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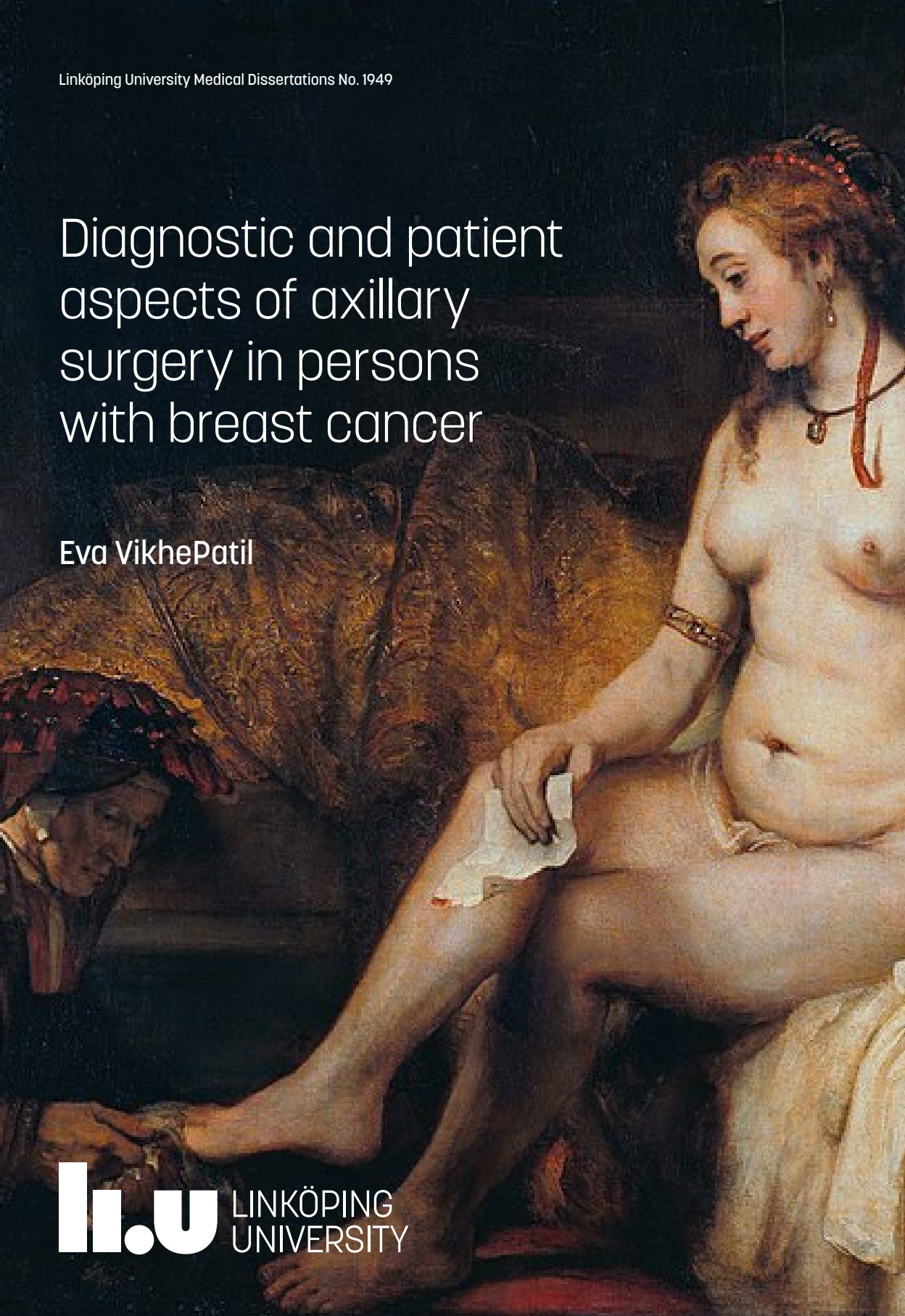
Eva VikhePatil



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Diagnostic and patient aspects of axillary surgery in persons with breast cancer

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Cover/picture/Illustration/Design: Bathsheba at Her Bath by Rembrandt, 1654.

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Dave and Neil you are the future, the sky´s the limit!

Amor vincit omnia!

CONTENTS

ABSTRACT

Breast cancer (BC) is the most common cancer in women. In western society many women are living with BC, with symptoms after treatment and the risk of recurrence. When a woman develops cancer all her relationships are affected. Today the survival rate is very high with nine out of ten surviving for five years, meaning that there are many lives affected by the outcome of BC.
The most important prognostic factor in BC is the status of the lymph nodes in the axilla. However, surgery in the axilla is associated with significant arm morbidity. Thus, there is an urgent need to deescalate the effect of axillary surgery. This thesis investigates how to perform oncologically safe surgery with as little harm as possible.
The main aim was to identify factors for predicting non-sentinel node metastases and investigate different methods for sentinel node (SN) identification in the primary and recurring BC setting as well as to explore patients' trajectory through BC treatment including axillary surgery. Furthermore, to reduce unnecessary suffering due to axillary surgery.

The first study aimed at identifying the clinicopathological predictive factors that are responsible for non-SN metastases. Using data from a large cohort from the National Quality Register for Breast Cancer (NKBC), we identified factors associated with non-SN metastasis. The findings showed how to differentiate between those with a risk for non-SN metastasis and in need of further axillary surgery and those with only a limited spread to the SN. A logistic regression model revealed statistically significant factors such as proportion of SN with macro metastases detected at SN biopsy, tumour size, HER2 positivity, lymphovascular invasion and multifocality as strong factors for non-SN metastasis. These factors were incorporated in a nomogram for predicting the risk of non-SN metastasis to avoid unnecessary axillary lymph node dissection.
In the second study the aim was to determine whether scintigraphy imaging can improve the detection rate for SN, SN metastases and non-SN metastases. The study explored which technique is best for identifying the SN, in order to better visualize it and thus facilitating the surgery procedure. The difference in SN outcome using the conventional radioisotope technique, Technetium-99m (Tc99), when adding scintigraphy to the gamma probe and blue dye was also compared. The findings showed a small difference of 2.3% in favour of adding scintigraphy images. However, it is unclear as to whether this will have any effect in the clinical setting.
The third paper adopted a person-centred approach to understand how healthcare professionals can facilitate women subjected to BC treatment

including axillary surgery. An interview study was conducted using a phenomenological hermeneutical method. The main finding was that the women were in a state of acceptance and adaptation to their situation. When healthcare professionals provided structure and consistency, the women's treatment and lived experience made sense. Uncertainty occurred when the women became lost in their own sense-making process, leading to low self-efficacy.
The fourth study was a feasibility study to identify better options for women with recurrence. An investigation of BC patients with recurrence and earlier axillary surgery was conducted to scrutinize if it is feasible to identify the SN with the magnetic tracer, superparamagnetic iron oxide, SPIO, compared to conventional methods with radioisotope (Tc99) and blue dye. The study was conducted at two hospitals, Sahlgrenska University Hospital and Linköping University Hospital. The findings showed that SPIO had a higher detection rate and a concordance rate of 92%. In conclusion, SPIO is a tracer with a smoother transition and easier handling eliminating the need for the radioisotope which has a short half-life and of which there is a limited global supply.

To conclude, this thesis emphasises the importance of being able to fine tune the factors that point to individual risk factors for non-SN metastases and transit to the next SN tracer with the magnetic technique. A person-centred approach during treatment and follow-up is warranted to support self-management among women with BC.

Keywords: Breast cancer, sentinel node, non-sentinel node metastases, person-centered

SVENSK SAMMANFATTNING

Många kvinnor i vår omgivning kommer att drabbas av bröstcancer som är den vanligaste cancerformen hos kvinnor. En av tio insjuknar innan 75 års ålder. Sjukdomen drabbar inte bara kvinnan utan också hennes partner, barn och vänner. Idag är överlevnaden hög då tillgängliga behandlingar är framgångsrika för bröstcancer. Nio av tio kvinnor överlever 5 år. Därför lever i vårt samhälle många kvinnor och några män länge efter diagnosen och med symptom av behandling. Cirka fem procent är män. Som överlevare är det en stor omställning att ha drabbats av en allvarlig sjukdom. Många är drabbade då cancersjukdomen och dess behandling även drabbar närstående.

Bröstcancer upptäcks till största delen vid hälsokontroll med mammografi, som alla kvinnor mellan 40-74 år kallas till. Enbart 77% deltar i denna screening. Om kvinnan själv känner en knöl i bröstet ska hon söka vård. Kvinnan genomgår då en trippeldiagnostik, bestående av klinisk undersökning, röntgen och ultraljud av bröst samt armhåla, och provtagning från tumören.

Behandling består av att operera bort tumör i bröst och undersöka om cancern spritt sig till armhålan där det finns lymfkörtlar. Att operera bort alla lymfkörtlar från armhålan ger kända symtom som svullnad av armen, så kallad lymfödem, smärta i axeln och nervsmärtor i armen. På grund av de här riskerna har utvecklingen av kirurgin i armhålan gått från att alla lymfkörtlar tas bort till att hitta den så kallade portvaktskörteln där endast 1-2 lymfkörtlar opereras bort. Denna metod minskar avsevärt risken för symtom i armhålan/armen utan att riskera säker cancerbehandling.

Genom att hitta identifierbara faktorer för de som har en risk för att ha fler lymfkörtlar med cancer och bara operera bort alla lymfkörtlar hos de fåtal patienter med denna risk är ett mål kan onödigt lidande minska liksom onödiga kirurgiska ingrepp. Sjukvårdens målsättning bör vara att arbeta salutogent med fokus på att främja hälsa hos kvinnan som får bröstcancer. Detta kan uppnås genom att patienten kan uppleva situationen begriplig, delges meningsfull behandling och att situationen blir hanterbar för hen (Antonovsky, 1987).

Avhandlingen avsåg att utforska hur vi kan minska onödigt lidande från för mycket kirurgi i armhålan, utröna våra patienters förståelse av vad de behöver genomgå och vilka nya metoder som finns för att underlätta idenifiering av portvaktskörteln.

Delstudie I handlade om att hitta tumörbiologiska faktorer från brösttumören och portvaktskörteln som har ett samband med risk för fler cancersjuka lymfkörtlar i armhålan. I 70-85% av fallen finns det inga fler lymfkörtlar med cancer än portvaktskörteln. Det finns en önskan att undvika onödig kirurgi i armhålan då det är behäftat med besvärliga symtom.

Delstudie II bygger på samma patientmaterial som i studie I. Vi undersökte vilken metod som användes vid identifieringen av portvaktskörteln. I samband med bröstkirurgi sprutas en liten mängd radioaktivt spårämne in i bröstet som sedan transporteras i lymfsystemet och fastnar i den första portvaktskörteln i armhålan. Portvaktskörteln kan identifieras vid en undersökning, så kallad scintigrafi där lymfkörtlarna avbildas och på så sätt kan kirurgen innan operationen se var portvaktskörteln ligger. Under själva operationen sprutas blå färg i bröstet som också transporteras i lymfbanan för att underlätta identifieringen av portvaktskörteln under operationen. Med hjälp av en gammadetektor kan vi se var det största utslaget är i armhålan och med hjälp av de här två teknikerna kan vi med stor säkerhet identifiera rätt lymfkörtel. Studien visade att om vi använde alla tre metoderna scintigrafibilder, gammadetektorn och blå färg kunde fler lymfkörtlar med upptag av spårämnet hittas. Om det har någon klinisk betydelse är dock osäkert.

I delstudie III intervjuades patienterna om hur de upplevde att bli opererade i armhålan. Sjukvårdpersonalen informerar patienten om vanliga symtom efter operationen i armhålan men vi vet egentligen inte vad patienten uppfattar av informationen. Här kunde vi se vikten av att ge patienten en begriplig information som de kunde hantera för att på bästa sätt hitta mening med den situation de befann sig i. Inom sjukvården har vi en tradition att tala om patienten som en anatomisk konstruktion, och det är här vi behöver personcentrera vården bättre.

I delstudie IV studerades patienter som fått återfall i sin bröstcancer och planerades för en ny portvaktskörteln kirurgi. Om identifieringen av lymfkörteln kunde ske med hjälp av ett nytt spårämne som inte är radioaktivt, så kallade järnfilspån. Detta skulle hjälpa till att identifiera körtlarna med magnetröntgen innan operationen och under operationen med en magnetometer. Det här spårämnet kan hanteras av sjukvårdpersonal på mottagningen vilket underlättar logistiken i samband med operationen i bröstet och armhålan.

Avhandlingens resultat visar på tumörbiologiska faktorer i form av vilka tumörer som har benägenhet att sprida cancerceller till lymfkörtlarna. Tekniken vid identifiering av portvaktskörteln har betydelse. Nya tekniker att använda för identifiering av portvaktskörtel underlättar för patienten. Vidare behöver vårdpersonalen bli bättre på att förstå patienternas meningsskapande för att möta dem som personer. Att lyssna på berättelsen och etablera ett partnerskap är centralt. Målet är att göra minsta möjliga skada vid

kirurgin med en samtidig säker och personcentrerad cancerbehandling för våra patienter.

LIST OF PAPERS

I. **Eva VikhePatil**, Ivan Shabo, Oliver Gimm, Lars-Gunnar Arnesson, Helena Fohlin. Prediction of Non-Sentinel Node Metastasis in Breast Cancer –A Population-Based Study. Advances in Cancer research & Clinical Imaging, 2022 March DOI: 10.33552/ACRCI.2022.03.000565

II. **Eva VikhePatil**, LarsGunnar Arnesson, Helena Fohlin. Evaluation of preoperative scintigram for the outcome of Sentinel Node Biopsy in Breast Cancer. Results from the Swedish National Quality Registry For Breast Cancer. (Manuscript)

III. **Eva VikhePatil**, Anna Forsberg, Carina Wennerholm, Jenny Drott. "It Is What It Is" - The Lived Experience of Women With Breast Cancer Undergoing Axillary Lymph Node Dissection. J Patient Cent Res Rev. 2024 October 15;11(3):222-230. DOI: 10.17294/2330-0698.2072. PMID: 39439542; PMCID: PMC11493309.

IV. **Eva VikhePatil,** Amalia Segerbard Planoudis, Kian Chin, Carlos Dussan, Henrik Leonhardt, Pontus Zaar, Pantelis Gialis, Fredrik Wärnberg. Use of magnetic tracer and magnetic resonance imaging for sentinel lymph node detection after breast cancer recurrence and previous axillary surgery. Journal of Womens Health and Development. 2025 January 28, Volume 8 Issue 1. DOI : https://www.doi.org/10.26502/fjwhd.2644-288400132. ISSN: 2644-2884

ABBREVIATIONS

ALND	Axillary lymph node dissection
BC	Breast cancer
Blue dye	Patent Blue V®; Guerbet, Paris, France
CRF	Clinical report form
DCIS	Ductal carcinoma in situ
Dye	Blue dye, Patent Blue V®; Guerbet, Paris, France
EPN	Swedish Ethical Review Authority
ER	Estrogen receptor
HCP	Health care personnel
HER2	Human epidermal growth factor receptor2
Ki67	is a nuclear antigen present only in cycling cells.
Luminal A	ER positive and HER2 negative breast cancer
Luminal B	ER positive and HER2 positive breast cancer
LVI	Lymphovascular invasion
MM	Malignant melanoma
MRI	Magnetic resonance imaging
NHG	Nottingham Histological Grade I-III
Non-SNm	Non sentinel node metastases
pN0	TNM staging system, pN0=no metastases in the lymph nodes, pathological staging
P^{risk}	a calculated risk for non-SNm
Probe	Gamma probe
SN	Sentinel node
SNm	Sentinel node metastases
T1	TNM staging system, T1=tumour size of ≤2 cm
T1a-b	TNM staging system, T1a=0.1-0.5 cm, T1b=0.5-1.0 cm
Tc^{99}	Technetium-99m, radioisotope

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When I am down and, oh, my soul, so weary
When troubles come and my heart burdened be
Then I am still and wait here in the silence
Until You come and sit awhile with me

You raise me up so I can stand on mountains
You raise me up to walk on stormy seas
I am strong when I am on Your shoulders
You raise me up to more than I can be

Josh Groban

Nothing had been possible without the support of my supervisors, family, colleagues and friends,

You are all part of my research journey.

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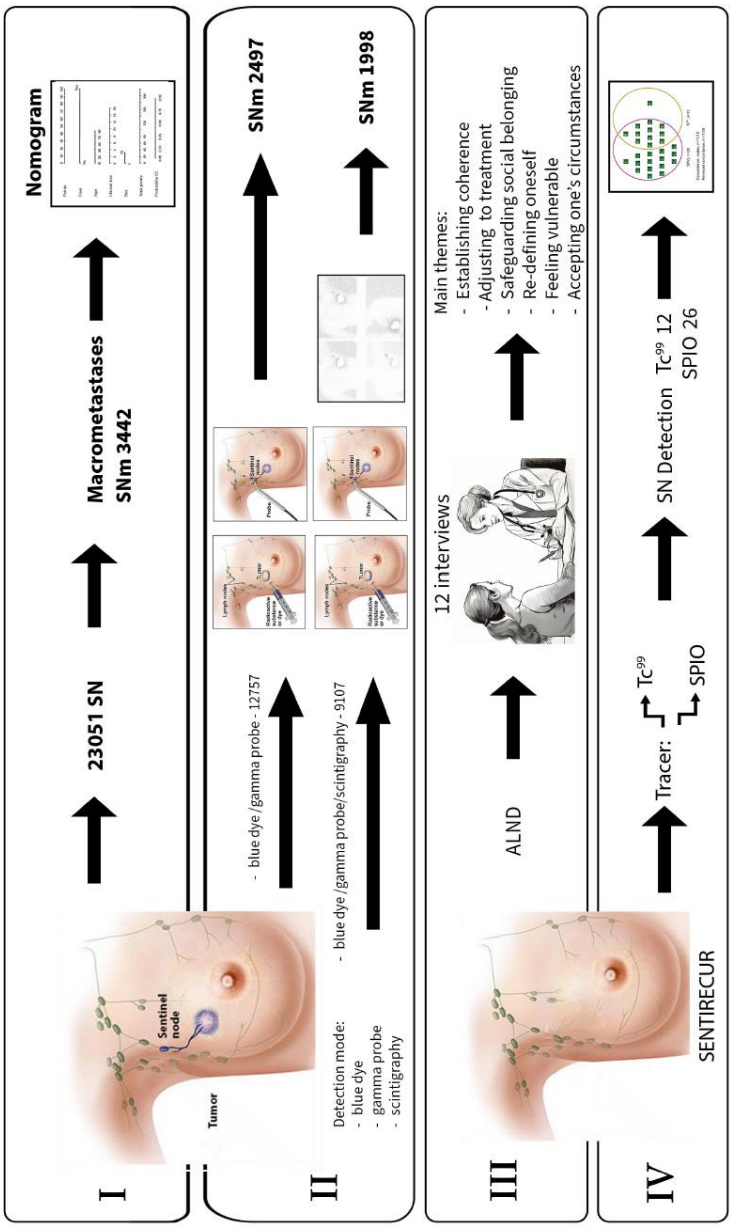
"Everything we hear is an opinion, not a fact. Everything we see is a perspective, not the truth."

– Marcus Aurelius , Meditations

THESIS AT A GLANCE



INTRODUCTION

Breast cancer (BC) is the most common cancer for women in Sweden. In 2023 nearly 8,900 women were diagnosed with BC [1]. Globally there were 2.3 million BC diagnoses and 670,000 deaths due to BC in 2022 [2]. In western society one out of every 10 women aged over 75 years has or has had BC. The prognosis after BC is very good. Nine out of ten women survive their disease [1]. The high survival rate is due to several factors. Early detection through our Swedish national surveillance programme with mammography monitoring of all women aged between 40-74 years every two years is successful in combination with awareness of the disease and effective adjuvant treatment [3]. The diagnostic workup for BC is mammography of the breast, ultrasound of the breast and the axilla, biopsy of the tumour and suspicious pathological nodes, as well as a clinical examination of the patient [4].

The primary treatment for BC is surgery, either a mastectomy where all the breast tissue is excised or breast-conserving surgery (BCS) where the tumour is removed with clear margins. At the time of surgery, the axillary lymph nodes are examined for metastasis. This is the most important prognostic factor and staging tool for further planning of adjuvant treatment [5]. Initially axillary surgery was therapeutic and all the lymph nodes were removed, axillary lymph node dissection (ALND) [6]. This procedure is accompanied by intrinsic morbidity such as lymphedema in the arm, pain, reduced shoulder movement and numbness [7].
Therefore, the minimal invasive sentinel node biopsy (SNB) procedure was introduced in the 1990s. Developing the technique and combining it with blue dye, radioisotope (Tc^{99}) and scintigraphy images led to the current standard technique for SNB and staging of the axilla [8].
This resulted in less radical axillary treatment and is now an accepted intervention for a clinically node negative axilla in BC surgery [9], [10].

After surgery most patients undergo some form of systemic treatment depending on the tumour characteristics and axillary nodes status, with or without metastases. The oncological treatment consists of endocrine treatment, radiotherapy and chemotherapy. Endocrine treatment comprises tamoxifen and aromatase inhibitors for hormone receptor positive tumours in 80% of the BC patient population. This treatment improves survival and considerably reduces the risk of invasive cancer recurrence [11]. However, it also entails known adverse effects such as hot flushes due to the low levels of oestrogen [12]. After BCS radiotherapy is provided to the breast and also the axillae depending on the sentinel node (SN) status, which improves sur-

vival [13]. In elderly individuals with favourable tumour characteristics irradiation can be omitted [14]. Furthermore, chemotherapy is added both as an adjuvant and neoadjuvant therapy in unfavourable clinicopathological tumour settings [4, 15]. Chemotherapy kills all fast-dividing cells such as cancer, hair, skin and gastrointestinal (GI) tract cells, and therefore comes with severe side effects. However, it reduces mortality rates by 40% in the first 10 years after early BC diagnosis [15] [16]. Patients face a challenging treatment trajectory and are in need of coherence, acceptance and adjustments while coping with the uncertainties. Healthcare staff members are important for helping patients create structure and make sense of the situation, which leads to self-efficacy instead of uncertainty[17]. Without such help, patients become lost in their own meaning-making of the treatment and symptoms they experience. There is an urgent need for more person-centred care to help patients adjust to their new situation [18, 19].

When planning further treatment the most important prognostic factor in BC is the status of the lymph nodes in the axilla. Unfortunately, surgery in the axilla is associated with significant arm morbidity. Thus, there is an urgent need to deescalate axillary surgery. This thesis investigates how to perform safe oncological surgery with as little harm as possible and what going through the BC treatment trajectory and axillary surgery means to the women concerned.

BACKGROUND

Perspective and viewpoints

Medicine and surgery have gone through an incredible development during the last century but it has unfortunately also led to an objectification of the human body within healthcare, as well as a focus on the biological material or anatomical construction rather than the person with a body, soul and spirit. One consequence of this is that what can be measured objectively is perceived as valid and a person's perception less so. My viewpoint in this thesis is that there is a need to combine positivism and humanism in a just way in order to treat the woman with BC as whole person and not merely biological material [20]. Thus, the focus in this thesis is the person with BC and not the BC in the person. The foundation for this assumption is the person-centred approach, emanating from Paul Ricœur's philosophy, which is an action ethic that recognizes the person, i.e. the woman with BC, as a capable being who can speak, act, narrate and assume responsibility [21].

In this thesis both quantitative and qualitative research methods were used, with knowledge developed through inductive and deductive approaches. Using a deductive approach enabled testing of hypothesis, where

the aim of a hypothetical - deductive approach is to test or statistically demonstrate whether a certain assumption is correct. The hermeneutic research tradition constituted the starting point when the inductive approach was used, which allowed interpretation and understanding of what it means to be a woman subjected undergoing BC treatment by means of ALND.

Treatment for BC involves three major entities, the woman, the breast and the treatment. Thus, the background will focus on these three parts starting with the woman, i.e. the person subjected with cancer in her breast.

The role of the woman

Being a woman involves many different roles. At various stages of their lives most women are a partner, life giver, mother, daughter, sister, friend and colleague. Some of these roles have changed over time in society, from being the rock and main caretaker of the home and family to also having one's own career. In society there are stereotypical conceptions about the female body and particularly the breast. The breasts are an attribute of femininity and sexuality. In the maternity context the breasts act as a food station, providing attachment and comfort. When subjected to BC the body image is altered and the symbolic nature of the breast, associated with social understandings of femininity, attractiveness, sexuality and mothering, is questioned [22]. A woman's body is expected to look a certain way due to societal norms. When subjected to potential trauma resulting from BC and its treatment, the whole self-perception might be altered. Women fear losing their attractiveness and desirability when a breast is altered. There is also a fear of losing their partner due to no longer being attractive [22].

The female body and health

A woman's health is a concern for all her relations as she is a daughter, sister, mother and spouse. Her partner, children and friends are all involved. Due to the altered embodiment of being a woman there is a need for directed psychological support. The female identity is challenged when the body is altered due to BC [23]. The bodily changes inherent in BC treatment affect the realm of being a woman and all the woman's relationships as well as herself [24]. The body is not only an object but a subject who is experienced and lived [25]. The breast is a feature strongly associated with sexuality and attractiveness, and BC poses a distinct threat to the woman's body image [26]. In particular, young women need to understand the short and long-term effect of extensive surgery due to the negative impact on body image [27].

Significant others are important for defining women's mental and physical self. Mental health is affected when diagnosed with BC. Who am I as a woman now? The relationships are more strongly affected in BC than in

other cancers due to the woman's different roles and the central role the breast has in her life [28, 29]. When a woman's health is affected, it has a major effect on all her contacts. The woman's health issues shake the foundation of being a woman [29]. The impact on the women's psychological well-being and feelings of being whole is complex and important to understand. The altered body leads to changes in the subjective being. It is thus important to guide women during their treatment to support their transition through the BC trajectory [30].
There is an perceived loss of femininity when undergoing mastectomy versus breast conserving surgery where only part of the breast is removed leading to a higher quality of life due to preserved body image [31]. Chemotherapy induced hair loss is also experienced as a loss of womanhood [24], [25].

The body is at the centre of our being and who we are, as it contains the soul and the dignity of being a person. When BC is diagnosed it is important for healthcare professionals to understand that this affects the woman profoundly not only physically, but both mentally and spiritually. The body is personal and we cannot divide the soul from the body and the soul cannot be separated from it. Thus, when the body is affected by disease the human cannot feel whole [32]. As human beings, we are always concerned about our appearance and come to terms and need to accept an altered body image, e.g. hair loss due to chemotherapy.

The breast as an anatomical construction

The breast consists of fatty and glandular tissue suspended by the fascial-ligamentous system. The volume of this tissue determines the shape and size of the breast. The glandular tissue consists of 15-20 lobules. Each lobule has its own duct with orifices on the top of the nipple [33]. The breast is located on the chest wall and posteriorly connected to the fascia of the pectoralis major and serratus anterior [34]. The lymphatic drainage of the breast is provided by a superficial network, a dense network underneath the nipple and a posterior plexus located in the pectoral fascia. The main drainage is into the axilla, responsible for 75% of the breast drainage. According to Berg [35], the axilla is divided into three levels, level one lateral to the pectoralis minor, level two behind the muscle and level three medially of the muscle. It is important to understand the location of the nodes in relation to the muscle at the time of surgery and radiation of the nodes. The remaining 25% of drainage is towards the deep internal mammary chain, which is important to note in previous axillary surgery.

Risk factors for developing breast cancer

Many risk factors for developing BC are linked to the female oestrogen levels. The risk is increased by early menarche, late menopause and obesity in postmenopausal women [36]. Prospective studies have shown that high concentrations of endogenous oestradiol are associated with an increase in risk. Childbearing reduces the risk, with greater protection for an early first birth and a larger number of births; breastfeeding probably has a protective effect. Both oral contraceptives and hormonal therapy for menopause cause a small increase in the BC risk, which appears to diminish once use stops. Alcohol increases the risk, whereas physical activity is probably protective [4]. Mutations in certain genes greatly increase the risk of BC, but only account for a minority of cases. During their lifetime, 60% of women with BRCA1 and BRCA2 mutations will develop BC compared to 13% in the general population with a risk of BC. BRCA1 has a germline mutation and dominant predisposition for early-onset BC [37],[38],[39].

Different forms of tumours in the breast

Tumours of the breast are a heterogeneous group, divided according to origin, i.e. the different anatomical/histopathological structures of the breast. The two major tumours are from the ducts, ductal cancers, and from the lobes, lobular cancers. Tumours can be further divided into different subgroups according to their immunohistochemical output and molecular division depending on expressed genes, Luminal A, B, HER2 and triple negative, the latter categorizing depending on targeted therapy [40]. Ductal cancers account for 75% of cases and lobular for 10%. They differ in clinicopathological characteristics and response to systemic treatment [41, 42].

Historical perspective on breast cancer treatment

Women have battled against BC in all eras and centuries. In the painting by Rembrandt of his mistress Hendrickje Stoffels from 1654, the left breast is swollen and there is discoloration of the skin. She later passed away after a long illness. After seeing the painting in 1967 the Italian surgeon, T.C. Grecos, wrote in a medical journal that she must have suffered from BC. “What has Queen Atossa and Dr Jerri Nielsen in common despite being born 2500 years apart? Among many other differences they both suffered a lump in the breast and the fear that transcends time and space”, (Bathsheba’s Breast, James S. Olson). Breast cancer is one of the oldest maladies in history. There are many who share this sisterhood, but now it is no longer a deadly foe that a woman must battle alone [43].

Surgical technique in breast cancer treatment

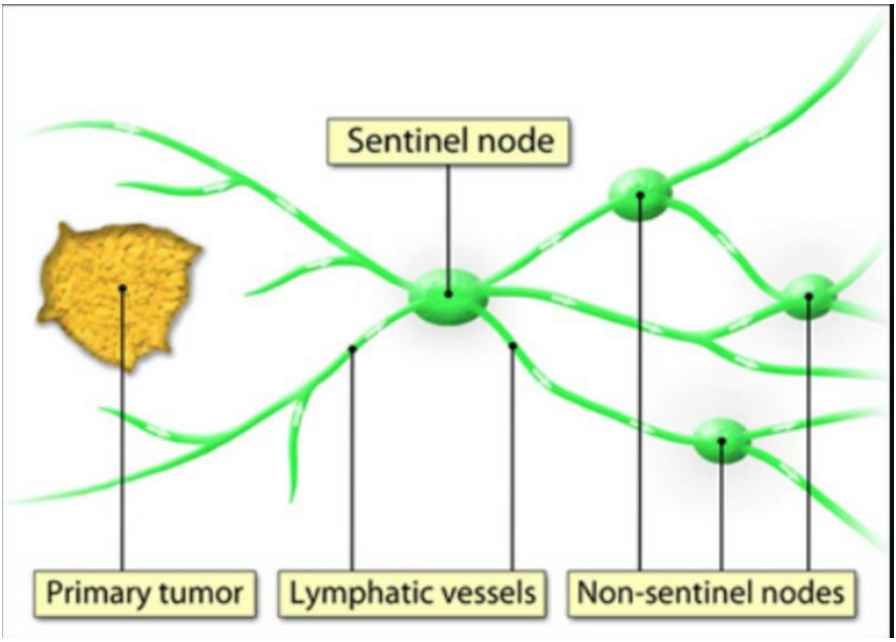
Breast Surgery

Halsted's theory of BC as a local disease spreading by contiguous extension resulted in the tradition of controlling the disease by means of mutilating mastectomy including removal en bloc of the pectoral muscle with the breast and axillary lymph nodes. This was the dominant technique until the late 1960s, when radiotherapy, systemic and hormonal treatment were developed [44]. Breast conserving surgery emerged in the Milan Cancer Institute with recruitment for a new procedure, quadrantectomy with postoperative radiation, which was found to have similar survival rates when compared to radical mastectomy [45].
This led to the present surgical intervention approach to BC. Today, BCS constitutes 80% of all BC surgery [46]. Due to unsatisfactory aesthetic outcomes after BCS and mastectomy, breast surgery has developed since the 1990s with oncoplastic techniques and reconstruction of the breast [47]. During recent years oncoplastic surgery has developed to minimize the change in appearance and loss of volume in the breast, by means of volume displacement, volume replacement and reduction techniques [48-50]. When using volume displacement, the remaining breast tissue is used to fill the space where the tumour was removed, volume replacement is moving tissue from outside the breast mound into the space where the tumour was removed. In this manner BCS integrates oncoplastic techniques and allows wider excisions without jeopardizing the aesthetic outcome and oncological safety.

Axillary surgery

At the time of breast surgery, the axillary lymph nodes are examined for the presence of metastasis. Axillary surgery has also gone through major changes since Halsted's procedure with the removal of all the axillary lymph nodes (ALND), leading to today's SNB [44]. The minimal invasive SNB procedure was introduced in the 1990s. The theory behind it is the step-wise pattern of tumour dissemination and lymphatic drainage identified by Halsted [51] and visualized by Cabanas [52]. Morton further investigated the technique in malignant melanoma using blue dye perioperatively for lymph node mapping and identification of the SN [53]. The blue dye acts as a tracer from the affected skin and follows the same lymph vessel as the metastases in an orderly manner, thus the SN harbour any deposits of metastases from the lesion. This minimally invasive procedure is an alternative to ALND for identifying nodes containing metastasis. When introduced in BC treatment, blue dye was administered in the breast before breast surgery, the SN was identified and a concomitant ALND performed [51].

Figure 1. The sentinel node theory.



With the permission from Rick Pleijhuis

Developing the technique and combining it with blue dye, radioisotope (Tc^{99}) and scintigraphy images led to the current standard technique for SNB and staging of the axilla [8, 54, 55]. Scintigram was used preoperatively for showing the number and the position of the nodes in the axilla to help the surgeon before surgery [53, 56] [57]. The method is precise with a reported false negative rate (FNR) of 6-8% and less than one percent axillary recurrence rates [58] [59]. This has led to less radical axillary treatment and is now an accepted treatment for a clinically negative axilla in BC surgery [10]. Furthermore, the clinically node negative patients have a positive SNB rate of less than 20% [60].
The need for ALND has also been questioned when 60 % of the nodes are not metastatic despite the positive SN [57]. ALND is not a therapeutic but a prognostic procedure accompanied by intrinsic morbidity such as lymphedema in the arm, pain, reduced shoulder movement and numbness [7]. The latest study by Boniface et al. shows that refraining from further axillary surgery when there is only a limited spread to the axilla is non-inferior to ALND when systemic adjuvant treatment is added [61].

Moreover, radioisotope comes with several drawbacks, i.e. limited availability, the need for a nuclear department, as well as radiation risk for the patient and healthcare professionals handling the isotope. Thus, there is a

need for other tracers such as the magnetic technique with superparamagnetic iron oxide (SPIO, Magtrace®; Endomag). This has been successfully implemented in SN surgery during recent years [62, 63].

Systemic treatment

The main aim of systemic treatment is to handle any microdeposits after surgery, either locally or at distant locations, and in so doing reduce the risk of recurrence and improve survival [11]. The choice of therapy depends on the sub-type of BC, based on immunohistochemical properties, Luminal A, B, HER2 positive and triple-negative [40].

Chemotherapy

The planning of the appropriate systemic treatment is based on the tumour characteristics and status of the axillary nodes. The immunohistochemical markers of the tumour such as the estrogen receptor (ER), progesterone receptor (PR), Ki67 (marker for cell proliferation) and human epidermal growth factor receptor (HER2) play a key role in subtyping the different tumours and their risks. Chemotherapy consists of cytotoxic drugs that kill all rapidly dividing cells such as cancer cells. It is intended for the treatment of micro-metastatic disease where it prevents relapse and death [64].
The most common regime is an anthracycline and taxane based one that reduces BC mortality by 40% during the first decade after diagnosis in early BC [15]. Chemotherapy is mostly administered postoperatively but in certain tumour subtypes such as HER2 positive and triple-negative BC (TNBC) it can be administered neoadjuvantly [16].
Well established targeted therapy for HER2 positive tumour are anti-HER2 antibodies in combination with chemotherapy[65].

Radiation therapy

Radiation therapy is recommended for all patients undergoing BCS on the residual mammary gland. It reduces local relapse and BC specific mortality, especially in high-risk patients [13]. In several randomized studies it was found that patients undergoing radiation after BCS have comparable long-term survival rates to those who had a mastectomy [13, 66, 67]. In a study by Boniface et al showing BCS with radiation has superiority over mastectomy in terms of overall and BC specific relative survival [68]. Node positive patients, mastectomy patients with larger tumours and locally advanced cancer also receive locoregional radiotherapy [69, 70]. Today, radiotherapy is also undergoing great changes due to the combination of other effective systemic treatments [71].

Endocrine therapy

Endocrine treatment is administered to all hormone receptor positive BC, which constitutes 80% of the BC patient population. It mainly consists of tamoxifen and aromatase inhibitors. The treatment improves survival and considerably reduces the risk of invasive cancer recurrence [11].

RATIONALE

For persons diagnosed with BC, axillary lymph node status is the most significant individual prognostic factor and facilitates treatment decisions. In the event of cancer recurrence in the breast, SNB is usually recommended if the patient is clinically node negative. As it has been clinically debated whether all BC patients with SN metastasis, SNm, need ALND, models for predicting non-SN metastasis, non-SNm, would probably be clinically beneficial.

Therefore, the first aim (Paper I) was to identify clinical markers to predict the presence of non-SNm. Identification of patients with SNm at low risk of non-SNm is essential to avoid unnecessary ALND and subsequently protect vulnerable women undergoing cancer treatment from needless complications. To further refine the diagnostic toolbox, preoperative mapping of the SN with scintigraphy has been shown to increase the chance of finding a new SN, especially if it is aberrantly located.

Thus, the second aim in this thesis (Paper II) was to evaluate the possible differences in SNB outcome between the use and non-use of preoperative scintigraphy from a large dataset of SNB operations. However, there are shortcomings associated with scintigraphy such as the need for a nuclear medicine department, issues with the availability of the SN tracer Tc99 and radiation exposure to healthcare professionals and patients. Additionally, as the half-life of Tc99 is only 6.1 hours, the surgery must be performed close to the time of Tc99 injection which involves logistical challenges. To meet these challenges a new SN localization technique has been proposed, using SPIO as the SN tracer and magnetic resonance imaging (MRI) of the axillae after the local SPIO injection for SN mapping.

The third study (Paper IV) was designed with a two-fold aim, i.e. to evaluate the feasibility of using SPIO in combination with MRI of the axillae for preoperative lymph node mapping and the magnetic probe to localize the SNs perioperatively in patients with BC recurrence after previous axillary surgery. The second aim to investigate if same lymph nodes were detected with the magnetic method compared to the standard method. It is essential to identify the methods with the greatest diagnostic value to save time and reduce suffering among the women concerned, preferably by moving away from radioactivity and scintigraphy.

The endeavour to tease out the most optimal diagnostic methods is based on concern for the vulnerable person in need of BC treatment and subjected to a three fold disadvantage inherent in being a patient. All Swedish healthcare is expected to be person-centred. However, there is a significant knowledge gap regarding the experiences and preferences involved

in BC treatment from the patient perspective as the lived experience of women undergoing axillary procedures as part of their BC treatment is unexplored.

Subsequently the fourth aim (Paper III) was to explore the lived experiences of women undergoing axillary lymph node dissection due to BC. There is a need for a paradigm shift in surgical care from viewing women with BC as anatomical constructions in need of repair to deeply understanding that they are persons with an illness who require ongoing self-management support. The current lack of in-depth understanding of the women's health situation during BC treatment could hamper implementation of person-centred care, which is a concern as BC is the most common form of cancer in women.

AIM

The overall aim was to minimize unnecessary suffering from axillary surgery by identifying factors for predicting non-SNm, investigating different methods for SN detection in the primary and recurrence setting in BC and exploring patients' trajectory through BC treatment including axillary surgery.

Specific aims for each paper

Paper I

To identify clinical markers to predict the presence of non-SNm in patients with SNm.

Paper II

To compare the two methods, radionuclide/blu dye/scintigram and radionuclide/blue dye, in terms of their ability in detecting SN metastases.

Paper III

To explore the lived experiences of women undergoing ALND due to BC.

Paper IV

To evaluate the feasibility of using SPIO in combination with MRI of the axillae for preoperative lymph node mapping and the magnetic probe to localize the SN perioperatively in patients with a BC recurrence and having had previous axillary surgery. The secondary aim was to investigate if same lymph nodes were detected with the magnetic method, compared to the standard method of using Tc^{99} in combination with lymphoscintigraphy and a gamma-probe.

METHOD

Table 1. Presents an overview of the design and methods of the included papers.

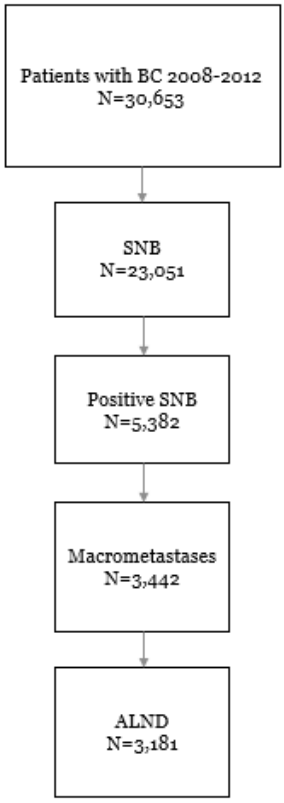
Paper	Design	Data Source	Study objective	Data analysis
I	Retrospective cohort study	Data from the NKBC.	To find predictive factors for non-SN metastasis in BC patients.	Pearson's Chi^2 test, Multivariable Logistic Regression analyses, ROC curve, OR and nomogram for predicting non-SN metastases in BC patients with positive SN.
II	Retrospective cohort study	Data from the NKBC.	To investigate whether scintigraphy improves the SN detection rate in BC patients.	Descriptive data, comparing the outcome of variabels with Pearson's Chi^2 test and means with the t-test.
III	Qualitative study	Narratives from patients with BC who had undergone an ALND.	To understand the lived experience of women going undergoing the BC treatment trajectory.	Phenomenologic hermeneutic approach.
IV	Feasibility study	Patients with BC recurrence and earlier axillary surgery invited to participate from two BC units in Sweden (Sahlgrenska and Linköping University Hospital).	Conduct an investigation to determine whether SPIO and MRI could identify SN detection in the recurrent setting of BC and earlier axillary surgery.	Descriptive statistics, percentage and medians with interquartile ranges. Fisher test comparing proportions, significance levels of 0.05. No power calculations as no hypothesis testing was conducted.

PARTICIPANTS

Papers I and II

In Papers I and II a dataset from the National Quality Register for Breast Cancer (NKBC) was included dating from January 2008 to May 2012. All participants (n= 30,653) had invasive cancer and/or ductal carcinoma in situ (DCIS), out of which SN was conducted in 23,051 patients. A further 3,181 patients had macrometastases in the SN and an ALND was performed. These patients constituted the study cohort on which the statistical analyses were based (Figure 2).

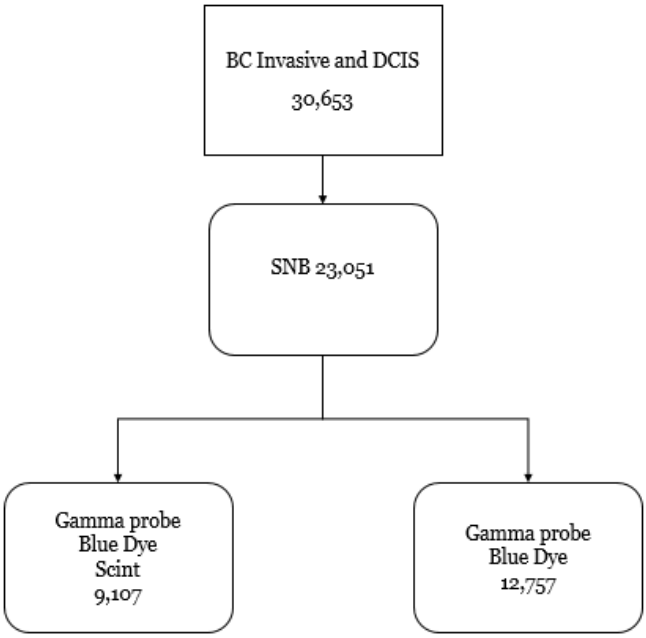
Figure 2. Consort diagram Paper I.



NKBC, a national quality breast cancer register in Sweden with a 99 % coverage for BC. It collects information about new BC, oncologic treatment and postoperative care.

In Paper II the participants included 22,167 out of the 23,051 patients for whom the register contained information about the detection technique. At the time of the study radioisotope was the conventional tracer for SN. The material was divided into two groups of SN detection methods: Scintigraphy/gamma probe and blue dye in 9,107 patients and gamma probe and blue dye in 12,757 patients, (Figure 3). After May 2012 the detection technique mode was no longer documented in the NKBC.

Figure 3. Consort diagram Paper II.



Paper III

The participants included patients who underwent axillary surgery at the breast clinic at the University hospital Linköping but were not operated on by the researcher. Inclusion took place between spring 2021 and early summer 2022. They were purposefully selected from the breast clinic register of patients who had undergone ALND from 6 months up to 6 years before

the start of the study. Purposeful selection ensured a range of age and time from ALND to the data collection. Exclusion criteria were distant metastases, younger than 18 years, cognitive impairment, unable to understand the Swedish language and other ongoing cancer treatment.

The researcher phoned the patients and asked if they wanted to participate in the study. Twelve patients accepted the invitation and received a letter asking them to sign a written consent form (Table 2). The interviews were performed etiher by phone or at a location suggested by the patient during the Covid-19 pandemic.

Table 2. Characteristics of the 12 participants in the study

Mean age (range)	59 years (34-74 years)
Mean time from axillary surgery to interview (range)	3.91 years (2-6 years)
Vocational status (n): Working Retired	 6 6
Marital status (n): Married/cohabitating. Single	 9 3
Antihormone therapy (n): Yes No	 11 1

Paper IV

Consecutive patients who were diagnosed with BC recurrence, both invasive and DCIS, and previous axillary surgery were eligible for the study. Exclusion criteria were women younger than 18 years of age, not planned for a SN, pregnant women, women with regional and distant metastases and

patients with MRI contraindications or Iron overload disease. The study was conducted at two University Hospitals, namely Sahlgrenska University hospital, Gothenburg and Linköping University Hospital, Linköping, from April 2022 to June 2023. A total of 30 patients were included, of whom 22 received both SPIO and Tc99 and were included in the final analyses. At the time of the study there was a shortage of Tc99 and therefore not everyone received both tracers.

DATA COLLECTION AND ANALYSES

Paper I

The key research question in study one was how to predict non-SNm to avoid unnecessary ALND. Biological factors that were available after primary breast surgery were extracted from the register and analyzed. To explore the association between the effect of categorical variabels on the outcome of a dicotomos result, the presence of non-SNm or not, the Pearson Chi-Square test was used. The purpose of the test is to examine whether a difference between the observed and expected data is due to chance or to a relationship between the variabels. It compares the actual counts in the cross-table with what would have been expected if the null hypothesis had been true, i.e. no association between exposure and outcome. The level of significance was set to $p<0.05$.

Variables that had a significant correlation with the presence of non-SNm were included in a logistic regression analysis to calculate a non-SNm (P^{risk}) risk value for each patient. Logistic regression calculations are a robust way to establish the effect of different variables on a dichotomous outcome, i.e. associated with non SNm or not. This is especially relevant when the question concerns whether or not are there more metastases in the axilla than those in the SN [72], [73]. The logistic regression model evaluated the impact of different independent variables such as tumour size, proportion of SNms detected at SNB, lymphovascular invasion (LVI), ER, HER2, multifocality and the Nottingham Histological Grade (NHG) on the dependent variable non-SNm or not.

The impact of each of the regression coefficients from the logistic regression model was illustrated graphically in a nomogram with the user-contributed nomolog for Stata program [74]. The statistical explanation of a nomogram is a graphical illustration of a mathematical formula.

In logistic regression, the exponentiated regression coefficients represents the odds ratio (OR). OR is used to determine a variabel's prediction of an outcome and compare the significance of different risk variabels [75].

A score factor proportional to the regression coefficients was allocated to each risk value included in the multivariable logistic regression model. By so doing, a straightforward method of predicting and visulazing the probability of non-SNm on a scale was provided by means of a scoring system for easily calculating a patient's risk of non-SNms [74].

Receiver operating characteristic (ROC) curves were used to evaluate the discriminatory ability of the regression model in predicting non-SN metastases. A ROC is frequently used to estimate classifiers performance, a curve with 1-specificity/false positive on the x-axis and sensitivity/true positives on the y-axis plotted at different cut-offs [76]. The area under the curve (AUC) is a measurement of the test's discrimination given a certain cut-off, depending on the test's sensitivity and specificity. Calculations were made with the IBM SPSS Statistics 22.

Paper II

Sentinel node detection at the time of the study was performed with radisotope, Tc99. The radioactive substance was used as an SN tracer with the addition of blue dye. The radisotope was injected into the breast, near the areola, either the afternoon before or the morning of the day of the planned surgery. When scintigraphy was done, dynamic images with gamma detection cameras were retrieved preoperatively. The detection modes were divided into two groups scintigram/gamma probe/blue dye and gamma probe/blue dye.

Data were collected for the methods used for SN detection; the number of SN retrieved per detection mode during surgery. The pathologic report was obtained and the number of metastases if present was registered (micrometastases is 0.2- 2.0 mm and a macrometastases is >2.0 mm [77]). A positive SN both micro and macro metastases went for ALND as per the guidelines at the time for the study.

Computations of association between the detection mode and the size of the tumour and finally the number of SNm and non-SNm after ALND were performed. The Pearson chi-square test was used to compare the association between the groups and the outcome of the SN, SNm and non-SNm at a significance level of $p<0.05$. The T-test was applied to compare means between the groups. Calculations were done with the IBM SPSS Statistics 22.

Paper III

Research that deals with experiences, perceptions and meaning making is qualitative, where the purpose is to obtain an in depth understanding of human experiences of a specific occurrence from an inside perspective [78]. In this qualitative study the focus was the experience of axillary surgery due to BC. By performing interviews, we explored the lived experience of women who had all axillary lymph nodes removed. The data comprises the women's narratives instead of second-hand information from healthcare professionals. The motive is to understand the meaning of being subjected to ALND by letting the women tell their story [79]. The interviews were transcribed verbatim and analysed by a phenomenological hermeneutical method developed by Lindseth and Norberg [80]. The hermeneutic tradition of interpreting text has been described by Ricoeur [81] in addition to the phenomenological part described by Husserl, leading to the elucidation of essential meaning. When we gain the women's inside perspective [82] it is possible to grasp their personal understanding of the BC trajectory and view the treatment, in particular ALND, in terms of consequences for daily life and interpret its meanings.

I interviewed twelve patients using an interview guide with open-ended questions.

The analysis of the transcripts was performed in three steps. First the patients' narratives were read several times. This so-called naïve reading creates an understanding as a primary conjecture, which then confirmed or not in relation to the subsequent structural analysis. In the second step, the structural analysis, the text was divided into meaning units and sorted into subthemes and themes. The themes were compared with the naïve understanding for confirmation. During the third step the text was read including the themes where the findings were interpreted and presented in a comprehensive understanding. The lived experience of the women was thus presented as interpreted by the researchers. During the analysis process the interviewer and the supervisors, who are qualified qualitative researchers, triangulated the data and discussed the themes and quotations to answer the research question.

Paper IV

The fourth paper reports a prospective feasibility study comparing SN identification between two tracers, a conventional radioisotope and a recently added SPIO. We used descriptive data, presented as numbers with percentages and medians with interquartile ranges. For comparing proportions the

Fisher test was used, with a significance level set at $p<0.05$. In a CRF (Appendix 1) the data entries were reported and percentages calculated for the number of nodes seen on MRI/scintigraphy, identified nodes perioperatively per patient and method as well as number of nodes retrieved per the two methods. The MRI of the axillae was performed according to a specific MRI protocol (Appendix 2) Additional calculations of concordance were made, defined as the total number of nodes identified by SPIO and radioisotope divided by the number of nodes identified by radioisotope (irrespective of SPIO). Reversed concordance was defined as the number of lymphnodes detected with both SPIO and radioisotope divided by the total number of nodes detected by SPIO.

The tracers were injected into the breast or near the recurrence on the thoracic wall. SPIO was injected a few weeks before the visit to the out-patient clinic and MRI images generated. Radioisotope was administered the afternoon before or the morning of surgery and scintigraphy images were retriewed/added. The surgeon had access to the MRI and scintigraphy images before surgery. Data about the detection rates of the two different methods and the number of nodes retrieved were registered during the surgery. The retrieved nodes were analysed by the pathologist and compared with the registered data perioperatively.

ETHICAL CONSIDERATIONS

All studies were approved by the Swedish Ethical Review authority. In Studies I and II data extraction from the National Quality Register for Breast cancer (NKBC) was approved from their steering committee as well as the Swedish Ethical Review authority (Dnr 2020-06061). Study III was also approved (Dnr 2021-01571). Study IV were granted approval (Dnr 2021-06668-02), which is an amendment to the ethical application for the Mag US trial Dnr 2016/385. All studies conform to the ethical principles for medical research involving human subjects as defined in the Declaration of Helsinki (WMA 2013) and Swedish research ethics legislation (SFS 2003:460).

RESULTS

Predicting non-Sentinel node metastasis

Important variables for the prediction of non-SNm in BC surgery are the proportion of SNm detected at SNB, tumour size, LVI, HER2 and multifocality. In our data there were 23,501 patients who had a SN performed. The mean number of nodes removed at the time of SNB was two, as seen in the literature [83]. Fewer nodes were removed in older patients and those detected with mammography ($p<0.001$).

Of these 23,051 patients, 5,382 had a positive SN (23%), 3,442 (64%) of whom had macrometastases. Not all patients with metastases underwent ALND but the reason was not documented in the register. A total of 3,181 patients with macrometastases revealed by SNB underwent ALND, where 41 % of the cancers were detected by mammography. In total, 3,181 patients (92%) underwent ALND and 1,263 (39.7%) had non-SNm. When comparing variables present after primary breast surgery and their association with the presence of non-SNm, the results showed that the proportion of SNm detected by SNB, tumour size, LVI, multifocallity, NHG and immunoreceptors such as HER2 and ER were statistically significant.

Presented here are the results found to be associated with non-SNm in ALND in relation to tumour size; >20 mm in 47% compared to ≤20 mm in 32% ($p=0.001$). Furthermore, when the number of SNm at SNB was one, non-SNm were found in 34% compared to ≥3 in 63% ($p=0.001$) and if the proportion of SNm at SNB was <0.5, non-SNm were found in 26% and 3/3 or more in 71% ($p=0.001$). In addition, LVI, HER2 positivity and NHG were also highly significant for non-SNm (Table 3).

Table 3. Presence of non-SNm related to biological and clinical data in patients with SNm.

	Patients with non-SN metastases, N (%)		
	No	**Yes**	**P value[b]**
Sex			
Female	1901 (60)	1253 (40)	0.78
Male	17 (63)	10 (37)	
Tumour size (mm)			
≤ 20	1033 (68)	488 (32)	< 0.001
> 20	861 (53)	763 (47)	
Unknown	24	12	
No. of SN with macrometastases			
1	1498 (66)	778 (34)	< 0.001
2	329 (50)	328 (50)	
≥ 3	91 (37)	157 (63)	
Proportion of SN with macrometastases			
< 0.5	464 (74)	161 (26)	< 0.001
0.5 – 0.99	683 (66)	345 (34)	
1 of 1	562 (56)	436 (44)	
2 of 2	156 (43)	206 (57)	
3 of 3 or more	45 (29)	111 (71)	
Unknown	8	4	
LVI			
No	1154 (65)	633 (35)	< 0.001
Yes	406 (49)	425 (51)	
Unknown	358	205	
Nottingham Histologic Grade			
NHG I	293 (68)	135 (32)	< 0.001
NHG II	1044 (60)	689 (40)	
NHG III	557(56)	430 (44)	
Unknown	24	9	
ER			
Negative	196 (55)	159 (45)	0.042
Positive	1699 (61)	1094 (39)	
Unknown	23	10	
HER2			
Negative	1540 (61)	983 (39)	0.004
Positive	222 (54)	192 (46)	
Unknown	156	88	
Multifocality			
No	1473 (62)	886 (38)	< 0.001
Yes	277 (52)	251 (48)	
Unknown	168	126	
Mammography detected			
No	1102 (59)	762 (41)	0.08
Yes	810 (62)	492 (38)	
Unknown	6	9	
Age			
<40	91 (57)	68 (43)	
40-49	342 (60)	226 (40)	
50-59	469 (62)	292 (38)	
60-69	564 (61)	365 (39)	
70-79	304 (59)	207 (41)	
≥80	139 (58)	99 (42)	0.88
Unknown	9	6	

ER= Estrogen receptor; HER2= Human Epidermal Growth Factor Receptor 2; LVI= lymphovascular invasion; NHG= Nottingham Histologic Grade; SN= Sentinel node; [b]Pearson's chi-squared test

We also investigated the risk factors that are drivers for non-SNm and incorporated the statistically significant ones in a logistic regression model. All patients with complete data were included in the subsequent analyses, i.e. 2,139 patients. In the logistic regression model an OR for the different variables estimated the P^{risk} for every patient, showing a high OR for tumour size, HER2 positive tumours, LVI, multifocality and proportion of lymph nodes with macrometastasis at SNB. The regression coefficients were used in a nomogram for visualizing the probability of non-SN ms, using a STATA nomogram. A scoring system was developed where every variable was weighted in order of importance for causing non-SNms, as shown in the STATA nomogram.

The OR for tumour size, the proportion of SNm detected at SNB, LVI, NHG, multifocallity and immunoreceptors such as ER and HER2 is presented in Table 4.

Table 4. The logistic regression showing the OR for non-SNm
.

	OR	**95% CI**	**P value**
Tumour size (>20 mm vs. ≤ 20 mm)	1.70	1.41 - 2.05	< 0.001
HER2 (Pos. vs Neg.)	1.49	1.14 – 1.95	0.004
Lymphovascular invasion (Yes vs No)	1.63	1.34 – 1.97	< 0.001
ER (Pos. vs Neg.)	0.85	0.64 – 1.14	0.27
Multifocality (Yes vs No)	1.28	1.01 – 1.62	0.04
NHG (II & III vs. I)	1.15	0.86 – 1.53	0.34
Proportion of SNm at SNB			
Proportion 0.5–0.99 vs. Proportion <0.5	1.41	1.07 – 1.86	0.02
Proportion=1, with only one SN investigated vs Proportion <0.5	2.25	1.71 – 2.95	< 0.001
Proportion=1 with more than one SN investigated vs Proportion <0.5	3.75	2.73 – 5.15	< 0.001
Constant	0.21	0.14 – 0.33	< 0.001

Type of detection method used for identification of the Sentinel Node

In the second study we focused on the type of detection method used for SN identification and the outcome of identifying the SN, the number of SNm retrieved and the number of non-SNm. The same dataset as in Paper I was used, in which 23,051 patients underwent SN procedure. The detection mode was only documented in 22,167 of these patients. The two detection groups observed and studied were gamma probe/blue dye and scintigram/gamma probe/blue dye.

The group in which the gamma probe/blue dye was used included 12,757 patients, while 9,107 patients were in the scintigram/gamma probe/blue dye group. The two methods were used with the same frequency during the 4.5 years that the study took place. When viewing the comparisons between the groups in the tables it is clear that some data are missing.

There was a small difference between the groups related to tumour size. If the tumour size was ≤20mm, the distribution was 68.4% in the gamma probe/blue dye group and 72.6% in the scintigram group. If the tumour size was >20mm the distribution was 31.6% in the gamma probe/blue dye group and 27.4% in the scintigram/gamma probe/blue dye group ($p<0.001$).

The number of SNs removed during SNB was 2.12 in the scintigram group compared to 1.91 in the gamma probe/blue dye group, with a significance of $p<0.001$. The number of SNs found in SNB with the two different detection techniques is presented in Table 5. With a significance of $p<0.01$, please note that the total number is 21,458, due to missing data in the register. In 186 cases no SN were found.

Table 5. The number of sentinel node(s) extracted by the two detection methods with and without preoperative scintigraphy (sign. $p<0.01$).

Number of SN	1	2	3	≥4
Scintigram/probe/dye N=8,940	3,380 (37.5%)	2,793 (31.0%)	1,677 (18.6%)	1,090 (12.1%)
Probe/dye N=12,518	5,545 (43.9%)	4,021 (31.8%)	1,852 (14.7%)	1,100 (8.7%)

The outcome of positive SN, both micro- and macro-metastases, for the scintigram group was 21.9% (n=1,998) compared to 19.6% (n=2,497) in the gamma probe/blue dye group, p<0.001. The distribution of the number of SNm is shown in Table 6.

Table 6. The total number of SNm distributed for the two detection groups.

No of SNm	1	2	3	≥4
Scin-tigram/Probe/Dye	1,476 (73.9%)	378 (18.9%)	95 (4.8%)	49 (2.5%)
Probe/Dye	1,888 (75.6%)	459 (18.4%)	106 (4.2%)	44 (1.8%)

Patients with positive SN went on to further ALND as per guidelines at that time, showing a non-SNm distribution as per 33.5% (n=650) in the scintigram group and 31.4% (n=737) in the gamma probe/blue dye group, not statistically significant (p=0.13). According to the registry, not all who had SNm underwent ALND. Our results show a 2% higher detection rate for SNm and non-SNm when scintigram is added.

The experience of women undergoing ALND

To understand the experience of women subjected to BC treatment, patients who had undergone ALND were interviewed. The findings revealed two major aspects, i.e., acceptance and adaptation to life with cancer treatment. The main themes were establishing coherence, adjusting to treatment, safeguarding social belonging, redefining oneself, feeling vulnerable and accepting one's circumstances (Table 7). Below, each theme is illustrated by quotations, presented with kind permission from JPCRR • Volume 11, Issue 3 • Fall 2024.

Once diagnosed with BC the women tried to make sense of what had happened to them, through a process of sense making and meaning making to achieve a sense of coherence. When attempting to make sense of why this happened to them, they speculated and were sometimes lost in their own thoughts. If abandoned with their thoughts, they became uncertain and lonely in the absence of feed-back from credible authorities, i.e. healthcare professionals (HCPs).

Table 7. Main themes and sub-themes illustrating 12 women's experiences of BC treatment and ALND

Main themes	Sub-themes
Establishing coherence	Making sense. Making meaning. Mastering uncertainty.
Adjusting to treatment	Dealing with side-effects of hormonal treatment. Dealing with symptoms and complications after surgery.
Safeguarding social belonging	Protecting significant others from grief. Assisting friends and relatives in how to approach them.
Re-defining oneself	Comparing with previous health status. Comparing with others. Changing self-perception.
Feeling vulnerable	Mastering one's anxiety. Feeling abandoned by professional caregivers.
Accepting one's circumstances	Feeling embraced and cared for by professional caregivers. Feeling embraced and cared for by significant others. Feeling safe despite being far away.

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Establishing coherence.

"You simply must be cool in this situation. On one hand it is shit (the cancer), and on the other hand great that it hadn't spread to the axillary nodes. If there is no other way to find out, you simply must accept it."

Adjusting to treatment.

"You are sort of in a state of shock because of the things that are happening in your life. Not so easy to grasp the information you get".

Safeguarding social belonging

"I asked my husband if he wanted a wife with one breast or one with a reconstructed breast. It doesn't matter he said. So, I don't know if my close relationships are affected that much. I don't think my kids are bothered. The only thing is that they don't understand my frustration. You can't expect people to understand what you're going through. My best friends respect me and ask questions about my treatment. And I am not in a context where it matters to my friends whether I have one breast or two."

Redefining oneself

"I can't walk around identifying myself as `a BC patient´. I am so much more than that."

Feeling vulnerable

"I was anxious when I had pain and there was a lot of fluid. So, I visited the contact nurse. She measured the fluid, and it was a lot. Then she talked to the surgeon, and I had to keep the drainage tube for a few more days. And that was enough to give me distressing thoughts. You are vulnerable. I felt abnormal."

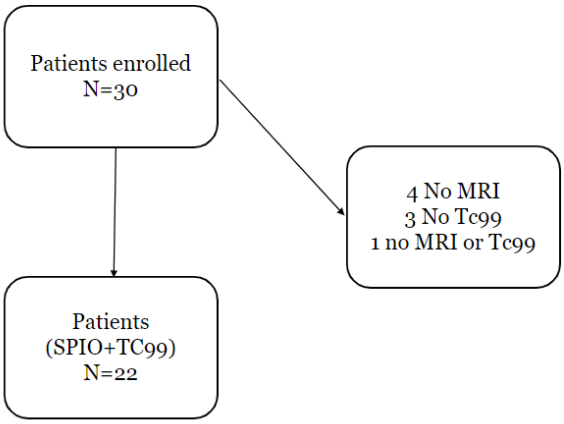
Accepting one´s circumstances

"When you have a question, one of the four contact nurses is always available"

The prospective feasibility study

In this study 30 patients were included, 28 from Sahlgrenska University Hospital in Gothenburg and two from the University Hospital in Linköping. Of these, 22 received both Tc^{99} and SPIO and images with scintigraphy and MRI were collected. The enrollment procedure is presented in Figure 4.

Figure 4. Workflow of patients eligible for inclusion in the study of lymph node mapping before surgery for breast cancer recurrence.



The identification rate per patient with SPIO and MRI was 16/22, while Tc^{99} and scintigraphy was 11/22. While significance was not achieved (p=0.2) there was a clinical difference of 23% in favour of SPIO/MRI. Perioperative identification per patient with SPIO and magnetic probe was 17/22 and Tc^{99} and gamma probe 11/22(p=0.06). Please see Table 8.

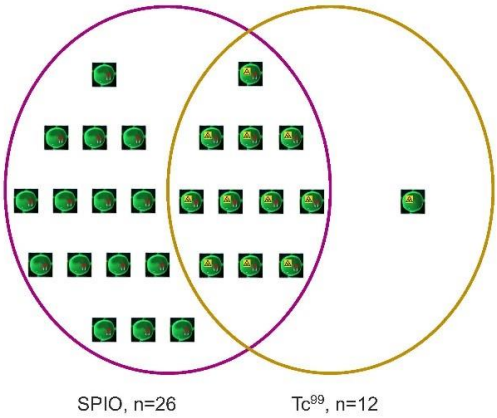
Table 8. Result of imaging and preoperative signalling, detection rate per patient with recurrence, receiving both SPIO and Tc^{99}.

	SPIO/MRI/Sentimag	Tc^{99}/Scint/Gamma-probe
Preoperative mapping	16/22 (73%)	11/22 (50%)
Perioperative signalling	17/22 (77%)	11/22 (50%)

Abbreviations: MRI = Magnetic resonance imaging, SPIO = Superparamagnetic iron oxide nanoparticles, Scint = scintigraphy, Tc^{99} = Technetium-99m

The median nodes identified with SPIO and Tc^{99} was one (IQR=1), SPIO with an average of 26/22 (1.18) identified with SPIO and with Tc^{99} 12/22 (0.55). The identification rate of the SNs retrieved with the different tracers was as follows: A total of 27 SN were identified and retrieved, 26/27 detected with SPIO and 12/27 with Tc^{99} (p= 0 (0.00003)). Concordance rates were calculated 11/12 (92%) and reversed concordance 11/26 (42%). There was only one SNm, which was detected by SPIO/MRI and SPIO/ magnetic probe. Figure 5.

Figure 5. Concordance Paper IV.



DISCUSSION

Discussion of the findings

The prevention of unnecessary ALND

The first study reveals important variables to take into account when planning further surgery in the axilla and adjuvant treatment. The ROC curve demonstrated the ability to discriminate and the area under the curve (AUC) was calculated, 0.68 with 95% CI 0.66-0.70. An AUC of one indicates perfect discrimination ability of the test, while an AUC of 0.5 is no better than chance.

It is vital to understand the drivers of non-SNm as it is valuable to know when to use ALND because it is accompanied with severe morbidity as shown in several studies. ALND is afflicted with serious complications such as lymphedema, reduced movement of the arm and nerve pain [7], [84], [85], [86]. Acute complications are not the only issue, but as shown by Appelgren et al. [87] long-term problems have a great impact on women's quality of life long after the BC treatment is finished. Axillary surgery has been questioned due to its morbidity there is a need to deescalate axillary surgery due to the better understanding of BC disease biology and in line with improved systemic therapies.

Going back to earlier discussions about the importance or necessity for axillary clearance, we need to understand its history. Originally, axillary clearance was a therapeutic procedure, a way of controlling the disease by removing overt and occult nodes. There has been a discussion among surgeons about the need or function of axillary interventions in BC. Removing nodes is not as therapeutic as historically believed. Current evidence highlights the fact that it is only for staging purpose, as regional lymph nodes are indicators but not instigators of distant disease [88].

Returning to the history of axillary surgery, a century after Halsted's extensive surgical technique, the SN made its way into the history of surgical development of axillary status [89]. Scientists now understood how the tumours' metastatic pattern spread in the lymphatic system. This is described in the literature in several studies. In 1987 Veronesi et al. [90] presented findings showing that the metastatic spread happens in an orderly manner,

very rarely skipping the first level in the axilla to the next. This happens in only 2% of cases as verified by Morton et al. [53] and Smith et al. [91].

This new understanding of the prognostic value of axillary lymph node involvement as a sign of distant disease led to a more conservative approach when reliable identification of the first node in the axilla, the sentinel node, developed. The era of the SN dawned and was developed by several institutions, starting with Morton using it in malignant melanoma [9, 92]. In addition, the introduction of mammography screening led to the detection of more women with node negative BC and eliminated the unnecessary removal of healthy lymph nodes.

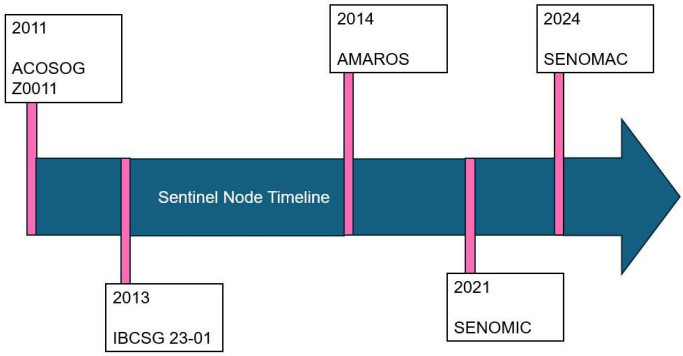
Furthermore, the introduction of modern systemic treatment and radiation reducing the need for extensive axillary surgery [93]. In Sweden, the proportion of BC detected by screening is estimated to be in the region of 60-70%, 60 % in the whole screening population and 70% in Östergötland [94]. Screening decreases death in BC by 16 % in the 40-49 year age group and 20% in the 50-74 year age group [94].

The evidence for axillary surgery suggests that axillary clearance is not always the most efficient way to treat the axilla. The development of effective treatment by means of radiation towards the axilla has been shown to be just as efficient, resulting in less severe side effects [95]. In addition, adjuvant chemotherapy is also effective in taking care of microscopic residual tumour traces in a far more efficient way than surgery [11].

Previous studies investigating the possibility of deescalating axillary surgery include ACOSOG Z0011, showing that if there are one or two SNm in an clinically node negative axilla that was planned for BCS and whole breast radiation, omitting further axillary surgery, ALND, does not diminish the outcome. A follow up 10 years later showed no need for ALND [96], [97]. In another study, the so-called AMAROS study, the positive SN patients were randomized for radiation therapy of the axilla or ALND, showing no difference in locoregional control, disease free survival or overall survival [95] [98]. Both these studies were underpowered and did not meet their endpoints, but after them ALND was less frequently used in clinically node negative axillae. Furthermore, in the IBCSG 2311 investigation of early BC and limited SN involvement, it was shown that further axillary surgery could be avoided in cases of SNm with 1-2 micrometastases.

A follow up 5 and 10 years later revealed that no further axillary surgery was needed for SN micrometastases [99], [100, 101].

Figure 6. Sentinel node timeline.



An international multi-centre study by Boniface et al. showed that for patients with limited spread to the axilla, i.e., not more than two macrometastases, no further axillary surgery was not inferior to the extensive axillary procedure ALND treatment when systemic treatment and radiation were added. The trial group wanted to validate earlier studies, hence only patients with macrometastses were eligible. Their recently published study presents strong evidence for the omission of ALND in clinically node negative axilla and SNm with not more than two macrometastases when adding systemic treatment [61].

Our study shows similar results that there is a lower risk of non-SNm when having up to two macrometastases and favourable tumour factors. Moreover, when looking at the result of ALND, the percentage of a further number of non-SNm is low, only 39.7%, meaning that 60.3% of patients were subjected to more harm than necessary. Stable results in earlier studies by Veronesi et al. confirm that when finding a positive SN at the first level in the axilla, further spread is only seen in 40% as also shown in our study [90]. Today, the SN is a well-established routine for determining the axillary status in clinically node negative axilla [102, 103]. There is a need to deescalate axillary surgery.

The aim should always be oncologically safe surgery and avoiding overtreatment in favour of a more personalized approach. The development of

surgical interventions to investigate the axilla and improved surgical techniques in the breast together with advanced personalized systemic treatment enables us to safely avoid ALND in patients with favourable tumour parameters.

In the SN identification endeavour scintigraphy is a procedure through which the lymphatic drainage is visualized. With scintigraphy, visualization of the lymph nodes by means of the injection of a radioactive tracer, colloidal proteins labelled with technetium-99m, accumulated in the lymph node by macrophages that are lymph-node as opposed to tumour seeking. Scintigrams are obtained via gamma camera images. Before surgery the surgeon can identify the position of the hot nodes in the patient. In an early attempt to visualize the lymphatic pathways in healthy breast tissue, an important study in 1972 showed that the axilla is not the only breast drainage basin. Here gold was used as a tracer [104].

The evolution of the SN identification technique was dependent on the availability of the necessary resources at the hospital and the stance of the available surgeons. It developed from the initial use of scintigraphy to adding blue dye in addition to ocular visualization of the lymph vessel to the node during surgery. The gamma probe was also added to enhance identification during surgery of the axilla [8], [51]. The different techniques have been used together, or in various combinations or alone [59], [105].

SN became a conventional treatment of the clinically node negative axilla in BC, with the SN visualized in 99% of cases where the false negative rate is 5% or less [106], [54], [10]. The NSABP B-32 trial showed an equivalent overall survival, disease free survival and regional control in node negative BC patients with only a SN done [107], [108]. Further studies demonstrated a good outcome, 0.3 % recurrence rate after node negative SN and no ALND [109]. The technique has a low false negative rate and low recurrence rate, especially when two or more nodes are removed during SNB [57], [110]. Overall, scintigraphy is an established technique and shows a more accurate number of “hot nodes”, as seen in our study. However, it is not certain that this is important today due to the assistance of the gamma probe in identifying the “hot nodes” during surgery and additional adequate systemic treatment for handling any microscopic disease [105].

There is an urgent need for tracers other than radioisotope due to the global shortage of molybdenum-99, which is used to generate Tc^{99} [111]. A nuclear medicine department is also necessary. Complicated legislation and restrictions regulate the handling and disposal of radioactive material. The

short half-life of radioisotope is also an issue, in addition to the possible risk for staff handling the radioisotope and the patients subjected to it.

The SPIO magnetic tracer, a superparamagnetic iron oxide combined with carboxydextran coating and mixed with injectable saline, offers the advantages of identifying nodes with a magnetometer, Sentimag® (Endomagnetics Inc, Cambridge, UK) and colouring the nodes. The SPIO can also be used during a longer time frame and handled by HCPs in the outpatient department [112]. With the global lack of radioisotope, problematic logistics and short half-life, hence the magnetic technique is filling the gap as a validated tracer for SN and a simplified technique in which we detect the SN in the most efficient manner as shown in Paper IV [113],[63], [114].

In the event of BC recurrence, a new SN can be aberrantly located due to earlier surgery and radiation. Prognostic factors for recurrence are disease-free interval, size of recurrence and primary nodal status, recurrence rates are approximately 20%, and in >70% there is a distant recurrence [115]. In such cases the repeat SN is more accurate in identifying any aberrantly located SN due to visualization with scintigraphy or MRI, thus an unnecessary ALND can be avoided. The Dutch study group, Sentinel Node and Recurrent Breast Cancer (SNARB), has shown that a repeat SN is manageable, success rate of 54%, other studies showing success rate 50-74%, depending on the different cohorts [116].[117] [118].

In 80% of cases with a clinically node negative axilla there is no further spread and the patients are spared an ALND with its negative side effects such as lymphedema and nerve pain [119].

In the recurrent setting, the initial need for a repeat SN was that it aids in systemic treatment decision making [119] as also seen in other studies showing that it might improve locoregional disease control, accurate prognostication and better survival [120]. The importance of regional lymph node staging in a clinically node negative axilla is debatable. When the prognosis depends on a disease-free interval, prognostic characteristics of the primary breast tumour biology and the recurrent tumour, restaging of the axilla is of limited value [120], [121]. Probably due to improved knowledge of tumour biology and enhanced systemic treatments the risk of regional recurrence after five years in an unsuccessful repeat SN was less than 5%. Hence in an unsuccessful repeat SN there is no need for further axillary surgery and restaging the axilla is of limited or no use in this setting [117].

The women's lived experience

Two major factors were important for women in the BC trajectory to achieve a sense of coherence and cope with uncertainty, i.e. feeling embraced by significant others and HCPs. As an HCP it is vital to be a part of the women's sense- and meaning-making. If not invited the HCP must take the initiative to listen to the patient's understanding. When doing so self-efficacy can be strengthened. The patient's sense of coherence, i.e. comprehensibility, manageability and meaningfulness, are important during the BC treatment process leading to self-efficacy [122]. Understanding and gaining self-efficacy helps the patients to make sense of the process, which facilitates the ongoing treatment [18].

The sense of coherence was introduced by Aaron Antonovsky as a part of salutogenesis promoting wellness as opposed to pathogenesis. During the BC treatment the patients are somewhere stuck between coherence and uncertainty and as HCPs we need to enable them to move forward. This can happen when piloting them from their positions in meaning- and sense-making as well as supporting their vital social relationships. To meet the psychosocial challenges they face, person-centred support should be implemented in the care [123].

When the patients find themselves in this vulnerable situation, they need to acknowledge the world as a manageable resource for living and in so doing gain coherence. To strengthen their management, they need comprehensible clarity where HCPs act as structure providers creating some sort of order in their treatment. When the HCP asks the patient about her concerns her needs can be met and her own coping resources enhanced. It all culminates in the patient experiencing the current situation as meaningful [122].

It is vital to understand what the patients comprehend. In the study by Fagerlin et al., it was revealed that despite both oral and written information patients still did not fully comprehend their situation due to the stressful situation of a life-threatening diagnosis and information sources outside the healthcare system [124]. When understanding the inside perspective of the women HCPs can reflect on their own perspective and understanding and interact with the women in a person-centred manner.

A systematic review examined the impact of ongoing symptoms on survivorship, including persistent pain, fatigue and weakness, feeling unwell, sleep difficulties, lymphoedema, impaired cognition (including 'chemobrain'), skin conditions, menopausal symptoms, sexual problems and

fertility issues [123]. The patients' perspective of going through BC treatment differed from the HCPs' objective understanding, leading to a more post positivistic paradigm of research [125]. The magnitude of the symptoms that can be experienced by women surviving BC must be fathomed by the healthcare system to do justice to all women who survive. Several issues must be addressed to facilitate women to survive and cope after BC treatment. Our findings illuminate some vital aspects in this context.

Methodological considerations

Nomograms can be a tool for supporting clinicians in decision-making pertaining to how to proceed with further treatment. The weakness of the nomogram is that it is good at predicting risk in the homogeneous population in which it was created but validation studies of heterogeneous groups or in other populations have not demonstrated similar success [126], [127]. The strength of our study is that the cohort is large and there is scope for predicting the risk of non-SNm and aiding clinical decision-making as seen in other studies [128]. At the time the study was conducted the guidelines indicated that when a SN exhibited metastases (micro- and macro-metastases) an ALND were planned and performed. Due to this fact we had the opportunity to investigate the association between SNm and non-SNm [129].

Scintigraphy is a validated procedure for detection of the SN, developed for the SN in BC during the 1990s. Studies show how the technique evolved from Morton et al. investigating it in patients with malignant melanoma [53] to Krag et al. using it in BC patients [8] together with Albertini et al. [130]. As an aid for identifying the nodes preoperatively a gamma probe was added to identify the nodes in the axilla during surgery. The need for scintigraphy has been questioned, as it is a costly and time-consuming procedure with complicated logistics. Moreover, it requires a nuclear department and the availability of the radioactive tracer is also an issue. As a result, it became obsolete when the gamma probe was an established as a peroperative routine [105].

When performing the qualitative study, the selection took place as purposive sampling. Thus, we deliberately selected participants based on their features/characteristics to enable a detailed exploration of objectives, gather rich, in-depth information and range of views and experience [78]. Inter-

views with open-ended questions enhance flexibility and enable the participant to freely express her understanding in her own words. During the interview it is important to listen to the participant's narrative and not interfere. During the interview the researcher is a part of the process, the subjective interpretation. This is a vital aspect but also difficult to balance [131]. In addition, when conducting a qualitative study the researcher has to consider prior assumptions and be aware of personal biases in relation to the data collected [132]. Another important element when conducting interviews is to record them, which is a robust way of collecting the data compared to taking notes [78].

One study limitation is that patients were only included from one institution and therefore few surgeons were involved in the surgery. Even fewer were available when the researcher's patients were excluded from the study. The research question was lived experience of women going through the BC trajectory, as we approached the matter in an inductive manner. The narratives involved reflections about life as a whole not solely the ALND procedure. As HCPs we tend to view our patients as an anatomical entity and here, we learned that patients could handle their trajectory if their needs are met. It is important that our health system is person-centred. The answer to the research question was much more profound than just "how do you feel after axillary surgery?".

During the data collection I reflected on my perspective as totally new to the qualitative research method including my understanding, prejudices and assumptions as a surgeon. I was well aware of the fact that "I am way out in deep water". An advantage was that the research group consisted of experienced supervisors in qualitative research. The interviewer was educated in the paradigm of positivism, which posed a challenge but with the guidance of qualified qualitative researchers the result became solid [133].

When adopting a qualitative research method or paradigm as a positivistic researcher you enter the world of wonder. The scientific approach enables the study of a phenomenon and the meaning our patients bring to that. Their understanding is a mix of human interpretation, culture, context and language. In exploring the lived world of our patients, we are able to meet their needs instead of what we think they need. We are able to better organize our clinical setup and be prepared for how to communicate with the patient [134, 135].

A limitation of the prospective feasibility study is the small sample. However, the discussion in the research group concluded that this number was

sufficient as SPIO is already accepted as a tracer in the primary setting [113] and the patient was her own control when the two tracers were used simultaneously.

CONCLUSION

The key conclusion from this thesis is the importance of deescalating axillary surgery due to the morbidity effects on arm function after ALND, while at the same time maintaining oncological safety and not compromising survival or regional control. When putting the patient at the center of research we gain access to the inside perspective and this understanding enables us as HCPs to strive for a better outcome for patients undergoing BC treatment. Specific conclusions that can be drawn are as follows:

- Well defined factors for non-SNm can aid clinical decision making regarding whether or not to proceed with ALND.
- The nomogram provides a straightforward method for predicting and visualizing the probability of non-SNm.
- Having up to two macrometastases and favourable tumour factors mostly indicates a lower risk of non-SNm.
- A small but important higher detection rate for SNm and non-SNm might be achieved if scintigram is added.
- Scintigraphy is an established technique with the potential to show a more accurate number of “hot nodes”.
- The optimal information about the SN in the axilla is probably obtained by scintigraphy combined with a gamma probe and blue dye.
- In the recurrent setting radioisotope and scintigraphy do not outperform SPIO and MRI in mapping a repeat SN.
- There is a need for a paradigm shift in surgical care from viewing women with BC as anatomical constructions requiring repair to deeply understanding that these women are persons with an illness in need of ongoing self-management support.
- A more person-centred care approach is essential in BC care. The team that meets the patient should be able to work together for a longer period, thus ensuring continuity.
- The contact nurses should support patients throughout the whole cancer treatment and rehabilitation journey.

Future perspectives and implications

In all BC surgery axillary staging is the established method of care. Today's vast knowledge of tumour biology, genetics and individualized systemic treatment as well as the existing deescalation of axillary surgery, may make the case for prediction with biological factors in favour of non-SNm. Several authors have investigated the omission of ALND when there are micrometastases in the SN and when there are 1-2 macrometastases in the SN in an negative axilla [61],[136] so the future lies in tumour biology and the SN result. A recent study also showed that in cases of clinically node negative axilla and favourable tumours (T1, ER positive, HER2 neg) omission of axillary staging was non inferior to the conventional regimen [137], similar results was seen in a study by Ingvar et al with pT1a–b, cN0 and NHG I/II tumours and no axillary surgery done [138].

Scintigraphy provides an advantage at the time of BC recurrence and a planned repeat SN detection, as it helps with mapping the SN, which in this situation is often located aberrantly. This is also true for SPIO as illustrated in Paper IV and other studies [117].

It is crucial to emphasize the findings of Paper III. There is a need for changes in follow-up care including person-centred support to strengthen the women's meaning- and sense-making processes. When the women make sense of their situation, they become less distressed and probably find useful coping strategies to master difficult situations. Feeling embraced by significant others is a vital part of feeling safe. Thus, spouses or other significant others should also be invited to be a part of the treatment trajectory. Moreover, the most important task is to enhance the women's self-efficacy, which will occur when uncertainty is relieved. As HCPs we need to adopt a more person-centred approach and establish routines that enable us to treat the women as capable persons. When inviting the women to a partnership they become active partners instead of passive receivers of care.

Future perspective

Personalized treatment should be the focus of every aspect, i.e. when performing breast conserving surgery and deescalating axillary surgery for a better quality of life without compromising the staging and systemic treatment planning, thus ensuring an individualized treatment plan.

Our treatments and follow-up should be structured in a way in which the patient is central. Firstly, by letting the patient give us her narrative, then initiating the partnership and safeguarding the relationship by documenting the patient's wishes, preferences and participation in the treatment. We should continue the shared decision-making by presenting the alternatives in all steps of the treatment trajectory. In so doing, we create person-centred care with the best evidence-based treatment options.

"We make a living by what we get, but we make a life by what we give"
Churchill

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APPENDIX

APPENDIX 1: Case Report Form (CRF) version 1.0

Insändes till: Forskningssjuksköterska Désirée Bourghardt Wiklund, Kirurgi SU/Sahlgrenska,
413 45 Göteborg. Tfn 031–342 11 19. desiree.bourghardt.wiklund@vgregion.se

Protocol SentiRecur

Pnr (only registered at study site, remove before sending CRF): _____

Name

_____

Patient code _____

Inclusion criteria

Informed consent

☐ Yes ☐ No

Patient is 18 years of age or older ☐

Yes ☐ No

Patients with recurrent DCIS or invasive breast cancer planned for surgery including sentinel node biopsy ☐ Yes ☐ No

Exclusion criteria

Intolerance or hypersensitivity to iron or dextran compounds or SPIO

☐ Yes ☐ No

Patient who are required to undergo MR to evaluate tumour response

☐ Yes ☐ No

Patient pregnant and/or breastfeeding ☐

Yes ☐ No

Patient with an iron overload disease ☐

Yes ☐ No

Patient under guardianship or deprived of liberty ☐ Yes ☐ No

Patient with inability to understand given information and give informed consent or undergo study procedures ☐ Yes ☐ No

Patient who cannot undergo MRI (e.g., conditions contraindicating MRI including, but not limited to, BMI > 40 kg/m^2, metallic implants or internal electrical devices (e.g. Pacemaker), claustrophobia.) ☐ Yes ☐ No

Patient who has previously participated in the SentiNot study

☐ Yes ☐ No

Previous Breast Cancer

Year at first diagnosis_____

Earlier tumour location ☐ Left breast ☐ Right breast

☐ UOQ ☐ UIQ ☐ LOQ ☐ LIQ ☐ Central ☐ Not known

Upper Outer-, Upper Inner-, Lower Outer-, Lower Inner Quadrant

Earlier performed surgery ☐ Mastectomy ☐ Breast Conserving Surgery (BCS)

Oncoplastic BCS ☐ Yes ☐ No

If yes: Tech-nique_____

Reconstructive surgery ☐ Yes ☐ No

If yes: Tech-nique_____

Earlier axillary staging ☐ SLNB ☐ ALND

Number of lymph nodes removed _____

Number of metastatic lymph nodes _____

Surgery for lymphedema ☐ Yes ☐ No

Adjuvant Radiotherapy ☐ Yes ☐ No

If yes: ☐ Breast ☐ Breast + axilla ☐ Breast + axilla + neck and parasternal nodes

Recurrent tumour

Preoperative data

Age_____ Sex ☐M ☐F
BMI……kg/m^2

Recurrent tumour location ☐ Left breast ☐ Right breast ☐Thoracic wall

☐ UOQ ☐ UIQ ☐ LOQ ☐ LIQ ☐ Central

Upper Outer-, Upper Inner-, Lower Outer-, Lower Inner Quadrant

Tracers **Tc^{99} injection** _____mBq Date of injection_____

Injection site ☐ peritumorally ☐ periareolarly

Blue Dye injection: ☐ Yes ☐ No If yes:_____ml Date of injection_____

Injection site ☐ peritumorally ☐ periareolarly

MagTrace injection: Date: _____ Time: _____ Volume_____ml

Injection site ☐ peritumorally ☐ periareolarly

Transcutaneous axillary SentiMag signal after at least 20 minutes (optional)
…….……

If yes: Localization ☐ Right axilla ☐ Left axilla ☐ Other……

Lymphoscintigraphy Date_____

SLN detected ☐ Yes ☐ No

If yes: Number of SLN(s)_____

Localization ☐ Right axilla ☐ Left axilla ☐ Other……

MRI Date_____

SLN detected ☐ Yes ☐ No

If yes: Number of SLN(s)_____

Localization ☐ Right axilla ☐ Left axilla ☐ Other……

Surgery Date _____

☐ Mastectomy ☐ Breast Conserving Surgery (BCS)

Performed Surgery Axilla: ☐ SLNB ☐ ALND ☐ Sampling ☐ None

Perioperative SentiMag and Gammaprobe measurements:

			SentiMag	Gamma-probe
Counts transcutaneous axilla			_____	_____
Counts Lymph nodes Ex vivo:				
	Blue	Brown		
Sentinel Lymph Node 1	Yes	Yes	_____	_____
SLN 2	Yes	Yes	_____	_____
SLN 3	Yes	Yes	_____	_____
SLN 4	Yes	Yes	_____	_____
SLN 5	Yes	Yes	_____	_____
Non-SN axillary nodes	Yes	Number	…….	

<u>Postoperative data</u>

<u>Histology from surgical specimen</u>

Invasive cancer Size _____mm

1. Invasive tumour Grade ☐ Grade 1 ☐ Grade 2 ☐ Grade 3

2. DCIS present : ☐ Yes ☐ No Size: mm

If yes: Grade of DCIS: ☐ Grade 1 ☐ Grade 2 ☐ Grade 3

4. ER_____% PR_____%

5. HER2 Normal Overexpressed

6. Ki67_____%

Postoperative lymph node data

SLN 1 Macromet Yes/No, Micro Yes/No, Isolated tumour cells Yes/No, SPIO Yes/No

SLN 2 Macromet Yes/No, Micro Yes/No, Isolated tumour cells Yes/No, SPIO Yes/No

SLN 3 Macromet Yes/No, Micro Yes/No, Isolated tumour cells Yes/No, SPIO Yes/No

SLN 4 Macromet Yes/No, Micro Yes/No, Isolated tumour cells Yes/No, SPIO Yes/No

SLN 5 Macromet Yes/No, Micro Yes/No, Isolated tumour cells Yes/No, SPIO Yes/No

Non-Sentinel Nodes Macromet Yes/No Micromet Yes/No Isolated tumour cells Yes/No

Number of Sentinel lymph node(s) /number with Metastases _____/_____

Number of Non-sentinel lymph nodes / Number with Metastases _____ / _____

Skin staining Brown ☐ Yes ☐ No ____ x____ cm

Skin staining Blue ☐ Yes ☐ No ____ x____ cm

Safety

Incidence of Serious Adverse Events ☐ Yes ☐ No

If yes: please complete SAE-form.

Appendix 2: MR-protokoll: SentiRecur-studien

Multicenterstudie för jämförelse mellan SPIO (Magtrace) + MRT axiller och standard (Tc^{99m}-lymfscintigrafi) för sentinel node lokalisering vid återfallskirurgi för bröstcancer.

Ansvarig radiolog: Henrik Leonhardt

System: 3 T. Phase-array ytspole.
Patientförberedelser: Efter att kirurgen har injicerat SPIO (Magtrace) interstitiellt nära recidivtumören.
Undersökningstid: Cirka 30 min.
Notering 1: Undersökningen kommer att jämföras med Tc-scint och armarna bör därför om patienten klarar det vara utåt-uppåt.
Notering 1: Bröstet är inte mål för undersökningen och kan med fördel försöka undvikas i FOV för att minimera artefakter från Magtrace-injektionen.

Observera att båda axiller ska undersökas!

	Sekvens	Orientering	FOV (mm)	Snittjocklek (mm)	Täckningsområde
1	Survey	3 plan			
2	T2W TSE	cor			För planering
3	T2W TSE	tra	150	3	Thoraxapertur-axiller
4	T1W TFE DIXON	tra	150	1,5	Thoraxapertur-axiller
5	2D T2*W	tra	150	3	Thoraxapertur-axiller

Papers

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