect on patients' quality of life (Gupta and Moore 2018; Warren et al. 2007; Hayes et al. 2012). In a single prospective cohort study of 964 patients who underwent ALND, the incidence of lymphedema (as defined by >200 ml difference in upper limb volume) was 13.5 % at two years of follow-up, but 30.2 % at five years, reflecting the slow progression of the condition (Ribeiro Pereira et al. 2017).

When the lymphedema has already developed, the treatment is challenging, especially in high stage disease. Lymphovenous anastomosis microsurgery is a novel method with promising but varying early results. (The procedure is made by anastomosing the lymphatic channels from the upper limb to nearby veins or using vascularized lymph node transplants with or without lymphangiogenic growth factors. The effect has been limited, and the best results have been gained when the procedure has been made in the early-stage disease and limited limb swelling (Hartiala and Saarikko 2016; Carl et al. 2017, Coriddi et al. 2020, Gupta et al. 2021).

As the lymphedema is chronic and slowly progressing condition, the importance of prevention must be emphasized. Patients suffering from lymphedema usually wear compression garment to ease the swelling and symptoms, but the benefit is limited when the lymphedema has already developed. To prevent the lymphatic damage and related lymphedema, axillary reverse mapping during ALND has been experimented and may be effective in preventing upper limb lymphedema (McEvoy et al. 2022). However, as the ALND is the most evident risk factor for lymphedema, the de-escalation of axillary surgery as a result of ongoing clinical trials may be the most promising way to prevent lymphedema in years to come.

2.8 Surgical instruments

Several different surgical instruments have been used and studied in a mastectomy. A traditional scalpel is nowadays used only rarely, as electrocautery (EC) is an economical alternative with superior intraoperative hemostasis (Sheen-Chen and Chou 1993). Modern more advanced technologies, such as instruments based on ultrasound or bipolar technique have also been used in mastectomy (Gambardella et al. 2019). The most investigated novel instrument appears to be Harmonic Scalpel® (Ethicon, USA) (Huang et al. 2015; Cheng et al. 2016). The ultrasound instrument used for mastectomy in Turku University Hospital is SonoSurg® (Olympus Medical Instruments, Tokyo, Japan), but no study considering the instrument for mastectomy is found in PubMed or Google Scholar. The operating principles of electrocautery and ultrasound instrument (US) are completely different, and to understand why the instruments may yield different rates of complications, it is essential to be familiar with these differences.

2.8.1 Electrocautery

The operating principle of electrocautery is electric current conducted from the instrument through the patient's body to the grounding electrode. The current causes the tissue to heat, either cutting or coagulating it. The effect is dependent on the characteristics of the used electric current. When interrupted current is used, the tissue is coagulated at high temperature (obliterative coagulation). The molecules of the tissue are dehydrated and oxidized, "burned", forming an eschar sealing the affected area. The cutting effect occurs when continuous current is used. The tissue vaporizes at temperatures over 200 °C, and the instrument reaches temperatures of 250–350 °C (Kunde and Welch 2003; Massarweh et al. 2006; Loh et al. 2009; Alkatout et al. 2012). Due to the high temperature, also the tissue with a considerable distance from the instrument is heated, suffering a thermal injury called "lateral

thermal damage" to the tissues not intended to be dissected (Perko et al 2006, Družijanić et al. 2012).

Particularly in the case of mastectomy, it is speculated that the lateral thermal effect of the electrocautery instrument may damage the subdermal vascular plexus. When compared to ultrasound instruments, the use of electrocautery in mastectomy is also shown to be associated with a higher rate of seroma formation, assumably since the technique does not permit complete occlusion of lymphatic channels (Khan et al. 2014).

2.8.2 Ultrasound instrument

The operating principle of ultrasound instrument is based on the high-frequency vibration of the cutting blade. The vibration is transmitted to the tissue, causing the collagen molecules to denature and form a coagulum. The mechanism produces notably less heating than electrocautery (Kunde and Welch 2003; Koh et al. 2008; Miccoli et al. 2010). The SonoSurg® instrument has not been investigated in breast surgery, but a trial considering the instrument in thyroid surgery showed that the blade of the instruments reached a mean temperature of 81.5 °C with the medium power setting and 99.2 °C with the maximum power, and the highest temperature measured was 114.41°C (Adamczewski et al. 2015). The temperatures are substantially lower than the ones presented for electrocautery, which should provide less lateral thermal damage and assumably fewer skin flap complications (Hambley et al. 1988; Hayami et al. 2019). In addition, the scissor mechanism of the instrument enables grasping the tissue, such as the blood vessels, allowing more controlled hemostasis. The direct application is reported to obliterate blood vessels up to 7 mm in diameter. After the obliteration, the burst pressure of the sealed vessel is reported to be 900 ± 579 mmHg for 4–5 mm arteries and 734 mmHg for 5–7 mm arteries (Clements and Palepu 2007; Seehofer et al. 2012). A single study has demonstrated that ultrasound scissors may also decrease the rate of postoperative seroma, which might result from better occlusion of lymphatic channels (Lumachi et al. 2004).

2.9 Cost of the treatment

The healthcare community faces increasing pressure to constantly increase the quality of treatment, keeping the expenses low at the same time (Nwaogu et al. 2015).

Breast cancer has the highest economic cost of treatment, compared to any other cancer. In 2020, the total cost of breast cancer treatment was approximately 227 million euros in Finland and 29.8 billion dollars in the USA, being 14.3 % of the expenses on all cancer treatment (Cancer Trends Progress Report 2021; Cancer

Foundation Finland 2022). The average cost of the treatment of a single breast cancer patient is approximately 44 000 euros in Finland (Cancer Foundation Finland 2022). As the total cost of the breast cancer treatment is so high and the number of patients large, small improvements may provide large absolute benefits.

Greenup et al reported, that shortening the radiation therapy to hypofractionated regime in eligible patients, following the evidence-based approach, would save 164 million US dollars annually in USA (Greenup et al. 2017).

There are only a few studies investigating the cost of the complications of mastectomy. Nwaogu et al estimated, that bleeding complications required 1.3 days of additional hospitalization and that the average cost of rehospitalization is 5495 dollars for a single patient and 5.3 million dollars at a national level (Nwaogu et al. 2015).

An often-overlooked complication of breast surgery is upper limb lymphedema. Moffat et al reported, that upper limb lymphedema is associated with severe infections requiring hospitalization and intravenous antibiotics, with a mean cost of £2300 (2600 euros), and that patients with lymphedema caused time off work in more than 80 % of patients, and even affected the employment status in 9 % of patients (Moffatt et al. 2003). The exact cost estimation of such findings has not been done, but some estimation may be done on the basis that the cost of a single sick-leave day is estimated to be 370 euros in Finland (Confederation of Finnish Industries, 2021).

3 Aims

The aim of this thesis is to provide evidence on the safety of mastectomy in breast cancer.

- Study I: The aim of the study was to evaluate the safety of same-day mastectomy.
- Study II: The study aimed to investigate the rate of local or distant recurrence in patients who have undergone a skin-sparing mastectomy and immediate breast reconstruction for extensive DCIS.
- Study III: The aim of the study was to define the efficacy of antibiotic prophylaxis in preventing surgical site infections after mastectomy.
- Study IV: The study aimed to compare the rate of complications between patients operated with the ultrasonic instrument and traditional electrocautery.

4 Materials and Methods

4.1 Forming the study cohort

The study cohort of each following study is based on patients treated in Turku University Hospital during the study period of years 2010–2019. All patients who underwent a mastectomy (surgical procedure code HACxx according to Nordic Classification of Surgical Procedures, NCSP) and having a diagnosis of breast cancer, either invasive (C50 in ICD-10 classification) or non-invasive (D05 in ICD-10 classification), were included.

The data were retrieved from Auria Clinical Informatics Register. The data were verified and supplemented from electronic patient records. The patient records for 30 postoperative days were studied. The collected information is presented in Table 3.

Patients included in each study were selected from this large cohort, based on the study design to answer a specific question which was investigated.

Each study was retrospective. Male patients were excluded.

4.2 Surgical protocol in mastectomy without immediate reconstruction

The patients who underwent a mastectomy without an immediate breast reconstruction (studies I, III, and IV) were referred to breast surgeons. The patients who underwent a mastectomy with an immediate breast reconstruction were referred to a plastic surgeon (study II) and the protocol is discussed in chapter 4.4.2.

Table 3. The data collected for the analysis.

Patient Characteristics	Details of surgery	Aberrations in recovery (30 postoperative days)	Histopathological assessment
Age[2]	Date of surgery[1]	Any Unplanned Return to Care[8]	Cancer subtype[1]
ASA Classification[1]	Planned manner of discharge[1]	Antibiotic prescriptions[9]	ER[1]
Diabetes[3]	Date of discharge[1]	Diagnosis of surgical site infection[8]	PR[1]
Smoking[3]	The actual manner of discharge[5]	Diagnosis of wound dehiscence[8]	HER2[1]
Height[1]	Bilateral procedures[1]	Diagnosis of skin flap necrosis[8]	KI-67 %[1]
Weight[1]	Operating surgeon[1]	Diagnosis of postoperative seroma[8]	Grade[1]
BMI[4]	Surgeon's experience[6]	Any reoperation[8]	Margin to the skin[1]
Previous breast surgeries[1]	Axillary procedure[1]	Any rehospitalization[8]	Margin to the chest wall[1]
Neoadjuvant therapy[3]	Preoperative antibiotics[1]	Date when complications were diagnosed[8]	Side margin[1]
Previous radiation therapy[7]	Duration of surgery[1]	Bacterial culture samples (blood/pus)[1]	Status of sentinel nodes[1]
Date of previous breast surgery[1]	Amount of bleeding[1]	Laboratory test: Leucocyte count[1]	Number of metastatic lymph nodes[1]
	Reported postoperative pain (NPRS)[1]	Laboratory test: CRP[1]	Number of all removed lymph nodes[1]
	Bleeding in recovery room[1]	Death[1]	The largest diameter of the tumour[1]
	Impaired alertness[1]		
	Nausea[1]		
	Surgical instrument(s) used in operation[1]		

ASA = American Society of Anesthesiologist, BMI = Body-Mass Index, NPRS = Numeric Pain-Rating Scale, CRP = C-reactive protein. ER= Estrogen-receptor status, PR = progesterone receptor status, HER2 = human epidermal growth factor receptor 2.

[1] Information retrieved from patient records as such. If not included in the information received from Auria Clinical Informatics Register, verified from patient records.

[2] Calculated based on the patient's birthday and the date of surgery.

[3] Information based on electronic patient record text mining.

[4] Defined as weight (kg) divided by the square of height (m)

[5] Defined based on the date of the operation and the date of actual discharge.

[6] Based on the information on the number of mastectomies the surgeon had performed.

[7] Verified from the patient records in case the patient had a previous breast operation(s).

[8] All patient records for 30 postoperative days were read to define the reason for unplanned contacts or readmissions.

[9] The information of all antibiotic prescriptions for 30 postoperative days was retrieved from the national Prescription Center and double-checked from electronic patient records.

The patients had a preoperative admittance approximately one to three weeks before the operation. Patient feasibility and willingness for SDS were evaluated on the admittance. The criteria for SDS were the following:

- stable general health and comorbidities
- age < 85 years
- the patient willing to be discharged on the operation day
- an available adult companion to collect the patient from the hospital and to accompany them for the first postoperative night
- the operation was scheduled to be finished before 2 p.m.

The surgical technique was decided on the admittance based on the feasibility of breast conserving surgery and patient preference. Mastectomy was planned for patients who were not suitable for BCS or opted for mastectomy. If an axillary metastasis was detected in preoperative ultrasound guided biopsy, an ALND was performed. Otherwise, the patients underwent SNB in triple technique, preoperative lymphoscintigraphy with ^{99m}Tc nanocolloid, perioperative use of blue dye, and a hand-held gamma probe for localization. The frozen section study was performed for all patients until the year 2018, but only for selected patients after that, following the updated treatment guidelines.

Before the year 2016, the patients received prophylactic antibiotics based on the surgeon's evaluation of the patient's individual risk of SSI. In April 2016, antibiotic prophylaxis was introduced for all patients, following several international guidelines recommending for the use. When the prophylactic antibiotic was administrated, a single dose of cefuroxime (1.5 grams intravenously) was given within 60 minutes before the surgical incision. In case of contraindications for cefuroxime, the patients received clindamycin 600 mg intravenously. If neither of these antibiotics was admissible, the proceedings were evaluated individually.

Patients consuming antithrombotic or anticoagulant medications were usually instructed to continue the medication unless there was a specific reason for discontinuation.

An elliptical horizontal incision was planned for the mastectomy. The incision was performed with a scalpel, and the breast was dissected from the skin flaps using a SonoSurg® ultrasound instrument (Olympus Medical Instruments, Tokyo, Japan) with few exceptions. The skin flaps were left approximately 5–10 millimeters thick. The pectoral fascia was removed with the mastectomy specimen. A single drain was applied and secured with a single suture. The wound was closed using intracutaneous sutures.

After the surgery, patients planned for SDS were discharged if they fulfilled the following conditions:

- Stable vital signs
- Normal orientation to space and time
- Ability to be mobilized in a normal manner
- No nausea or vomiting and ability to consume food and water
- Ability to pass urine
- No sign of acute complications
- Presence of an adult companion.

The patients who were admitted for the postoperative night were discharged the following day. The patients not fit to be discharged were usually resettled to primary health care for aftercare.

The removal of the drain was instructed to primary health care. The drain was removed when the amount of secretion was less than 80 milliliters per day, but no sooner than three days after or later than seven days after the operation. In case of postoperative seroma formation after the removal of the drain, the seroma was removed with punctures in primary health care.

A follow-up admittance was instructed two to three weeks after the operation.

4.3 Study I

4.3.1 Patients

The same-day mastectomy was introduced in Turku University Hospital late in 2013 and the study period was defined as years 2014–2019. All patients treated with a mastectomy but without an immediate breast reconstruction were evaluated. The comparison was made between patients who were discharged on the same day of the surgery (SDS group) and the patients hospitalized for one night (OS group).

The data of patients who were planned to be discharged on the day of surgery but were hospitalized were examined. The information used in the analysis was collected as described in chapter 4.1. and the surgical protocol was as described in chapter 4.2.

4.3.2 Statistical analysis

The SDS and OS groups were compared using the chi-square test for the categorical variables and a two-sample *t*-test for normally distributed and a Wilcoxon test for nonnormally distributed continuous variables.

A bivariate analysis was performed with all the Patient Characteristics and Details of surgery with the Aberrations in postoperative recovery presented in Table 3. The variables with p-value less than 0.15 were included in multivariable logistic regression analysis. Variables including less than five patients were combined to reach an adequate number of patients for the analysis. All variables that qualified for multivariable logistic regression analysis were cross evaluated to eliminate correlating variables. In cases a correlation was found in this phase, the clinically more meaningful variable was included in the final analysis. In the multivariable logistic regression analysis, the variable with the highest p-value was removed and the analysis was repeated until only variables with $p<0.05$ were remaining. The analysis was then repeated including the discharge regime factor (SDS vs. OS) to define whether the discharge regime factor would correlate with any single complication or other aberration in recovery.

Using the same method, a subgroup analysis was performed for all individual variables of patient characteristics and Details of surgery including a minimum of ten patients. As a result, the odds ratio (OR) for all variables in Aberrations in postoperative recovery was defined in relation to the discharge manner (SDS vs. OS).

The analysis was performed with JMP Pro 15 -statistical software (SAS Institute, Cary, North Carolina).

4.4 Study II

4.4.1 Patients

The information of all patients undergoing mastectomy and immediate breast reconstruction for ductal carcinoma in situ (D05 in ICD-10 classification) during the study period from January 2010 to December 2019 was evaluated. The data were retrieved from Auria Clinical Informatics Register as described in chapter 4.1. All patient records were studied to verify the correctness of the received data. Only patients undergoing a latissimus dorsi (LD) flap breast reconstruction were included in the study, as it has been almost exclusively used method of immediate reconstruction in case of extensive DCIS in Turku University Hospital. In extensive DCIS, skin-sparing mastectomy has been preferred over nipple-sparing mastectomy since the DCIS lesion is often present close to the nipple-areola complex. Patients with previous ipsilateral breast surgery were excluded.

4.4.2 Surgical protocol and follow-up

The patients underwent a skin-sparing mastectomy and immediate reconstruction performed by a plastic surgeon. All patients had a sentinel-node biopsy with a triple technique described in chapter 4.2. An intraoperative frozen section study was performed for all patients, and the patients with sentinel node metastasis underwent ALND. The skin-sparing mastectomy was performed leaving the skin flaps approximately 5–10 millimeters thick. The pectoral fascia was removed with the mastectomy specimen. If the myocutaneous latissimus dorsi flap could not sufficiently replace the missing volume, an additional breast implant was used. All the patients were admitted to the surgical ward after the operation for surveillance.

The patients were postoperatively discussed in a multidisciplinary meeting to evaluate the need for adjuvant therapy or reoperations. The information on the largest size of the tumour, surgical margins, and the final histopathological assessment were collected for analysis. The patient records were studied for postoperative complications.

The follow-up information was collected from electronic patient records, including clinical controls and imaging controls. The patients not receiving adjuvant therapy were followed in primary health care. The patients who received adjuvant therapy were followed at the Department of Medical Oncology and Radiotherapy for five years and in primary health care thereafter. The follow-up consisted of mammography of the contralateral breast and a clinical examination. The follow-up was arranged every year in patients followed in the Department of Medical Oncology and Radiotherapy and/or in patients who were aged 50 years or younger. The patients who had follow-up in primary health care and were aged over 50 years had the follow-up every other year.

The date of the latest control was recorded to define the duration of follow-up.

4.4.3 Statistical analysis

The statistics were collected in frequency tables. Patients with and without upgrading to invasive cancer in the final histopathological assessment were compared by using Fisher's exact test for frequency tables. Continuous variables were compared using Mann-Whitney U-test. The binomial exact value calculation was used to define the confidence interval for the risk of recurrence. A one-sided 97.5 % confidence interval was used to define the upper limit of the confidence interval.

The analysis was performed with JMP Pro 15 -statistical software (SAS Institute, Cary, North Carolina).

4.5 Study III

4.5.1 Patients

Surgical antibiotic prophylaxis (SAP) was introduced in Turku University Hospital for all patients undergoing mastectomy in April 2016. Before that, the decision on whether SAP was described was based on surgeons' evaluation of the patient's individual risk of having an SSI. The study period was defined as June 1st, 2012, to December 31st, 2019. The decision of the starting point was based on the perception, that many patients lacked the information of the SAP before the starting point, as it was handwritten on a paper form and scanned into the electronic patient records only after the surgery. Later during the study period, the information was documented directly to the electronic patient records and the information was available for all patients.

The data used in the analysis was collected as described in chapter 4.1. In addition, patient records of all patients who had been prescribed any antibiotics during the postoperative 30 days period, were revised to ensure whether the patients had suffered an SSI. In case of uncertainties, the re-evaluation was made on basis of the following CDC (Centers for Disease Control and Prevention) and NHSN (National Healthcare Safety Network) Criteria (Horan et al. 2008; Mangram et al. 1999).

- purulent drainage from the incision or puncture
- organisms isolated from an aseptically obtained culture of fluid or tissue
- deliberate opening of the incision by a surgeon in patients having clinical manifestations of infection, either tenderness, localized swelling, redness, or warmth: or
- diagnosis of SSI by the surgeon or attending physician.

4.5.2 Statistical analysis

First, the overall rate of SSIs before and after the introduction of regular SAP was introduced (comparison I). Then the comparison was repeated for patients receiving and not receiving SAP before the introduction of the regular SAP (comparison II). Third, a one-to-one matched case-comparison group was formed from the patients receiving SAP to match the demographics of the patients not receiving SAP (comparison III). The matched group was formed using a Visual Basic (Microsoft Corporation, Redmond, United States) platform, which was programmed to sift different compositions of patients receiving SAP until the iteration reached the composition best matching the group of patients not receiving SAP.

The statistical comparison was performed with the chi-squared test for categorical variables and Student's *t*-test for continuous variables following normal distribution and the Mann-Whitney U-test for variables not normally distributed. A two-tailed test with a significance level of 5 % was considered significant. A subgroup analysis with logistic regression analysis was performed to define OR for SAP vs no-SAP in patients often considered to have an increased risk of SSI.

The variables with p-value <0.20 in univariable analysis were included in the logistic regression analysis. In logistic regression analysis, the variable with the highest p-value was removed and the analysis was repeated, until only variables with p<0.05 were remaining. Each analysis was finally repeated with the SAP vs. no-SAP factor included in the analysis to define the OR for SAP in preventing the SSI.

4.6 Study IV

4.6.1 Patients

The data from Turku University Hospital was collected as described in chapter 4.1. To evaluate the effect of ultrasound instrument on bleeding complications, the results were compared to the results of Helsinki University Hospital, where electrocautery was used as an instrument in mastectomy. The few patients operated in Turku University Hospital with any other instrument than ultrasonic instrument were excluded. The ultrasonic instrument was used both in mastectomy and axillary surgery. In Helsinki University Hospital, electrocautery was used in mastectomy dissection, and bipolar forceps were used for hemostasis, and when ALND was performed, a bipolar instrument, most often LigaSure®, (Medtronic, Dublin, Ireland) was used.

As the Helsinki University Hospital data was available from January 1st, 2012, to June 30th, 2018, this was determined as the study period. As the Helsinki University Hospital data included only patients receiving adjuvant chemotherapy, the corresponding exclusion was made to Turku University Hospital data. In a preliminary evaluation, it was detected that the number of patients consuming anticoagulant or antithrombotic medications was rather small, mostly because the patients consuming such medications had an inverse probability to be given adjuvant chemotherapy. Furthermore, the practice around these medications differed in the two hospitals, making the direct comparison unreliable. Thus, these patients were excluded from the study.

A propensity score matching was executed to retrieve the maximum similarity between the patient groups in each hospital. The one-to-one matching without

replacement by the nearest-neighbor principle with a caliber size of 0.2 was used. The groups received were compared to each other in relation to all baseline characteristics to ensure no need for double adjustment. The following variables were used in propensity score matching:

- Age
- ASA Classification
- Body-Mass Index
- Diagnosis of diabetes
- Smoking
- Extent of axillary surgery

There were also some minor other differences in local protocols, as same-day mastectomy was not utilized in Helsinki University Hospital during the study period, and the antibiotic prophylaxis was used according to the surgeon's preference throughout the study period. Referring to the results in Study I and III, these differences were not considered significant, as neither of these factors had proven to affect the rate of postoperative complications in Turku University Hospital.

The differences in the perioperative protocol in each hospital are illustrated in **Figure 1**.

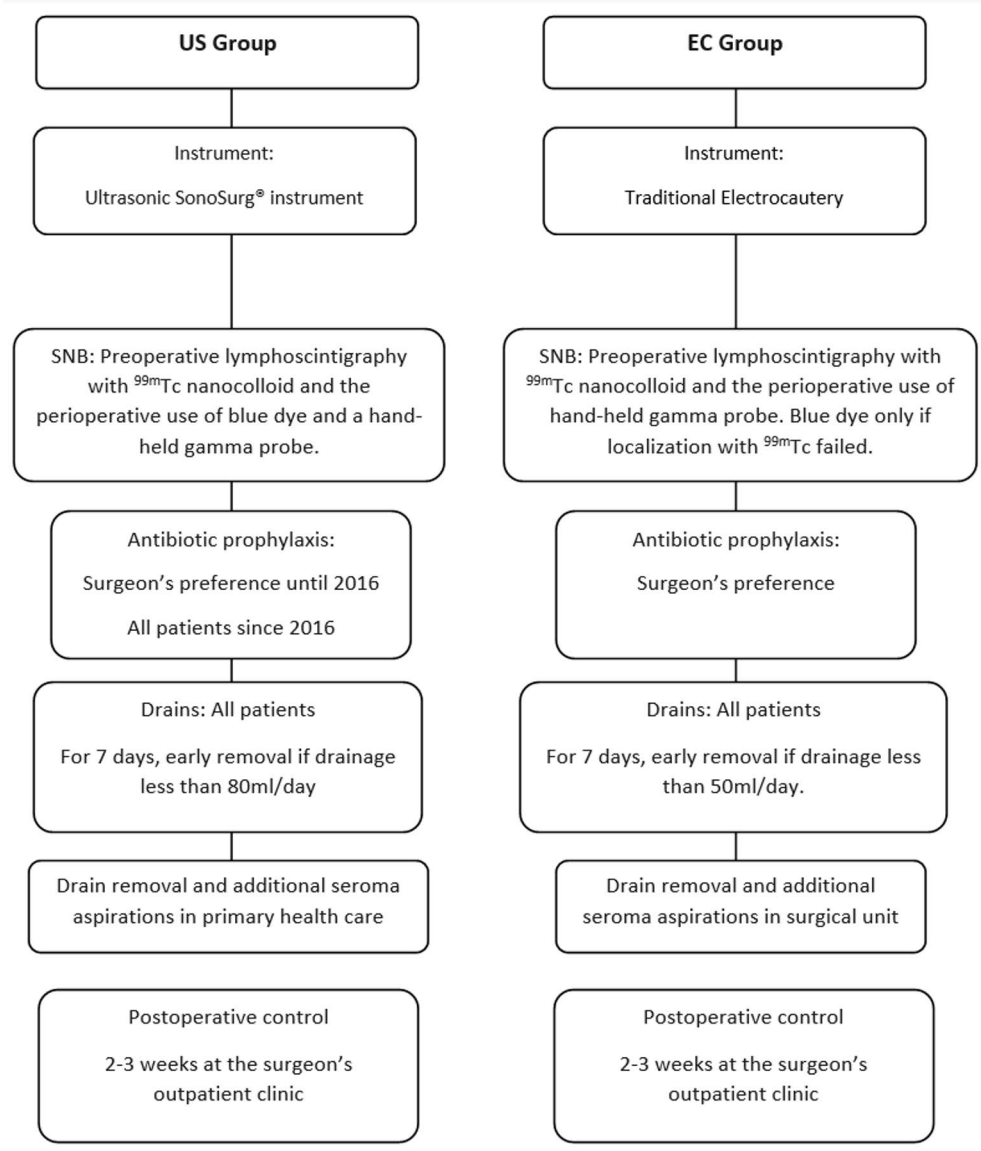

Figure 1. The perioperative protocol followed in mastectomy. US = ultrasound instrument, EC = electrocautery. SNB = sentinel node biopsy. Modified from the original publication.

4.6.2 Statistical analysis

The sample size needed for the analysis was estimated by assuming the rate of bleeding complications in patients operated with ultrasound instrument to be 3 % and in patients operated with electrocautery to be 9 %, respectively. To prove the difference with a 0.05 probability for type I error and power of 90 %, the required sample size was 654 patients.

A bivariate analysis was performed for all Patient Characteristics and Details of Surgery in relation to complication rates. The variables with a relationship of $p<0.15$ were included in multivariable logistic regression analysis, in which the variable with the highest p-value was removed until only the variables with $p<0.05$ were remaining. The OR for the used instrument in relation to each complication was defined.

All data were analyzed using JMP 15 Pro (SAS Institute Cary, North Carolina, USA) software except the propensity score matching, which was performed using R statistical software (version 4.2.0, R core Team, Vienna, Austria).

4.6.3 Cost analysis

As electrocautery is an inexpensive instrument, and the ultrasound instrument is rather expensive, a cost analysis was made to evaluate the usefulness of the instrument. The number of unplanned returns to care, reoperations and rehospitalizations was recorded. The cost of the primary hospitalization was counted, and the total cost of the surgical instruments was summed. The total cost of care was divided by the number of treated patients to define the total cost of the treatment per the instrument used in the surgery.

5 Results

5.1 Study I

In total, 913 patients were included in Study I. In total 259 patients were discharged on the day of the operation (SDS Group) and 654 patients stayed in the hospital overnight (OS Group). The patients in the SDS Group were detected to be younger, healthier, and having less often extensive axillary surgery (**Table 4**). It was also noted that the proportion of patients treated in SDS slightly increased during the study period.

Before the surgery, 318 patients were planned to be operated in the SDS regime. Thus, 59 patients (19 %) planned to be discharged on the day of the operation had to be hospitalized. The reason for hospitalization was most often not having required adult caretaker for the first post-operative night, or other social reasons (32 patients, 54 % of those admitted to the hospital). The second largest group of unplanned admittance was patients whose surgery was delayed and finished at 2 p.m. or later. The day surgery unit of the hospital was not planned for late discharge, and 24 patients (41 %) had to be admitted for scheduling reasons. Three patients had to be admitted since they reported excessive pain (higher than 4 on the Numeric Pain Rating Score). None of the patients had to be admitted due to nausea, bleeding, or impaired alertness.

The patients who had unplanned admission on the day of the surgery were included in the OS Group. The Patient characteristics and Details of surgery of these patients were compared with the remaining patients in the SDS group. The only difference detected was a higher proportion of extensive axillary surgery, as 37 patients (63 %) underwent SNB with ALND, being correlated with longer operation time than scheduled and therefore having a higher risk of finishing the operation later than feasible for same-day discharge.

Table 4. Patient Characteristics. Data expressed as n (%) unless otherwise specified.

	Same-day surgery	Overnight stay	p-value
Number of patients	259 (28 %)	654 (72 %)	
Age, years (mean, IQR)	61 (49–67)	68 (58–77.25)	p<0.001
BMI, kg/m^2 (mean, IQR)	25.5 (22.7–29)	26.3 (23.1–29.7)	p=0.11
ASA Class			
ASA I	58 (22 %)	78 (12 %)	p<0.001
ASA II	162 (63 %)	305 (47 %)	
ASA III	39 (15 %)	257 (39 %)	
ASA IV	0 (0 %)	14 (2.1 %)	
Diabetes	11 (4.2 %)	70 (11 %)	p=0.003
Smoking status			p=0.24
Smoker	46 (18 %)	90 (14 %)	
Non-smoker	206 (79 %)	527 (80 %)	
Not known	7 (3 %)	37 (6 %)	
History of ipsilateral BCS and Radiation Therapy	16 (6.2 %)	33 (5.0 %)	p=0.49
Neoadjuvant therapy	30 (12 %)	66 (10 %)	p=0.51
Year of operation			p<0.001
2014	28 (19 %)	121 (81 %)	
2015	29 (22 %)	105 (78 %)	
2016	49 (31 %)	110 (69 %)	
2017	35 (25 %)	105 (75 %)	
2018	50 (32 %)	107 (68 %)	
2019	68 (39 %)	106 (61 %)	
Axillary procedure			p<0.001
None	2 (0.7 %)	13 (2.0 %)	
Operated previously	52 (20 %)	54 (8.3 %)	
SNB only	79 (31 %)	226 (35 %)	
ALND	126 (49 %)	361 (55 %)	
Bilateral breast cancer and bilateral surgery	4 (1.5 %)	35 (5.4 %)	p=0.01
Symmetry procedure on the contralateral side	10 (3.9 %)	53 (8.1 %)	p=0.02
Mastectomy as a reoperation after BCS	45 (17 %)	47 (7.2 %)	p>0.001

BMI = Body Mass Index, ASA = American Society of Anaesthesiologists, IQR = interquartile range. BCS = breast conserving surgery, SNB = sentinel lymph node biopsy, ANLD = axillary lymph node dissection. Modified from the original publication.

The rate of Aberrations in postoperative recovery in SDS and OS Groups is presented in **Table 5**. None of the investigated Aberrations in postoperative recovery was detected to be more common in the SDS Group. The OR for any unplanned return to care was 0.79 (95 % 0.53–1.18, p=0.26) for SDS vs OS Group. There were fewer "other surgery-related issues" in the SDS Group, including drainage issues, minor wound problems requiring no intervention, or seroma punctations (OR 0.39, 95 % CI 0.17–0.87, p= 0.021).

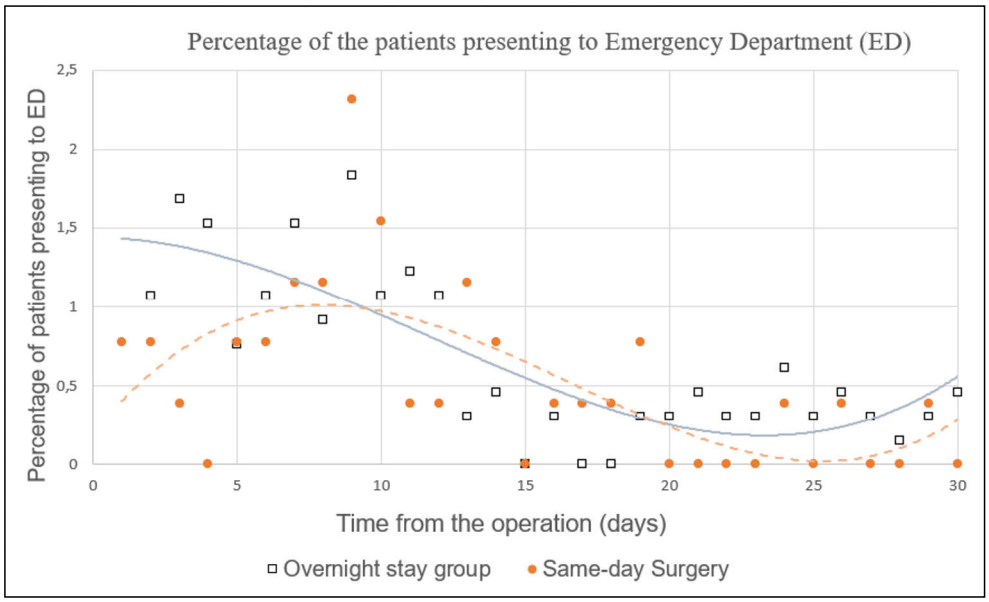

Figure 2. The percentage of patients presenting to the Emergency Department in respect to the time from the surgery. The trend line is a fitted polynomic function of 3rd degree. Modified from the original publication.

The rate of non-surgery-related major complications was low (~1 %) in each group.

The patients who had unplanned admission on the day of the surgery were evaluated separately. The numbers were similar to the SDS and OS Groups, as these 59 patients had 11 unplanned returns to care (19 %), one reoperation (1.7 %), three hospitalizations (5.1 %), and three SSIs (5.1 %). Due to the low number of cases, detailed statistical analysis was not performed on this patient group separately.

Table 5. Summary of complications in the 30 postoperative days. When reasonable, the categories with less than five events were combined to reach an adequate quantity for statistical evaluation.

Complication	SDS Group	OS Group	Odds Ratio (SDS vs OS)	95 % CI	p–value
Any RTC	40 (15 %)	131 (20 %)	0.79	0.53-1.18	p=0.26
Rehospitalization	12 (4.6 %)	32 (4.9 %)	1.09	0.54–2.20	p=0.81
Re–operation for complications	3 (1.6 %)	11 (1.7 %)	1.12	0.27–4.67	p=0.87
Surgical site infection	13 (5.0 %)	37 (5.7 %)	0.86	0.45–1.67	p=0.66
Unplanned return to ED	39 (15 %)	125 (19 %)	0.66	0.43–1.00	p=0.05
- for infection	12 (4.6 %)	33 (5.0 %)	0.88	0.71–1.72	p=0.71
- for seroma puncture	17 (6.6 %)	41 (6.3 %)	0.83	0.44–1.58	p=0.57
- for any other surgery related issue^	7 (2.7 %)	44 (6.8 %)	0.39	0.17–0.87	p=0.021*
Admission regarding another specialty	3 (1.1 %)^^	7 (1.1 %)^^^	1.08	0.28-4.22	p=0.91

RTC = unplanned return to care, ED = emergency department, SDS = same-day surgery, OS = overnight stay, CI = confidence interval. Modified from the original publication.

* Statistical significance p<0.05

^ wound dehiscence or other problems with wound healing, drainage issues, surgical site pain

^^ including nonspecific interstitial pneumonia, pneumonia, infection of unknown origin after the initiation of adjuvant chemotherapy

^^^ including transient ischemic attack (2), pyelonephritis, diabetic hyperglycaemia, atrial fibrillation, wrist fracture, bradycardia after too high betablocker dosage

Only two of the 259 patients (0.8 %) operated in the SDS regime had an unplanned return to care before the morning following the operation. The number of patients having unplanned returns to care on each postoperative day is presented in Figure 2.

The results of subgroup analysis for any unplanned return to care are presented in **Table 6**: In statistical analysis, the patients undergoing SNB had a slightly lower risk for unplanned return to care (OR 0.40, 95 % CI 0.16–0.99, p=0.049). In all other patient subgroups, the difference was non-significant.

None of the patients died during the 30 postoperative days follow-up period.

Table 6. Odds ratio (OR) for any return to care (Same-day surgery vs Overnight surgery) in all patient subgroups reviewed.

Patient group (number of patients)	The OR for any RTC (SDS vs. OS)	95 % Confidence interval	p-value
Age of 75–84 years (195)	0.20	0.03–1.52	p=0.12
BMI 30–35 (136)	0.57	0.21–1.53	p=0.27
BMI 35–40 (48)	0.40	0.07–2.36	p=0.31
ASA I (136)	0.48	0.18–1.34	p=0.16
ASA II (467)	0.93	0.56–1.55	p=0.78
ASA III (296)	0.47	0.15–1.43	p=0.18
Mastectomy as a re-operation after BCS with positive margins (92)	1.05	0.25–4.47	p=0.95
History of ipsilateral BCS and Radiation Therapy (49)	2.04	0.43–11.90	p=0.43
Surgeon´s experience			
Fewer than 20 mastectomies (64)	0.20	0.02–1.72	p=0.14
21–50 (116)	0.21	0.07–1.77	p=0.21
51–100 (124)	1.11	0.43–2.86	p=0.83
Over 100 (605)	0.86	0.53–1.40	p=0.55
Axillary procedure			
SNB (305)	0.40	0.16–0.99	p=0.049*
ALND (487)	0.85	0.52–1.40	p=0.53
Bilateral Procedure (102)	1.43	0.26–7.96	p=0.68
Diabetes (81)	0.89	0.17–4.58	p=0.89
Smoker (current or former) (289)	0.89	0.49–1.60	p=0.69
Neoadjuvant therapy (96)	0.96	0.33–2.79	p=0.94

BMI = body-mass index, ASA = American Society of Anaesthesiologists, BCS = breast conserving surgery, SNB = sentinel node biopsy, ALND = axillary lymph node dissection, SDS = same-day surgery, OS = overnight stay surgery, RTC = unplanned return to care
*Statistical significance p<0.05. Modified from the original publication.

5.2 Study II

The Auria Clinical Informatics Register data included 132 patients matching the inquiry criteria. After the verification of the data from patient records, 60 patients were detected not to fulfill the inclusion criteria, preoperative diagnosis of DCIS with no invasive cancer, immediate breast reconstruction with LD flap, and no previous ipsilateral breast surgery (**Figure 3**).

The 71 patients included in the study were evaluated. It was detected that majority of the patients had presented with screen-detected asymptomatic DCIS (45 patients, 63 %) and only 26 patients (37 %) had symptomatic DCIS (**Table 7**).

Table 7. Patient characteristics and clinical findings related to the DCIS. All numbers are given as (n, %) unless otherwise specified.

Total number of patients	**71**
Age (years)	57 (51–63)*
BMI (kg/m^2)	24.4 (22.0–29.0)*
DCIS size in imaging (mm)	60 (45–80)*
Preoperative MRI performed	50 (70 %)
Manner of presentation	
Asymptomatic	45 (63 %)
Symptomatic	26 (37 %)
Palpable mass	10 (14 %)
Nipple discharge	10 (14 %)
Mammary Paget's disease	3 (4 %)
Nipple retraction	2 (3 %)
Mastitis	1 (1 %)

BMI = body-mass index, DCIS = ductal carcinoma in situ, MRI = magnetic resonance imaging
*median and interquartile range. Reproduced with permission from original publisher

In total, 65 of the 71 patients (92 %) had a DCIS diameter of 40 mm or more. The three smallest DCIS lesions were 28 mm, 33 mm, and 35 mm in size, each in a small-sized breast and mastectomy specimen weighting less than 200 grams.

Despite all the patients being diagnosed with DCIS and no invasive cancer before the surgery, 29 patients (41 %) presented invasive disease in the final histopathological assessment. Several patient characteristics, imaging, and core needle biopsy findings were evaluated, and it was detected that none of the investigated factors could predict the upgrading to invasive disease (**Table 8**).

In total, ten patients underwent ALND. One patient had a metastasis in two sentinel lymph nodes, three patients had a macro metastasis (>2 mm) in a single lymph node, three patients had a micro metastasis (0.2 – 2 mm) in a single lymph

node, and two patients presented with isolated tumour cells (ITC). One of the patients had an unsuccessful SNB and underwent ALND. Three of the patients undergoing ALND had a single additional metastatic lymph node, and the remaining seven patients had no additional metastatic lymph nodes in the histopathological assessment.

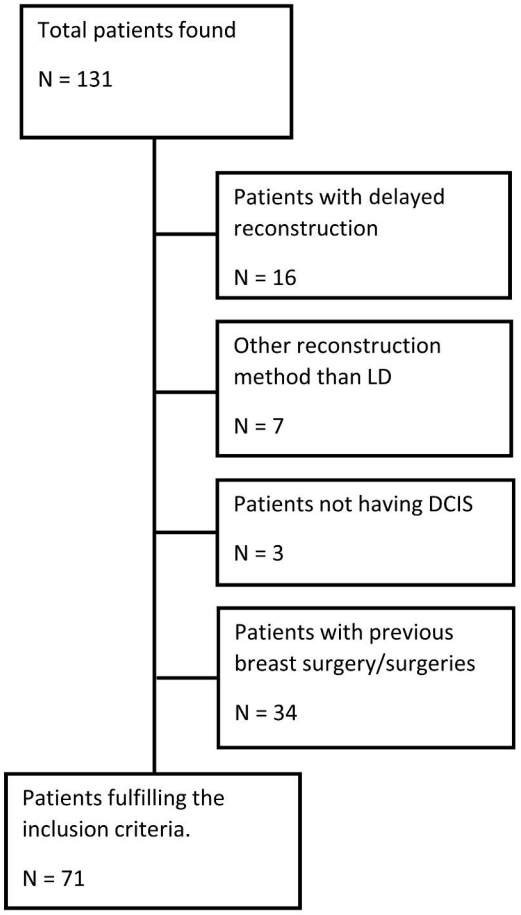

Figure 3. Flow chart illustrating the study population selection. Reproduced with permission from original publisher.

The invasive breast cancer foci in the mastectomy specimen were usually small, as the median size was 6.5 mm, and the range was 1 to 26 mm. Due to the extensive size of the DCIS lesion compared to the breast size, the histopathological resection.

Table 8. Factors associated with invasion vs. no invasion found in the histopathological assessment. All numbers are given as (n, %) unless otherwise specified.

	Invasion (29)	No invasion (42)	p–value
Age (years)	54.3 (48.0-62.5)*	58.4(53.8-64.0)*	0.15
Mastectomy specimen weight (g)	399 (272–553)*	337 (276–564)*	0.50
Preoperative MRI			0.33
No MRI	11 (52 %)	10 (48 %)	
MRI	18 (36 %)	32 (64 %)	
DCIS diameter (mm) in preoperative imaging	75 (45–90)*	56 (45–80)*	0.18
Grade			0.34
I	2 (22 %)	7 (77 %)	
II	9 (53 %)	8 (47 %)	
III	16 (41 %)	23 (59 %)	
Manner of presentation			0.89
Asymptomatic	17 (32 %)	28 (62 %)	
Lump	5 (50 %)	5 (50 %)	
Nipple discharge	4 (40 %)	6 (60 %)	
Mammary Paget's disease	2 (67 %)	1 (33 %)	
Nipple retraction	1 (50 %)	1 (50 %)	
Mastitis	0 (0 %)	1 (100 %)	
Body Mass Index (kg/m^2)			0.24
Normal (18.5 – 25)	13 (34 %)	25 (66 %)	
Overweight (25–30)	6 (40 %)	9 (60 %)	
Obese (over 30)	9 (60 %)	6 (40 %)	

MRI = magnetic resonance imaging, DCIS = ductal carcinoma in situ. *Median and interquartile range. Modified from the original publication.

margins (RM) were narrow. The median resection margin was 2.0 mm. Nine patients (13 %) had ink-positive resection margin and 20 patients (28 %) had an resection margin less than 0.5 mm (**Table 9**). The ink-negative margins (>0.1 mm) were considered sufficient by the multidisciplinary meeting. The treatment of the patients with positive resection margin is presented in **Table 10**. Six of the patients underwent a reoperation. Four patients had no residual DCIS in re-excised tissue. Two patients had DCIS which was this time removed with negative margins. One of the patients (patient number 5 in **Table 10**) underwent a postoperative MRI presenting enhancement suggesting wide residual DCIS towards the axilla. The multidisciplinary meeting recommended radiation therapy. The MRI was repeated after the treatment. The enhancement seen in the MRI before the radiation therapy was absent, but the patient underwent a reoperation to ensure the absence of DCIS. The histopathological assessment of the re-excised tissue presented no malignant cells but only fibrosis. The patient has been under close surveillance for 58 months and has not presented recurrence during that time.

The complications during the postoperative period were recorded. Two patients required reoperation for partial skin flap necrosis and four patients had minor necrosis requiring only a topical treatment.

The mean follow-up time of the patients was 71 months, and the median follow-up time was 68 months (IQR 46–94 months). None of the patients suffered a local or distant recurrence during the follow-up (0 %, 95 % CI 0–0.051 %).

One patient, presenting primarily with invasive ductal carcinoma, developed a contralateral lobular carcinoma four years after the reconstruction surgery.

One patient died of mesothelioma 86 months after the reconstruction surgery.

Table 9. Distribution of smallest histopathological margins. Numbers are given as (n, %).

Smallest Histological Margin (mm)	N
0	9 (13 %)
0.1–0.5 mm	11 (15 %)
0.6–1.0 mm	6 (8.5 %)
1.1–2.0 mm	16 (23 %)
2.1–5 mm	12 (17 %)
5.1 mm – >	17 (24 %)

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Table 10. Information of the patients presenting zero-margin in the histopathological assessment.

Patient	1	2	3	4	5*	6	7	8	9
DCIS width (mm)	120	21	50	86	80	26	150	59	87
Direction of 0-margin	Lateral	Skin	Skin	Lateral	Lateral	Medial	Skin	Skin	Skin
Re-operation	Yes	Yes	Yes	Yes	Late	No	Yes	Yes	No
Invasive disease	ductal	lobular	ductal	ductal	No	No	No	No	No
Adjuvant treatment	yes**	yes***	no	yes****	yes*****	No	No	No	No
Multifocal invasion	yes	no	no	yes					
SLNB	macro	0	0	macro	0	0	0	0	0
Axillary status	2/21	0/3	0/1	3/17	0/4	0/3	0/4	0/4	0/4
Follow-up (months)	37	56	112	60	58	50	78	59	29

*Patient underwent an MRI and received radiation therapy before reoperation. Reoperation confirmed only fibrosis. **RT, CT, HT ***CT, HT **** RT, CT, HT, trastuzumab *****RT,
DCIS = ductal carcinoma in situ, SLNB = sentinel lymph node biopsy, RT= radiation therapy, CT =chemotherapy, HT = hormonal therapy. Modified from the original publication.

5.3 Study III

In total, 1423 patients underwent a mastectomy during the study period of June 1st, 2012 – December 31st, 2019. Ten of the patients were missing the information of

SAP and were excluded from the study, leaving 1413 patients eligible for the study. In total 706 patients were operated before the introduction of regular SAP in April 2016 and 707 patients after that. Of the 706 patients who were operated before April 2016, 330 patients (47 %) received the SAP, and 376 patients (53 %) did not. After the introduction of the regular SAP, five patients were operated without SAP. In a case-comparison study two highly similar patient groups of 330 patients, each were acquired (**Table 11**).

Cefuroxime was the most used antibiotic (927 patients, 86 %). Clindamycin was used in 134 patients (12 %). Three patients were prescribed penicillin, two patients levofloxacin, and one patient cefalexin. Eleven patients were given SAP, but the selection of antibiotics was not recorded. The rate of SSI was similar in patients receiving cefuroxime and clindamycin, respectively (6.7 %, 62/927 vs. 7.5 %, 10/134, p=0.74).

The patients receiving SAP were younger and healthier on average than patients not receiving SAP. Obese patients had a higher probability to be prescribed SAP, as were the patients undergoing a reoperation or a bilateral surgery.

The demographics and details of surgery were compared between patients with and without postoperative SSI. It was detected that obese patients, patients with a history of ipsilateral RT, and patients undergoing a longer operation had an increased risk of SSI (**Table 12**). In a detailed analysis, the latest association was noted to result from more patients having an SSI in the ALND group, although the ALND itself was not shown to be a risk factor for SSI. Different axillary procedures were investigated in relation to operating time and it was shown that the patients with or without SSI had no difference in operating time when the analysis was made within the specific axillary procedure.

Table 11. Demographics of the patients operated before and after the introduction of the regular SAP and for all patients receiving SAP and not receiving SAP, respectively. All numbers are given as n (%) unless otherwise specified.

	Prior April 2016	Post April 2016	p-value	No-SAP	SAP	p-value
Patients	706	707		335	1078	
Age, years (median, IQR)	67 (55–78)	70 (58–80)	0.03*	66 (52–77)	69 (58–80)	0.002*
BMI, kg/m^2 (median, IQR)	26.1 (22.9–29.8)	25.7 (22.5–29.4)	0.34	25.4 (22.7–28.6)	26.0 (22.8–30.0)	0.02*
Under 25	283 (40.8 %)	323 (45.7 %)	0.16	153 (46.6 %)	453 (42.3 %)	0.01*
25–30	241 (34.8 %)	225 (31.8 %)		119 (36.3 %)	347 (32.4 %)	
30–35	121 (17.5 %)	103 (14.6 %)		42 (12.8 %)	182 (17.0 %)	
Over 35	48 (6.9 %)	56 (7.9 %)		14 (4.3 %)	90 (8.4 %)	
ASA I	105 (14.9 %)	83 (11.7 %)	0.14	58 (17.3 %)	130 (12.1 %)	0.003*
ASA II	283 (40.1 %)	320 (45.3 %)		155 (46.3 %)	448 (41.6 %)	
ASA III	285 (40.3 %)	277 (39.2 %)		114 (34.0 %)	448 (41.6 %)	
ASA IV	33 (4.7 %)	27 (3.8 %)		8 (2.4 %)	52 (4.8 %)	
History of ipsilateral breast cancer and RT	29 (4.1 %)	42 (5.9 %)	0.11	7 (2.1 %)	64 (5.9 %)	0.004*
reoperation for BCS	65 (9.2 %)	55 (7.8 %)	0.34	11 (3.3 %)	109 (10 %)	<0.001*
Axillary operation			0.007*			<0.001*
None	92 (13.1 %)	92 (13 %)		22 (6.6 %)	162 (15 %)	
SNB	204 (28.9 %)	258 (36.5 %)		114 (34.0 %)	348 (32.3 %)	
ALND	410 (58.1 %)	357 (50.5 %)		199 (59.4 %)	568 (52.7 %)	
Bilateral mastectomy	31 (4.4 %)	39 (5.5 %)	0.33	3 (0.9 %)	67 (6.2 %)	<0.001*
Operation time (min)	99 (±28)	102 (±29)	0.05	101 (±28)	101 (±29)	0.99
Operation time over 2 hours	142 (20 %)	182 (26 %)	0.01*	71 (21.4 %)	253 (23.6 %)	0.39
Diabetes	81 (11.4 %)	72 (10.2 %)	0.44	30 (9.0 %)	123 (11.4 %)	0.21
Smoking			0.22			0.57
Current	110 (17.2 %)	92 (13.7 %)		52 (17.0 %)	150 (14.9 %)	
Former	102 (16.0 %)	108 (16.1 %)		51 (16.7 %)	159 (15.8 %)	
Never	428 (66.9 %)	470 (70.1 %)		202 (66.2 %)	696 (69.3 %)	
NACT	73 (10.3 %)	58 (8.2 %)	0.17	23 (6.9 %)	108 (10.0 %)	0.08

IQR = interquartile range, BMI = body-mass index, ASA = American Society of Anesthesiologists, SNB = sentinel node biopsy, ALND = axillary lymph node dissection, BC = Breast Cancer, NACT = Neoadjuvant chemotherapy, RT = radiation therapy, BCS = breast conserving surgery, SSI = surgical site infection, SAP = surgical antibiotic prophylaxis. Modified from the original publication.

Table 12. Patients categorized according to the SAP vs. no-SAP before April 2016 and matched control -patients in the SAP group (p-value in comparison to no-SAP group). All numbers are given as n (%) unless otherwise specified.

	No SAP	SAP	p-value	Matched SAP	p-value
Patients	330	376		330	
Age, years (median, IQR)	66 (52–77)	67 (57–80)	0.01	68 (56–78)	0.07
BMI, kg/m^2 (median, IQR)	25.4 (22.7–28.5)	26.6 (23.4–31.2)	<0.001	25.4 (22.3–28.9)	0.91
Under 25	151 (46.7 %)	132 (36 %)	<0.001	157 (48.2 %)	0.99
25–30	118 (36.5 %)	123 (33 %)		115 (35.3 %)	
30–35	40 (12.4 %)	81 (22 %)		40 (12.3 %)	
Over 35	14 (4.3 %)	34 (9.2 %)		14 (4.3 %)	
ASA I	58 (17.6 %)	47 (12.5 %)	<0.001	58 (17.6 %)	0.99
ASA II	153 (46.4 %)	130 (34.6 %)		153 (46.4 %)	
ASA III	111 (33.6 %)	174 (46.3 %)		110 (33.3 %)	
ASA IV	8 (2.4 %)	25 (6.6 %)		9 (2.7 %)	
History of ipsilateral breast cancer and RT	7 (2.1 %)	22 (5.9 %)	0.01	7 (2.1 %)	1.00
Reoperation for BCS	11 (3.3 %)	54 (14 %)	<0.001	11 (3.3 %)	1.00
Surgeon experienced (50+)	232 (70.3 %)	304 (80.9 %)	0.001	232 (70.3 %)	1.00
Surgeon unexperienced (50-)	98 (29.7 %)	72 (19.1 %)		98 (29.7 %)	
Axillary operation			<0.001		1.00
None	22 (6.7 %)	70 (19.7 %)		22 (6.7 %)	
SNB	112 (34.0 %)	92 (24 %)		112 (34.0 %)	
ALND	196 (59.4 %)	214 (56.9 %)		196 (59.4 %)	
Bilateral mastectomy	3 (0.9 %)	28 (7.4 %)	<0.001	3 (0.9 %)	1.00
Operation time (min)	101 (±28)	98 (±28)	0.19	101 (±26)	
Operation time over 2 hours	70 (21 %)	72 (19 %)	0.48	70 (21 %)	0.98
Diabetes	28 (8.5 %)	53 (14 %)	0.02	28 (8.5 %)	1.00
Smoking			0.79		
Current	52 (17.3 %)	58 (17 %)		52 (16.7 %)	0.95
Former	51 (16.9 %)	51 (15 %)		51 (16.4 %)	
Never	198 (65.8 %)	230 (68 %)		209 (67.0 %)	
NACT	22 (6.7 %)	51 (14 %)	0.002	22 (6.7 %)	1.00

BMI = body-mass index, IQR = interquartile range, ASA = American Society of Anesthesiologists, SNB = sentinel node biopsy, ALND = axillary lymph node dissection, breast cancer = Breast Cancer, NACT = Neoadjuvant chemotherapy, RT = radiation therapy, BCS = breast conserving surgery, SSI = surgical site infection, SAP = surgical antibiotic prophylaxis. Modified from the original publication.

The rate of SSIs, unplanned returns to care, and rehospitalization was compared between all the patient groups, and the results are shown in **Table 13**. It is seen that the numbers are similar in all patient groups. The demographics of the patients suffering and not suffering SSI are compared in **Table 14**.

To define subgroups of patients, who could benefit from the SAP, a subgroup analysis was performed. It was shown, that although the risk of SSI was elevated in some patient groups, such as obese patients, the SAP was not shown to decrease the risk of SSI in any of the subgroups (**Table 15**).

Table 13. All unplanned returns to care, surgical site infections, and rehospitalizations are listed in relation to SAP. The p-value given for Matched SAP -group is defined in comparison to No SAP-group. Days to infection is given as days from the surgery to the diagnosis of SSI. All numbers are given as (n, %) unless otherwise specified.

	Entire study period		**Before April 2016**		**Entire study period**		
	Before April 2016	After April 2016	No SAP	SAP	Matched SAP	No SAP	SAP
Patients	706	707	330	376	330	335	1078
Any RTC	111 (15.7 %)	123 (17.4 %)	51 (15.5 %)	60 (16.0 %)	53 (16.1 %)	52 (15.5 %)	182 (16.9 %
	p=0.40		p=0.85		p=0.83	p=0.83	
SSI	49 (6.9 %)	46 (6.5 %)	21 (6.4 %)	28 (7.5 %)	22 (6.7 %)	21 (6.3 %)	74 (6.9 %)
	p=0.74		p=0.57		p=0.87	p=0.87	
Rehospitalization	21 (3.0 %)	28 (4.0 %)	10 (3.0 %)	11 (2.9 %)	10 (3.0 %)	10 (3.0 %)	39 (3.6 %)
	p=0.31		p=0.93		p=1.00	p=1.00	
Days to infection (Mean, SD)	10.8 (± 7.9)	14.4 (±8.8)	9.0 (±7.7)	12.7 (±8.1)	12.8 (±7.8)	9.0 (±7.7)	13.7 (± 8.5)
	p=0.13		p=0.22		p=0.19	p=0.19	

RTC = return to care, SSI = surgical site infection, SD = standard deviation, SAP = surgical antibiotic prophylaxis. Modified from the original publication.

When the entire study cohort was studied in multivariable logistic regression analysis for the efficacy of SAP in the prevention of SSI, the OR for SAP vs. no-SAP was 1.04 (95 % CI, 0.62–1.73, p=0.88). In that analysis, the risk factors for SSI were found to be high BMI (p=0.106), previous BCS and radiation therapy (p=0.018), and extensive axillary surgery (p=0.023).

Table 14. Patients having SSI and not having SSI, respectively. All numbers are given as n (%) unless otherwise specified.

	SSI	No SSI	p-value
Patients	95	1318	
Age (median, IQR)	66 (54–76)	68 (57–80)	0.11
BMI (median, IQR)	27.5 (22.8–36.7)	25.8 (22.7–33.5)	0.007*
under 25 kg/m^2	33 (34.7 %)	573 (43.9 %)	0.009*
25–30 kg/m^2	30 (31.6 %)	436 (33.4 %)	
30–35 kg/m^2	17 (17.9 %)	207 (15.9 %)	
over 35 kg/m^2	15 (15.8 %)	89 (6.8 %)	
ASA I	11 (11.6 %)	177 (13.4 %)	0.96
ASA II	41 (43.2 %)	562 (42.6 %)	
ASA III	39 (41.1 %)	523 (39.7 %)	
ASA IV	4 (4.2 %)	56 (4.2 %)	
Surgeon experienced (50+)	78 (82.1 %)	1019 (77.3 %)	0.28
Surgeon unexperienced (50-)	17 (17.9 %)	299 (22.7 %)	
Reoperation for BCS	3 (3.2 %)	117 (8.9 %)	0.05
Axillary operation			0.09
None	7 (7.4 %)	177 (13.4 %)	
SNB	27 (28.4 %)	435 (33.0 %)	
ALND	61 (64.2 %)	706 (53.6 %)	
Bilateral mastectomy	7 (7.4 %)	63 (4.8 %)	0.26
Operation time (mean, SD)	107 (±29) min	100 (±29) min	0.021*
Operation time over 2 hours	27 (29.7 %)	297 (22.7 %)	0.12
Diabetes	10 (10.5 %)	143 (10.9 %)	0.92
Smoking			
Current	14 (15.2 %)	188 (15.4 %)	0.18
Former	21 (22.8 %)	189 (15.5 %)	
Never	57 (62.0 %)	841 (69 %)	
NACT	10 (10.5 %)	121 (9.2 %)	0.66
History of ipsilateral breast cancer and RT	9 (9.5 %)	62 (4.7 %)	0.04*
SAP	74 (77.9 %)	1004 (76.2 %)	0.70
No SAP	21 (22.1 %)	314 (23.8 %)	

BMI = body-mass index, IQR = interquartile range, ASA = American Society of Anesthesiologists, SNB = sentinel node biopsy, ALND = axillary lymph node dissection, breast cancer = Breast cancer, RT = radiation therapy, BCS = breast conserving surgery, SSI = surgical site infection, SAP = surgical antibiotic prophylaxis. NACT = Neoadjuvant chemotherapy. Reproduced with permission from the original publisher.

Table 15. Subgroup analysis of the patients having SSI. Odds ratio < 1 indicates benefit on using SAP. None of the differences is of statistical significance.

	SSI in No-SAP group	SSI in SAP group	Odds Ratio (CI 95 %)
Age <70 years	6.9 % (13 of 189)	8.2 % (45 of 551)	1.20 (0.63–2.28)
Age 70–80 years	7.6 % (7 of 92)	5.3 % (14 of 263)	0.68 (0.27–1.75)
Age > 80 years	1.9 % (1 of 54)	5.7 % (15 of 264)	3.19 (0.41–24.7)
BMI under 25	5.9 % (9 of 153)	5.3 % (24 of 453)	0.90 (0.41–1.97)
BMI 25–30	5.0 % (6 of 119)	6.9 % (24 of 347)	1.40 (0.56–3.51)
BMI 30–35	9.5 % (4 of 42)	7.1 % (13 of 182)	0.73 (0.23–2.37)
BMI Over 35	14.3 % (2 of 14)	14.4 % (13 of 90)	1.01 (0.20–5.06)
ASA I	5.2 % (3 of 58)	6.2 % (8 of 130)	1.20 (0.31–4.71)
ASA II	7.1 % (11 of 155)	6.7 % (30 of 448)	0.94 (0.46–1.92)
ASA III	5.3 % (6 of 114)	7.4 % (33 of 448)	1.43 (0.58–3.50)
ASA IV	12.5 % (1 of 8)	5.8 % (3 of 52)	0.43 (0.04–4.71)
Surgeon experienced (50+)	5.5 % (13 of 236)	7.6 % (65 of 861)	1.40 (0.76–2.59)
Surgeon unexperienced (50–)	8.1 % (8 of 99)	4.2 % (9 of 217)	0.49 (0.18–1.32)
History of ipsilateral breast cancer and RT	0 % (0 of 7)	14.1 % (9 of 64)	–
Reoperation for BCS	9.1 % (1 of 11)	1.8 % (2 of 109)	0.19 (0.02–2.24)
Axilla			
None	4.6 % (1 of 22)	3.7 % (6 of 162)	0.81 (0.09–7.04)
SNB	4.4 % (5 of 114)	6.3 % (22 of 348)	1.47 (0.54–3.98)
ALND	7.5 % (15 of 199)	8.1 % (46 of 568)	1.08 (0.59–1.98)
Bilateral mastectomy	33.3 % (1 of 3)	9.0 % (6 of 67)	0.20 (0.02–2.50)
Duration of operation more than 2 hours	8.1 % (6 of 74)	9.6 % (25 of 261)	1.20 (0.47–3.05)
Diabetes	3.3 % (1 of 30)	7.3 % (9 of 123)	2.29 (0.28–18.8)
Smoking			
Current	7.7 % (4 of 52)	6.7 % (10 of 150)	0.86 (0.26–2.86)
Former	9.8 % (5 of 51)	10.1 % (16 of 159)	1.02 (0.36–2.96)
Never	5.9 % (12 of 202)	6.5 % (45 of 696)	1.09 (0.57–2.11)
Neoadjuvant therapy	8.7 % (2 of 23)	7.4 % (8 of 108)	0.84 (0.17–4.24)
All patients	6.3 % (21 of 335)	6.9 % (74 of 1078)	1.10 (0.67–1.82)

BMI = body-mass index, ASA = American Society of Anesthesiologists, SNB = sentinel node biopsy, ALND = axillary lymph node dissection, BC = breast cancer, RT = radiation therapy, BCS = breast conserving surgery, SSI = surgical site infection, SAP = surgical antibiotic prophylaxis. Reproduced with permission from original publisher

5.4 Study IV

In total, 1479 patients were operated during the study period, 854 in the ultrasonic instrument group and 625 patients in the electrocautery group. After the patients with missing data or meeting the exclusion criteria were eliminated, 427 patients in the ultrasonic instrument group and 459 patients in the electrocautery group were remaining. These patients underwent the propensity score matching, and finally, 364 patients could be matched for final analysis in each group (**Figure 4**). The number exceeded the number required by the sample size calculation.

The Patient Characteristics and Details of Surgery are presented in the **Table 16**. The size distribution of the tumour is very similar in both groups, and the amount of bleeding is also equal. The operating time was longer in the ultrasound instrument group, which corresponds to the clinical experience of quicker dissection with the electrocautery.

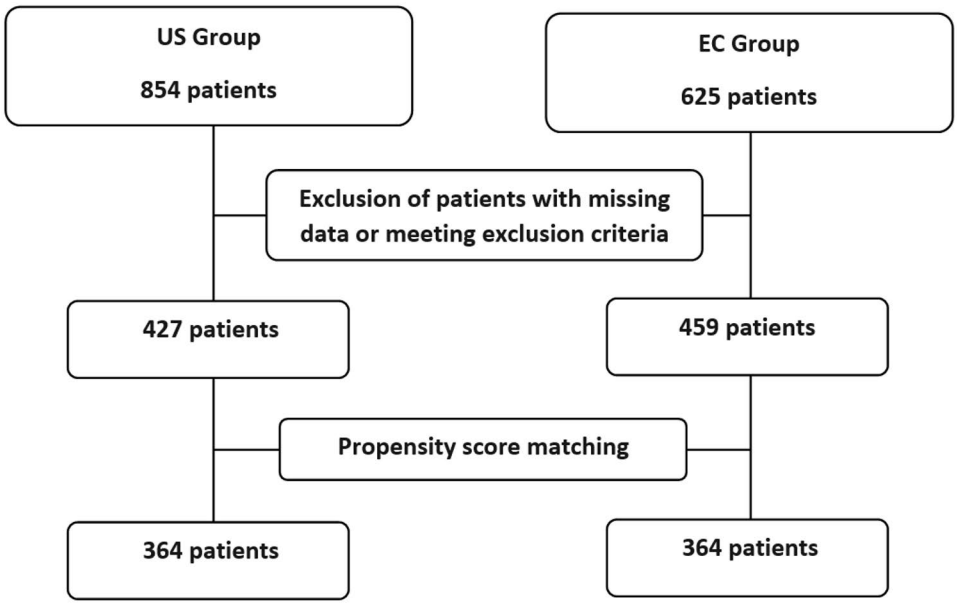

Figure 4. The total number of patients in each phase of the patient selection. Reproduced with permission from the original publisher.

Table 16. Patient characteristics. Data presented as (n, %) unless otherwise specified.

	US Group	EC Group	p-value
Number of patients	364	364	
Age, years (median, IQR)	56 (49–64)	55 (48–63)	0.29
BMI, kg/m^2 (median, IQR)	25.2 (22.3–28.6)	24.8 (22.2–27.9)	0.30
Diabetes	16 (4.4 %)	13 (3.6 %)	0.57
Smoking	85 (23 %)	74 (20 %)	0.32
ASA Classification			0.22
I	90 (25 %)	74 (20 %)	
II	228 (63 %)	247 (68 %)	
III	44 (12 %)	41 (11 %	
IV	2 (0.6 %)	0 (0 %)	
BC tumour size, mm (median, IQR)	27.5 (17–50)	27 (18–43)	0.35
Axillary procedure			
SNB	135 (37 %)	150 (41 %)	0.25
ALND	229 (63 %)	214 (59 %)	
Antibiotic prophylaxis	200 (60 %)	88 (24 %)	<0.001*
Operation time, min (median, IQR)	107 (91–124)	90 (77–114.5)	<0.001*
Intraoperative bleeding, ml (median, IQR)	50 (20–100)	50 (30–100)	0.34
Manner of discharge			<0.001*
Day-care	95 (26 %)	0 (0 %)	
Overnight	269 (74 %)	364 (100 %)	

BMI = body mass index, IQR = inter quartile range. ASA = American Society of Anesthesiologist, US = Ultrasonic instrument group, EC = electrocautery group, SNB = sentinel node biopsy, ALND = axillary lymph node dissection. Modified from original publication.

The number of complications is presented in **Table 17** and the results of the logistic regression analysis are presented in **Table 18.** The bleeding episodes appear to be much more frequent in the electrocautery group, but there is no difference in the rate of SSIs. The rate of skin flap necrosis is slightly higher in patients operated with electrocautery.

The difference in the rate of reoperations is explained mostly by the bleeding complications, as it was the cause of reoperation in 71 % (22/31) of the patients undergoing a reoperation. Interestingly, 48 % (20/42) of the bleeding episodes in the electrocautery group occurred within 24 hours of the mastectomy, indicating that same-day mastectomy might not be safe in this patient group. The ALND did not increase the risk for bleeding episodes, when compared to SNB only (25/214 = 11.7 % vs. 17/150 = 11.3 %) in the electrocautery patients. A total of 21 patients had

a skin flap necrosis, and four of them (19 %) had a prior bleeding complication requiring a reoperation

Table 17. The number of complications according to the surgical instrument. Data are presented as *n* (%).

	US Group	EC Group	p-value
Number of patients	364	364	
Bleeding complications	1 (0.27 %)	42 (11.5 %)	<0.001*
Surgical site infections	19 (5.2 %)	29 (8.0 %)	0.14
Skin flap necrosis	7 (1.9 %)	14 (3.9 %)	0.12
Any complication	25 (6.9 %)	75 (20.8 %)	<0.001*
Any reoperation	4 (1.1 %)	27 (6.9 %)	<0.001*

US = Ultrasonic instrument group, EC = electrocautery group. Modified from original publication.

Table 18. The odds ratio for complications in relation to the surgical instrument used in mastectomy.

	OR for ultrasound instrument	95 % confidence interval	p-value	Other variables of statistical significance
Bleeding complications	0.020	0.0028–0.15	p<0.001*	Older age (p=0.024)
Surgical site infections	0.65	0.35–1.23	p=0.21	High amount of intraoperative bleeding (p=0.021), High ASA Classification (p=0.024)
Skin flap necrosis	0.35	0.13–0.98	p=0.04*	Older age (p=0.019), high amount of intraoperative bleeding (p=0.003), smoking (p<0.001)
Any Complication	0.26	0.16–0.42	p<0.001	Older Age (p<0.001), High BMI (p=0.003)
Any reoperation	0.13	0.046–0.39	p<0.001	Older Age (p=0.039)

ASA = American Society of Anaesthesiologists, BMI = body mass index, OR = odds ratio. Reproduced with permission from original publisher.

None of the reoperations were performed for oncological indications. In multivariable logistic regression analysis, the use of SAP was not beneficial in this analysis, either (OR 1.04, 95 % CI 0.50–2.17, p=0.91).

The approximate price of the ultrasonic instrument is 350 euros (as of year 2021) compared to the 25 euros for the electrocautery. The cost of the treatment is calculated as an approximate value of treatment in Finnish public hospitals (price as of year 2022). The total sums are presented in **Table 19**.

Table 19. The total costs of the treatment protocol (all numbers in euro).

	US Group	EC Group
Instrument/piece	350	25
• **for 364 patients**	**127 400**	**9 100**
Primary operation	2 500	2 500
• **for 364 patients**	**910 000**	**910 000**
Cost of primary hospitalization/day	600	600
Number of patients	269	364
Total cost	**161 400**	**218 400**
Readmission to ED	400	400
• **Number of cases**	24	55
Total cost	**9 600**	**22 000**
Cost of hospitalization/day	600	600
• **Number of days**	39	68
Total cost	**23 400**	**40 800**
Cost of reoperation	1 700	1 700
• **number of cases**	4	27
Total cost	**6 800**	**45 900**
Cost of additional control visits (outpatient clinic)	250	250
• **number of cases**	25	75
Total cost	**6 250**	**18 750**
Total cost of treatment	**1 244 450**	**1 264 950**
Total cost/patient	**3 418.82**	**3 475.14**

ED= emergency department. US = ultrasound instrument, EC = electrocautery. Reproduced with permission from original publisher.

6 Discussion

Each Study I-IV produced new information, which is directly applicable to clinical practice. Study I convinced that the same-day mastectomy is safe in general, and that the protocol may be encouraged even further. Study II proved, that re-operations or adjuvant radiotherapy are not required in case of narrow margins in DCIS and immediate breast reconstruction, which is new information and solves a dilemma which has been pondered frequently in multidisciplinary meetings and resulted in various decisions. In study III it was shown that antibiotic prophylaxis is not usually required in mastectomy, which may help us to avoid unnecessary use of antibiotics with related adverse effects. In study IV the ultrasonic instrument was shown to be effective in preventing postoperative bleeding complications, which also supports the increase of SDS.

6.1 Safety of the same-day mastectomy

The rate of complications was similar in patients treated in SDS and OS regime. In a subgroup analysis, all 17 subgroups that were investigated, produced similar results. The most interesting finding was, that the rate of unplanned returns to care was lower but did not reach the significance level of $p<0.05$, in SDS patients in several subgroups, such as elderly patients (age 75–84 years), obese patients (as high as 40 kg/m^2) and the ASA Class's I–III. The patients undergoing mastectomy with SNB but without ALND had a lower risk of having an unplanned return to care ($p=0.049$), but the finding lacks a rational explanation. As there were 17 subgroups, it is not unexpected to have a single subgroup yielding results of statistical significance, even though the finding would be just coincidental. This is the most probable explanation for the result.

As the results show, even obese patients with BMI as high as 45 kg/m^2 were treated in the SDS regime without adverse events, although the number of patients was too low for statistical analysis. This finding with the overall results seems to assure, that the high BMI itself should not be considered as a contraindication for same-day surgery.

Two factors associated with increased risk of complications in previous literature, neoadjuvant therapy, and diabetes, were not associated with any

complications in the present study. The rate of non-surgery related major (pulmonary, cardiac, and central nervous system) complications was low (<1 %) in the present study, being consistent with the previous estimations (Amland et al. 1995; Olsen et al. 2008; Al-Hilli et al. 2015).

Postoperative haematoma requiring re-operation after discharge was rare (0 vs 4 cases, respectively), and no statistical analysis could be performed due to the low number of patients. Of the four patients, two consumed an ongoing anticoagulant therapy during the surgery, and one did consume an omega-3 product associated with an increased risk of bleeding. One of the patients did not have any medicine considered as a risk factor for bleeding. It is possible, that there were minor hematomas requiring no interventions nor readmittance, and thus were not visible in the statistics. However, the risk of bleeding episodes was lower (0.4 %) than the 2–11.6 % presented in previous literature (Hoefer et al. 1990; Nwaogu et al. 2015; Al-Hilli et al. 2015).

The study groups were different in terms of age, ASA Class, and the number of diabetic patients. This selection bias may also have effect on the results. It is possible that not all the factors related to the increased risk of complications are detectable in the data but may still have influenced the decision whether the patients are offered SDS.

The risk of reoperations was associated with high ASA Class, although the number of reoperations was relatively small. Old age or diabetes were not associated with any complications. On the contrary, the young patients required more readmissions for seroma puncture.

The rate of patients undergoing SDS increased during the study period. The criteria for SDS did not change during the study period, so the increase in exploiting the possibility is most probably due to the propitious experience of the practice. Additionally, the increase in exploiting the SDS was detected in all subgroups, so it was not a matter of expanding the practice to new patient groups.

Of the patients, who were planned to be discharged on the day of the surgery, a reasonably high proportion (19 %, 59/318) were admitted for the postoperative night. These patients were examined in detail. It was detected that the demographics were similar to the rest of the patients in the SDS group. The group and the number of postoperative complications was too small to be included in the analysis as a separate group, but the risk of complications was detected to be similar to the patients in the SDS and OS groups. The reason for unplanned admittance was solved in each patient. None of the unplanned admittances were due to surgical complications, but usually due to lack of appropriate arrangements to be discharged after the operation, social reasons, or delays in the operating schedule. The similar rate of postoperative complications in this group was an important finding, as the association between increased risk of complications and unplanned admittance would not be unexpected.

This study could not discover any factors to explain why the patients in the OS group had more minor postoperative problems than the patients discharged on the day of the operation. However, it may be that psychosocial factors are associated with both, selection to the OS group and returning to care. Additionally, the family circumstances of patients were not examined in this study, and it is probable that solitary patients were admitted more often than those with family, and this too might be associated with an increased risk of readmission.

The patient groups in this study differed, but the differences were rather small when compared to most previous studies. Considering the subject that was studied and the retrospective design of the study, the comparability of the study groups seems to be quite acceptable, and it is improbable to reach much more alike groups in a retrospective study. Thus, to receive data with significantly higher similarity between the study groups, an RCT setting is probably required.

None of the subgroups in this study proved to be unsuitable for SDS, especially not even the elderly nor the patients undergoing ALND, whose suitability to SDS has been previously questioned (Warren et al. 1998; Marchal et al. 2005;). It must be emphasized, that many patients included in the present study would have been excluded from most previous trials. According to the literature, most patients with notable co-morbidities have not been treated in the SDS regime, but this study seems to prove the feasibility of the protocol. The results of the study seem to assure, that the utilization of SDS could be increased as it is safe for most patients and is supposed to improve patient satisfaction and recovery (Margolese and Lasry 2000; Dooley 2002; Rovera et al. 2008; Keehn et al. 2019).

6.2 Oncological safety of skin-sparing mastectomy

None of the 71 patients had a recurrence during the 71 months of follow-up (0 %, 95 % CI 0–0.051), even though surgical margins were often scarce.

It seems that positive or close margins after skin sparing mastectomy do not necessarily confer a high risk of recurrence, even when the patient does not receive adjuvant RT. The result was not affected by the high frequency of DCIS upgrading to invasive disease (41 %). It can be concluded that skin sparing mastectomy is a safe procedure in DCIS, even when the size of the DCIS lesion is extensive and surgical margins prove to be scarce. The latissimus dorsi flap reconstruction is an unconventional reconstruction method in many centers, but during the study period (2010–19), it was dominantly used reconstruction method in the study center, However, we don’t expect this to influence the generalizability of the results to other reconstruction methods.

It has been suggested that symptomatic DCIS should have a higher risk of upgrading when compared to asymptomatic patients. This assumption did not get

support from the present study, as symptoms or any other preoperative factor could not predict the upgrading. The high proportion of upgrading is probably related to the large size of the DCIS lesion. In a previous meta-analysis, the risk of upgrading was 46 % in symptomatic patients. The reported percentage is close to the result of the present study (41 %). It remains to be unanswered, whether the risk of upgrading correlates more to the size of the DCIS or the symptoms, as these two have a mutual correlation. It has been shown that especially the small DCIS is often (>90 %) asymptomatic (Ernster et al. 2002).

The symptoms were similar in the patients who had an upgrade to invasive breast cancer and who had pure DCIS. Patients presented with similar symptoms that are usually present with breast cancer (lump, nipple discharge, nipple retraction, Mammary Paget's disease), but in the statistical analysis, none of the symptoms showed prognostic value for finding invasive cancer.

The limitations of imaging studies have been established before. Sanders et al showed that no imaging study can distinguish DCIS from invasive cancer reliably (Sanders et al. 2005). The findings of the present study are in concordance with the estimation. Furthermore, mammography and MRI were equally good in predicting the size of the DCIS lesion, which settles with the previous estimations, that mammography may underestimate (as the mammogram only reveals the microcalcifications, which determines the diameter of DCIS lesion in mammography, but not all DCIS is calcified), and MRI overestimate the size of DCIS (as also benign tissue around the DCIS may enhance similarly to DCIS). Furthermore, although the majority of the DCIS lesions are visible in both, mammography and MRI, a certain proportion of DCIS lesions are only visible in one of the modalities (Kuhl et al. 2007).

In the present study, the invasive breast cancer foci in the mastectomy specimen were usually small, as the median size was 6.5 mm, and the range was 1 to 26 mm. As the median size of the DCIS lesion was 60 mm, it is understandable that core needle biopsies with limited coverage were not successful in distinguishing the invasive disease from DCIS.

Additionally, most patients had scarce margins in histopathological assessment, as a major portion of patients (59 %) had a resection margin of 2 mm or less, which should, according to the present guidelines, impose a reoperation (Finnish Breast Cancer Group 2019). Despite the majority of the patients did not receive any adjuvant therapy, there were no recurrences. This may be interpreted in multiple ways. One interpretation is, that narrower margins than 2 mm are sufficient in DCIS, which has been supported by some studies (Wapnir et al. 2011; Matsen et al. 2016). It may also be suggested that the mastectomy and the removal of the breast tissue was complete, and therefore there were no ductal structures left behind. Additionally, the limited number of patients (71) must be taken into account in all considerations.

The risk of positive SNB (12.7 %) was concordant with the previous estimations, even though the rate of invasive cancer was rather high compared to previous studies (Intra et al. 2003; Leikola et al. 2007; Si et al. 2019; van Leeuwen et al. 2020). None of the patients had a high-burden axillary disease, and the only patient who would have been recommended ALND according to the current guidelines was the one patient with unsuccessful SNB (Giuliano et al. 2012).

Two patients presented with ITC in SNB but with no invasive cancer in the mastectomy specimen, although the specimens were closely re-examined. Similar findings have been made before (Leikola et al. 2007; van Leeuwen et al. 2020). It has been suggested that the preoperative core needle biopsy would cause the spreading of the tumour cells, but the theory has received no support in later research (Hansen et al. 2004; Peters-Engl et al. 2004; Mittendorf et al. 2008; Liikanen et al. 2016) Another explanation, although unsuitable with the comprehension of the non-invasive nature of DCIS, is that the DCIS itself could generate metastasis. The theory lacks rationale and would have no simple method of getting proven. Thus, the most probable explanation is, that the small invasive foci in the mastectomy specimen were just not found in the histopathological assessment. However, it would seem that the invasive focus must be diminutive, and the finding as such would prove that even very small invasive cancer may generate metastasis.

The conflicting complications, insufficient surgical margins, and SFN were both detected in the patients included in the study. The risk for positive margins was 13 %, and the rate of SFN was 8 %. The risk for SFN was similar to the ones presented in the previous studies (Chang et al. 2002; Kim et al. 2012; Du et al. 2018). As the surgical procedure was the standard used in Turku University Hospital in such cases, this was an expected finding. Only two of the six patients with SFN required a reoperation. According to the results of the present study, the skin flaps may not be left any thicker than we have done now, but it seems unlikely that there would be a possibility to make them much thinner either. Thus, the recommended 5 mm thickness seems to be appropriate (Verheyden 1998; Torresan et al. 2005). Margin positivity has not been published in a similar group of patients before, and thus it is difficult to compare this to the literature. The treatment protocol in the case of positive margins was proved to be highly heterogenous, reflecting the fact that no guideline exists for such occasion (Larson et al 2011; Robertson et al 2014).

6.3 Antibiotic prophylaxis in mastectomy

Overall, the incidence of SSI was almost identical in the patients who received SAP (6.9 %) compared to the patients who did not (6.3 %, p=0.70). The risk of SSI was similar in the case-control comparison (6.4 % vs 6.7 %, p=0.87) and in the patients

who were treated before (6.9 %) or after the introduction of regular SAP (6.9 %, p=0.74).

The risk of SSI after mastectomy seems to vary in previous literature quite significantly, but the risk of SSI is close to the rate of patients who received SAP in the Cochrane review (7.1 %) (Gallagher, Jones, and Bell-Syer 2019). However, there is wide variation in patients, procedures, and diagnostic criteria of SSI in the studies included in the Cochrane review, and the results cannot be compared directly to each other. A detailed analysis of the studies revealed that none of the included trials seem to correspond to the circumstances of current Finnish practice. Thus, there is no reliable baseline to which compare the rate of SSI. When considering only the studies reporting the rate of SSI for mastectomy specifically, the rate of SSI has usually reported to be 6–19 % (Wagman et al. 1990; Platt et al. 1990; Amland et al. 1995; Olsen et al. 2008). The risk of SSI in the present study is close to the lower limit of the scale, both in patients receiving and not receiving SAP.

Furthermore, a few large retrospective analyses have estimated the efficacy of SAP, usually showing no benefit from the use of SAP (Sanguinetti et al. 2009; Crawford et al. 2016; Zhang et al. 2020). Limiting the reliability of these studies, the patient records have not been evaluated and the coverage of the SSIs is uncertain. The strength of the present study is, that the patient records of all patients were evaluated to ensure the accuracy of the diagnostics and that the Turku University Hospital is the only hospital in the region to treat breast cancer and postoperative complications.

Also, the number of patients in the present study is rather high, exceeding the number of patients in any previously published RCT, most of which include rather a small number of patients. Additionally, the results of the present study are highly concordant, producing similar results in each comparison and showing no benefit for SAP in any investigated subgroup, although the absolute risk of SSI has differed from one subgroup to another. The finding is precisely what one should expect when investigating an intervention with minimal effect. Thus, the natural interpretation of the results seems to be, that SAP does not reduce the risk of SSI in the circumstances we operate in.

Furthermore, the mean time from the surgery to the diagnosis of the SSI was 9 days in the SAP group and 13 days in the no-SAP group. The previous literature estimates the mean time from surgery to the onset of SSI to be 9.6–11 days in patients with SAP and 11–17 days without SAP (Platt et al. 1990; Gupta et al. 2000; Prudencio et al. 2020). The results of the present study are concordant with that, but with no statistical difference between the times.

The factors predisposing to SSI were high BMI, ALND, and previous ipsilateral BCS and RT, both suggested to be risk factors in previous literature (Amland et al. 1995). The risk of SSI was especially high in obese patients with BMI over 35 kg/m^2

(14.4 %, 15/104), but the SAP did not manage to reduce the risk for SSI in this subgroup either. Conversely, many other factors associated with SSI, such as older age, smoking, diabetes, reoperations for BCS, or preceding neoadjuvant therapy (Amland et al. 1995; Olsen et al. 2008; Al-Hilli et al. 2015) were not risk factors for SSI in the present study.

The risk of SSI has been associated with prolonged operation time in the previous literature (Wagman et al. 1990). In the present study, the operating time was slightly longer in patients who suffered an SSI (107 min in SSI and 100 min in patients with no SSI, p=0.021), but this was shown to be a consequence of longer operating time in patients undergoing ALND. ALND was a risk factor for SSI in multivariate analysis, but when the analysis was performed separately for each different axillary procedure, the operation time had no association with SSIs.

6.4 Effect of surgical instruments

6.4.1 Postoperative bleeding

The use of ultrasound instrument seems to be significantly associated with a lower risk of postoperative bleeding complications when compared to traditional electrocautery. The risk of postoperative bleeding complications is reported to be 2–11.6 % in previous literature (Al-Hilli et al. 2015). Of the 364 patients operated with ultrasonic SonoSurg® instrument (US), only one (0.3 %) suffered a postoperative bleeding complication. At the same time, the risk of postoperative bleeding complications was 11.5 % in the patients operated with electrocautery, which is in the upper limit of the scale reported in the literature. The result seems to demonstrate that ultrasound instrument offers superior hemostasis compared to electrocautery.

Interestingly, there was no difference in the amount of intraoperative bleeding, as it was the same in each group (median 50 ml, IQR 20–100 ml in the ultrasound instrument group and 50 ml, IQR 30–100 ml in the electrocautery group, p=0.34). This would seem to support the comprehension, that the hemostasis during the surgery is similar, and that the difference in the risk of postoperative bleeding is due to different operational principle of the instruments. However, it is not clear, in which amount the difference is explained by the energy used for dissecting, and that does the scissor mechanism of the SonoSurg® instrument yield additional benefit to the hemostasis. There is a clear difference in the operating time, as ultrasound instrument seems to be remarkably slower (median operation time 107 vs 90 min, p<0.001). It may be, that the longer dissection time of the ultrasound instrument also improves the occlusion of the blood vessels.

The amount of intraoperative bleeding in both groups is low compared to the meta-analysis of 11 RCTs and 702 patients by Huang et al. Huang et al reported the mean blood loss during the surgery to be 300 ml in patients operated with ultrasound instrument (including only Harmonic Scalpel®) and 399 ml in patients operated with electrocautery (Huang et al. 2015). Both numbers appear to be very high compared to what is reported in the present study with no apparent explanation. The SonoSurg ® instrument has not been investigated in any trials considering breast surgery, before the present one.

In the electrocautery group, half of the bleeding episodes, equaling 5.8 % of all patients, occurred within 24 hours after the operation. The SDS protocol was not used during the study period in Helsinki University Hospital, and the high risk of early bleeding complications seems to demand monitoring in the ward.

The risk factors previously reported for postoperative bleeding complications are advanced age and medications affecting hemostasis, such as antiplatelet drugs, anticoagulants, non-steroidal anti-inflammatory drugs (NSAIDs), and selective serotonin reuptake inhibitors (SSRIs) (Friis et al. 2004). The patients consuming antiplatelet drugs and anticoagulants were excluded from the study, and the use of NSAIDs and SSRIs was not recorded. The information on the antiplatelet drugs and anticoagulants was recorded, but it was detected in the primary analysis, that only four patients with anticoagulant therapy and ten patients with antiplatelet therapy were present in the electrocautery group. The perioperative protocol regarding the bridging therapy (none in the ultrasound instrument group, often in the electrocautery group) and discontinuation of the medications (rarely in the ultrasound instrument group, often in the electrocautery group) differed substantially between the groups, so the patients could not be matched in propensity score analysis, and thus all patients consuming these medications had to be excluded. By doing this, much more balanced cohorts were acquired, adding the reliability of the results.

The primary pain medication prescribed for the patients operated with ultrasound instrument was paracetamol, and the patients in the electrocautery group received either NSAID or paracetamol. Although the use of NSAIDs is associated with an increased risk of postoperative bleeding, we don’t expect this to be a significant factor predisposing to the bleeding complications, as the medication was usually started only after the surgery, and a major portion of bleeding complications occurred within a day after the operation. It cannot be excluded though, that the medication would have been associated with some of the bleedings occurring later after the surgery.

Advanced age was detected to be a risk factor for bleeding complications also in the present study, concordant to the present literature (Friis et al. 2004).

6.4.2 Skin flap necrosis

In previous literature, the reported rate of SFN varies significantly and may be as low as 0.3 % (Al-Hilli et al. 2015) but is usually approximately 5 % (Robertson et al. 2017) and up to 30 % (Nykiel et al. 2014). Some of the variation may be explained by the different diagnostic criteria for SFN. As the incision in mastectomy is long and the skin flaps wide, minor problems in wound healing are common. Although a wide full thickness necrosis is most probably counted as SFN in the studies, inclusion criteria for minor partial-thickness necrosis, especially if no specific treatment is required, may vary from one study to another. Especially if the study is performed retrospectively, the coverage of the reported rate appears to be unreliable. The different demographics may have an effect, as for example, the proportion of smoking patients differs from one population to another. Furthermore, some studies include only simple mastectomy, but some also the patients undergoing immediate reconstruction, which has a higher risk of SFN (Robertson et al. 2017).

The rates of SFN in the present study (1.9 % in the ultrasound instrument group and 3.9 % in the electrocautery group) seem to be rather low when compared to the previous literature. It may reflect the overall good health of the patients, but also the retrospective nature of the study may be associated with underreporting the problem. As very few patients seem to have undergone a reoperation because of SFN, the numbers should be somewhat appropriate.

The rate of SFN was lower in the patients operated with ultrasound instrument (OR 0.35, 95 % CI 0.13–0.98, p=0.04). The wider lateral damage caused by electrocautery is a credible explanation for the difference. Furthermore, the postoperative bleeding episode preceded 19 % (4/21) of the SFNs, thus being an evident risk factor for SFN. Therefore, it may be assumed, that by preventing bleeding complications, the number of SFNs may be reduced likewise.

The other risk factors for SFN proved to be old age, high amount of intraoperative bleeding, and especially smoking, as the risk for SFN was five times higher in smokers than in non-smokers (8.2 % vs, 1.4 %, p<0.001). These risk factors are the same that are most often suggested in previous studies (Robertson et al. 2017). Radiotherapy and obesity have also frequently been associated with SFN, but obesity was not associated with SFN in the present study. The patients with previous ipsilateral breast surgery and associated radiotherapy were excluded from the study.

There is only little that can be done with the other risk factors, but it has been shown, that cessation of smoking, even shortly before the surgery, improves wound healing significantly (Mills et al. 2011).

6.4.3 Surgical site infections

The risk for surgical site infections was 5.2 % in the ultrasound instrument group and 8.0 % in the electrocautery group, the difference being non-significant in statistical analysis (OR 0.65, 95 % CI 0.35–1.23, p=0.21). The overall rate of infections seems to be similar to what is presented in previous literature (discussed in Chapter 6.3.).

In the previous literature, postoperative bleeding, smoking, and diabetes have been shown to be risk factors for SSI, but none of these associations were detected in the present study. The number of smoking and diabetic patients was similar in both groups, but the rate of postoperative bleeding complications was higher in the electrocautery group. It has been shown that blood is an optimal growth medium for bacteria (Lee et al. 2004). The manifestation of SSIs was not associated with postoperative bleeding episodes. However, it may be presumed, that the higher rate of diagnosed postoperative bleeding complications is associated also with a higher rate of subclinical smaller hematomas. As the patients having bleeding complications often underwent reoperation to ensure the hemostasis, it may be that these patients had in fact better hemostasis after the reoperation when compared to the patients who did not undergo a reoperation. Therefore, it is uncertain whether the patients undergoing a reoperation are the appropriate comparison when evaluating the risk of SSI after postoperative bleeding.

Although the SAP was more frequently used in the ultrasound instrument group and the same group had fewer SSIs, the use of SAP was not associated with a lower risk of having SSI in multivariate analysis. This is in concordance with the results from study III.

6.4.4 Overall reoperations

The rate of overall operations in the NSQIP data was 3.1 %[8]. In a study by Murphy et al., the overall rate of reoperations was 2.5 % (Murphy et al. 2019). In that study, approximately half of the reoperations were due to postoperative bleeding, whereas 60 % of the reoperations in NSQIP data were due to bleeding complications.

In the present study, the overall rate of reoperations was 1.1 % in the ultrasound instrument group and 6.9 % in the electrocautery group. The difference between the study groups and the difference in the numbers presented in the literature results almost entirely from the different rate of bleeding complications and related reoperations.

The risk for any complication was increased in the patients with older age and high BMI. This should be considered when deciding the optimal surgical treatment in these patients. For example, BCS might prove to be a better option, but this matter requires further study and more detailed analysis before any definite conclusions can be made.

6.4.5 Cost analysis

Although the ultrasound instrument is more expensive than traditional electrocautery, the total cost of the treatment was almost equal in both groups. Actually, the overall cost of treatment was slightly lower in the ultrasound instrument group (3418.82 euros vs 3475.14 euros in the electrocautery group).

Operation time was considerably shorter in the electrocautery group (90 min vs 107 min in the ultrasound instrument group), but the cost of the primary treatment was estimated to be the same, nevertheless. The difference in the operating time is not sufficient to enable more efficient usage of the operating theatre capacity. Secondly, the non-economical or long-term expenses were not observed. Furthermore, sick leaves comprise a major portion of total expenses, which are not included in the analysis either, as all these would require multiple assumptions. However, if these expenses would have been included, the ultrasound instrument would have been even better than the calculation shows now.

The cost of the treatment differs greatly from one health system to another, and therefore the comparisons are challenging to make. A single study from the USA investigated the cost of bleeding complications, but as the fares are multiple compared to the fares in Finland, the comparison is unavailing (Nwaogu et al. 2015). However, considering that the total cost of treatment was approximately equal in Finland, it would be reasonable to assume, that the benefit of the ultrasound instrument would prove to be even higher in the USA, where the cost of treating complications is even higher. Conversely, the cost of treatment in developing economies would probably prove the contrary.

6.5 Limitations of the study

The main limitation of the study was its retrospective nature. Thus, it is not possible to exclude biases in recording the information and in patient selection.

In Study I, we had no information on patients' psychosocial factors or family circumstances. We cannot exclude confounders or undetermined factors affecting the patient selection to SDS or OS groups. The patient groups treated in OS and SDS regime were different in terms of age and general health status and the extent of the performed surgery. These differences are discoursed by multivariate analysis, but regardless of that it is possible, that the results are biased. Further study is required to examine this topic.

In study II, the number of patients was limited, mainly because the study protocol included only patients with extensive DCIS and immediate breast reconstruction. The mean follow-up time in the study was 71 months, which exceeds the follow-up in most comparable studies, but as breast cancer is known to potentially recur many years after the primary treatment, future recurrences cannot be excluded.

Furthermore, the treatment in the patients having positive margins varied considerably, making comparisons difficult.

In study III, it is not possible to evaluate the accuracy of clinical diagnostics of SSI. However, it should be safe to conclude that the diagnostic criteria were similar in patients who received SAP and who did not, respectively, as the diagnosis of SSI was usually made only 1–2 weeks after the surgery, and the information on whether the patient had received SAP was probably not taken into account. Thus, the effect should be rather similar in both patient groups.

The electronic prescription was utilized in Finland during the study period, and private healthcare introduced it principally a year later than public healthcare, during the year 2014. Thus, it is presumable that some antibiotics have been prescribed to patients without being recorded in the prescription system or electronic patient records. However, in Study III, multiple parallel sources for detecting SSI were used and conformity was ensured. There were no notable differences in rates of antibiotic prescriptions, electronic patient records, or the hospital's infection reporting system (SAI). Additionally, all major complications were treated in Turku University Hospital, and no data on such complications should be missing.

In study IV, the comparison was made between two different hospitals with unavoidable differences in practice. Thus, it cannot be evaluated whether there were differences in diagnosing complications or recording them. The treatment practice has inevitably some variation, and it is challenging to evaluate to what extent it does affect the results. However, the surgeons in both hospitals adhere to the same national guidelines and there should not be a major difference in how the patients are treated. The primary data of Study IV was heterogenous, and although propensity score matching was used, it is possible that this could not eliminate all differences of the primary data. In Helsinki University Hospital, a bipolar instrument was used in axillary surgery, which may affect the results. However, the rate of postoperative bleeding complications was similar in patients who underwent SNB (17/150 = 11.3 %) vs. those who underwent ALND (25/214 = 11.7 %), which should support the assumption, that the bleeding is mainly originated from the mastectomy area.

Seroma formation is frequently encountered after mastectomy, and the surgical instruments used in operation have been shown to affect the rate of seroma formation, but this was not recorded for the study.

6.6 Further study

The study generated several topics for future research. First, the psychosocial effects affecting SDS should be studied further. The factors resulting in unplanned admittance of patients selected to SDS should be more closely investigated, as unplanned admittance increases the strain of the wards. The present study seems to

assure, that SDS is safe in all the patient groups investigated. An RCT on the subject may not be feasible but expanding the limits of SDS in close surveillance would produce more information on the subject. Additionally, the rate of unplanned returns to care in the OS groups was higher than in the SDS group and investigating these patients may reveal further subjects for study or provide information on the feasibility of the SDS procedure.

The current literature lacks a large high-level RCT on surgical antibiotic prophylaxis in mastectomy. The number of patients undergoing mastectomy is large, and although the use of SAP may seem to be a minor detail in the entire treatment of breast cancer, the multiplicative effects in a large group of patients may be substantial.

Seroma formation is a common problem after mastectomy, and the relationship between the surgical instrument and seroma formation should be investigated also for ultrasonic instruments.

Regarding bleeding complications, patients consuming antiplatelet or anticoagulant medications were excluded from the present study, and as these are major risks factor for bleeding complications, the subject necessitates further study.

7 Conclusions

I Same-day mastectomy is safe for patients with stable co-morbidities, regardless of the axillary procedure. Old age, obesity or ASA Classification of level 3 should not be considered a contraindication for same-day mastectomy.

II Immediate breast reconstruction is oncologically safe in extensive DCIS regardless of the possible upstaging in postoperative assessment. Close but negative surgical margins do not oblige adjuvant therapy.

III Antibiotic prophylaxis did not reduce the risk of postoperative surgical infections. Unselective antibiotic prophylaxis for all patients' undergoing mastectomy is not beneficial.

IV Ultrasonic instrument is associated with significant reduction in postoperative bleeding complications. Although the ultrasonic instrument is more costly, the total cost of the treatment may be lower in patients operated with ultrasonic instrument.

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Masku, December 2022
Anselm Tamminen

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