ARM, SHOULDER AND BREAST MORBIDITY AFTER BREAST CANCER TREATMENT

Arm-, schouder- en borstmorbiditeit na de behandeling van borstkanker

HANNE VERBELEN

Thesis submitted in fulfillment of the requirements for the degree of Doctor in Medical Sciences at the University of Antwerp

Proefschrift voorgelegd tot het behalen van de graad van doctor in de Medische Wetenschappen aan de Universiteit Antwerpen

Promotoren: Prof. dr. Nick Gebruers, Prof. dr. Wiebren Tjalma

Antwerpen, 2020

Faculteit Geneeskunde en Gezondheidswetenschappen

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GENERAL INTRODUCTION

In the first part of the general introduction, background information on breast cancer and its treatment will be provided. Furthermore, several arm, shoulder and breast complaints will be discussed in detail. The second part will discuss the objectives and outline of this doctoral this. In the last part, the organization of all chapters will be presented.

Breast cancer

Breast cancer starts when cells in the breast begin to grow out of control. Three conditions have to be fulfilled to call it breast cancer: 1) breast cells have to deteriorate into malignant cells, 2) they affect the normal tissues, and 3) they cause or can cause metastases in a more advanced stage. Metastasis is defined as the spread of cancer cells to other tissues, distant or nearby. A breast cancer can originate in different parts of the breast. Most breast cancers begin in the ducts that carry milk to the nipple (ductal cancers). Some originate in the glands which make breast milk (lobular cancers). Other types of breast cancer are possible as well, but are less common. Breast cancer can spread when the cancer cells get into the blood or lymph system and are carried to other parts of the body. Cancer cells can break away from the tumor, travel to other areas of the body, attach to the wall of blood vessels or lymph vessels and grow and thrive in a new location[1].

There is no clear cause for the development of breast cancer, however, several risk factors are known[2]. Risk factors for breast cancer include reproductive and hormonal risk factors such as a long menstrual history, recent use of oral contraceptives and never having children. Other risk factors include weight gain after the age of 18, being overweight or obese, use of menopausal hormone therapy, physical inactivity and alcohol consumption. Giving birth to children and breastfeeding decrease the risk of breast cancer[2].

Breast cancer is the most common cancer among women in the Western World. In Europe, 13.5% of all cancers are breast cancers. In women, breast cancer is by far the most frequently diagnosed neoplasm (28.8%)[3]. In Belgium, every year over 10 000 women are diagnosed with breast cancer compared to around 100 men (www.kankerregister.org). Unfortunately, Belgium has the highest incidence rates among Western European countries. At some point during their life, 1 in every 8 women will get diagnosed with breast cancer. For men it is around 1 in 150[3,4].

Mortality rates after breast cancer in Belgium are rather high, but they reflect the high incidence rate, not an unfavorable survival. Compared to other cancers, the survival of breast cancer is fairly good. Currently, in Belgium, the 5-year survival of female breast cancer is 90.4% (www.kankerregister.org). This can be explained either by an early detection and by improvements in treatment. The early detection is partly attributable to screening programs and partly to the increasing awareness[3].

Treatment of breast cancer

Breast cancer can be treated in several ways, depending on its type and stage. Surgery and radiation therapy are local treatments meaning they treat the tumor without affecting the rest of the body. Systemic treatment can be used as well, like chemotherapy, hormone therapy and targeted therapy. Most patients get treated with a combination of different therapy modalities. What follows is a more detailed description of breast cancer treatment.

The primary treatment for breast cancer is mostly surgery[5]. During breast surgery, the tumor in the breast can be removed by performing either a mastectomy or breast-conserving surgery (BCS). In case of a mastectomy, the whole breast is amputated. BCS means only part of the breast tissue is removed. In addition to surgery of the breast, axillary surgery may be indicated. To find out if the breast cancer has spread to axillary lymph nodes, one or more of these lymph nodes will be dissected and explored microscopically. The 2 main types of surgery to remove lymph nodes are the sentinel lymph node biopsy (SLNB) and the axillary lymph node dissection (ALND). During an ALND, the surgeon removes many lymph nodes from the axilla, whilst in a SLNB only the lymph node(s) to which the cancer would likely spread first, is/are removed.

In addition to breast surgery and axillary surgery, most patients receive radiation therapy and/or some form of systemic treatment. Radiation therapy is a treatment in which high-energy rays or particles are used to destroy cancer cells that may be left behind in the breast tissue (area of surgery) after surgery. Besides the breast itself (in case of BCS) or the chest wall (in case of mastectomy), regional lymph nodes such as axillary lymph nodes, supra- and infraclavicular lymph nodes and internal mammary lymph nodes can be radiated as well. After BCS, an extra boost of radiation therapy to the area where the invasive breast cancer is removed, is often applied. Drug/medication treatment used to treat breast cancer are considered systemic therapies because they can reach cancer cells almost anywhere in the body. Depending on the type of breast cancer, different types of drug treatment might be used, including chemotherapy, hormone therapy and targeted therapy. Chemotherapy can be used pre-operatively to reduce the tumor (neo-adjuvant chemotherapy) or post-operatively to kill remaining cancer cells (adjuvant chemotherapy). Often combinations of drugs are used. Hormone therapy is used in patients with hormone receptor-positive breast cancers. It works by stopping estrogen from stimulating breast cancer cells to grow. It is usually used after surgery to help reduce the risk of the cancer coming back and is mostly taken for a period of at least 5 years. In some breast cancers, the cancer cells have too much of a growth-promoting protein (HER2) on their surface. These cancers, known as HER2-positive breast cancers, tend to grow and spread more aggressively. A number of drugs have been developed that target this protein, such as trastuzumab (Herceptin®).

As previously mentioned, the primary treatment for breast cancer still is surgery. In the past, breast surgery was more extensive. Over the years, surgical techniques have changed dramatically with the introduction of breast-conserving techniques and the SLNB. Furthermore, as a result of the increasingly effective methods for the detection of breast cancer, the diagnosis is often made at an early stage. Therefore, more women are eligible for less invasive surgery.

The next paragraphs elaborate on 2 specific types of breast cancer surgery on which is focused in this dissertation, namely SLNB and BCS.

Sentinel lymph node biopsy

A SLNB is a procedure in which the sentinel lymph node is identified, removed and examined to determine whether cancer cells are present. The SLNB was introduced in the 1990s and was an important development in surgical oncology[6]. It has become one of the standard procedures to treat patients with early stage breast cancer. Many types of cancer can spread by the lymphatic system. This is also the case for breast cancer, which can spread to the lymph nodes in the axilla. A sentinel lymph node is the first lymph node in a chain or group of lymph nodes which drains lymph fluid from the area around the tumor, and is therefore the first lymph node to which cancer cells most likely spread. A SLNB is used to find out if cancer has spread to lymph nodes near where the cancer originated. This helps to stage the cancer, plan treatment and determine a prognosis. To detect the sentinel lymph node, a radioactive substance (radiotracer) or blue dye is injected in the area around the primary tumor. The surgeon uses a gamma probe to detect radioactivity in lymph nodes or looks for lymph nodes which are stained with the blue dye. Once the sentinel node is located, it is removed by the surgeon and send to the pathologist to determine whether the lymph node contains cancer cells. Due to the SLNB procedure many patients have the advantage to avoid a more extensive ALND, because removing additional nearby lymph nodes is not necessary if the sentinel node is negative for cancer. SLNB is now widely used as a standard procedure in breast cancer patients. Therefore, the number of patients treated with SLNB has increased spectacularly.

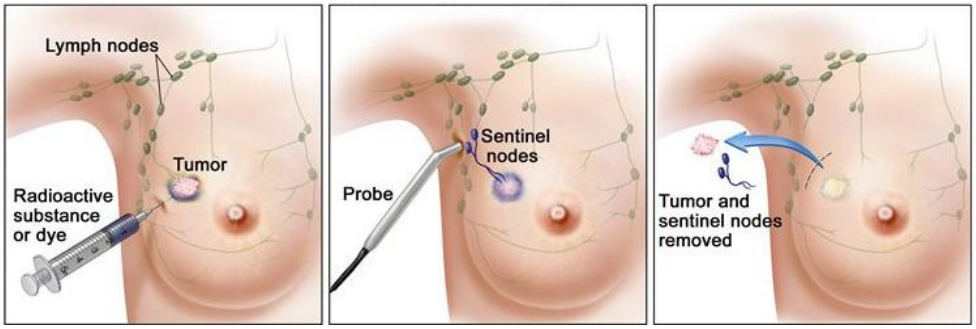

Figure 1. Sentinel lymph node biopsy (From https://www.cancer.gov)

Breast-conserving surgery

For many years, a radical mastectomy was the treatment of choice for breast cancer of any size or type[7]. In 1969 Veronesi introduced the BCS[8]. In this procedure, part of the breast which contains the malignant tumor is removed along with some healthy tissue and surrounding lymph nodes, leaving the majority of the breast intact. Veronesi received approval from the World Health Organization for a randomized trial comparing traditional mastectomy with his new conservative approach. Results of the trial showed that survival rates were equal after mastectomy and BCS. Today, more and more women with breast cancer are eligible for BCS. In most cases this treatment procedure involves radiotherapy, in addition to the local excision. BCS followed by radiotherapy is a safe and effective procedure to treat patients with early stage breast cancer[9]. In many women this type of treatment gives besides a good survival also a good cosmetic result[10]. However, some patients will be troubled by breast morbidity in the operated and irradiated breast.

Morbidity after breast cancer surgery

Because of the evolution in breast cancer surgery towards more conserving procedures, a considerable reduction in post-operative complaints could be expected compared to the more invasive procedures. Nevertheless, arm, shoulder and breast morbidity following breast cancer treatment should not be neglected. Over the years, the survival rate of breast cancer has increased significantly. As a result, the long-term health problems, including quality of life (QOL), related to breast cancer and its treatment are becoming more important. To cover all health-related QOL aspects, one should look at the bio-psychosocial framework. The International Classification of Functioning Disability and Health (ICF) is an extensively used framework to describe the health condition of a patient in a bio-psychosocial context (www.who.int/classifications/icf/en). The ICF covers all domains of disability. Disability involves dysfunctioning at one or more levels: impairments in body function or structures, activity limitations and participation restrictions. The outcome parameters in this thesis focus on all domains of ICF.

This thesis aims to investigate either arm and shoulder morbidity after SLNB and breast edema after BCS. What follows is a general overview to introduce these complaints.

Arm and shoulder morbidity

Compared with ALND, SLNB is a minimally invasive procedure of the axilla. Several studies compared SLNB with ALND, and all of them reported that the SLNB generates fewer arm and shoulder morbidity than ALND[11–19]. However, they should not be neglected.

Pain is a very common morbidity after breast cancer treatment. It can occur in various locations and is often associated with other morbidities. In the early treatment phase of breast cancer, pain can be associated with wound healing, scar tissue formation, fibrosis, seroma and skin reactions after radiation therapy. In a later phase, pain can be associated with axillary web syndrome (AWS), winged scapula, breast edema, lymphedema and nerve damage. Also, joint pain is reported in breast cancer patients who received systemic therapy. After chemotherapy up to 40% of patients reported pain, depending on the type of chemotherapy and 50% of menopausal patients who use aromatase inhibitors, a type of hormone therapy, reported joint pain[20,21].

Loss of mobility is often reported after breast cancer treatment, especially the first weeks after surgery. Mainly abduction and forward flexion are limited. Also, loss of mobility is a complaint which is associated with other morbidities such as wound healing and scar tissue formation, fibrosis, AWS, winged scapula, pain, lymphedema, nerve damage and shortened pectoralis muscles. Typically, breast cancer patients post-operatively have a fear of moving the arm. Consequently, they have the tendency to spare their arm which can influence range of motion (ROM) negatively.

Concerning loss of strength, the muscle groups which are most often investigated in literature are shoulder abductors and elbow flexors. Also grip strength is impaired in many breast cancer patients. This can possibly be explained by the protective posturing in the post-operative stage. Similar to what is mentioned in loss of mobility, the arm is often spared causing loss of strength in the entire arm.

AWS is a web of non-functional fibrosed lymphatic vessels palpable as thick strings from the axilla into the medial arm[12,22,23]. Sometimes it is not limited to the axilla. Cords may extent onto the breast, chest wall, back and sometimes reach the hand of the patient and is clinically associated with pain and limited shoulder ROM. AWS usually occurs between 1 and 8 weeks following breast cancer surgery[22].

Winged scapula, also known as scapula alata is caused by a muscle deficiency of the serratus anterior muscle, caused by impaired function of the thoracic longus nerve. Prolonged stretching of the nerve during axillary surgery or nerve manipulation may cause this nerve dysfunction. Clinically, this can be seen as winging of the medial border and/or inferior angle of the scapula[24,25]. As mentioned earlier, this complaint is also associated with other morbidities such as pain, loss of mobility and loss of strength.

Furthermore, damage of the sensory branch of the intercostal brachial nerve after breast cancer surgery can cause sensory disturbance at the region of the lateral chest wall, axilla and medial upper arm[26]. It presents as numbness in this region and can change into tingling or paresthesia in a later stage. Additionally, shortening of the pectoralis muscles can cause compression of the brachial plexus which can lead to numbness or tingling of the arm and/or hand as well.

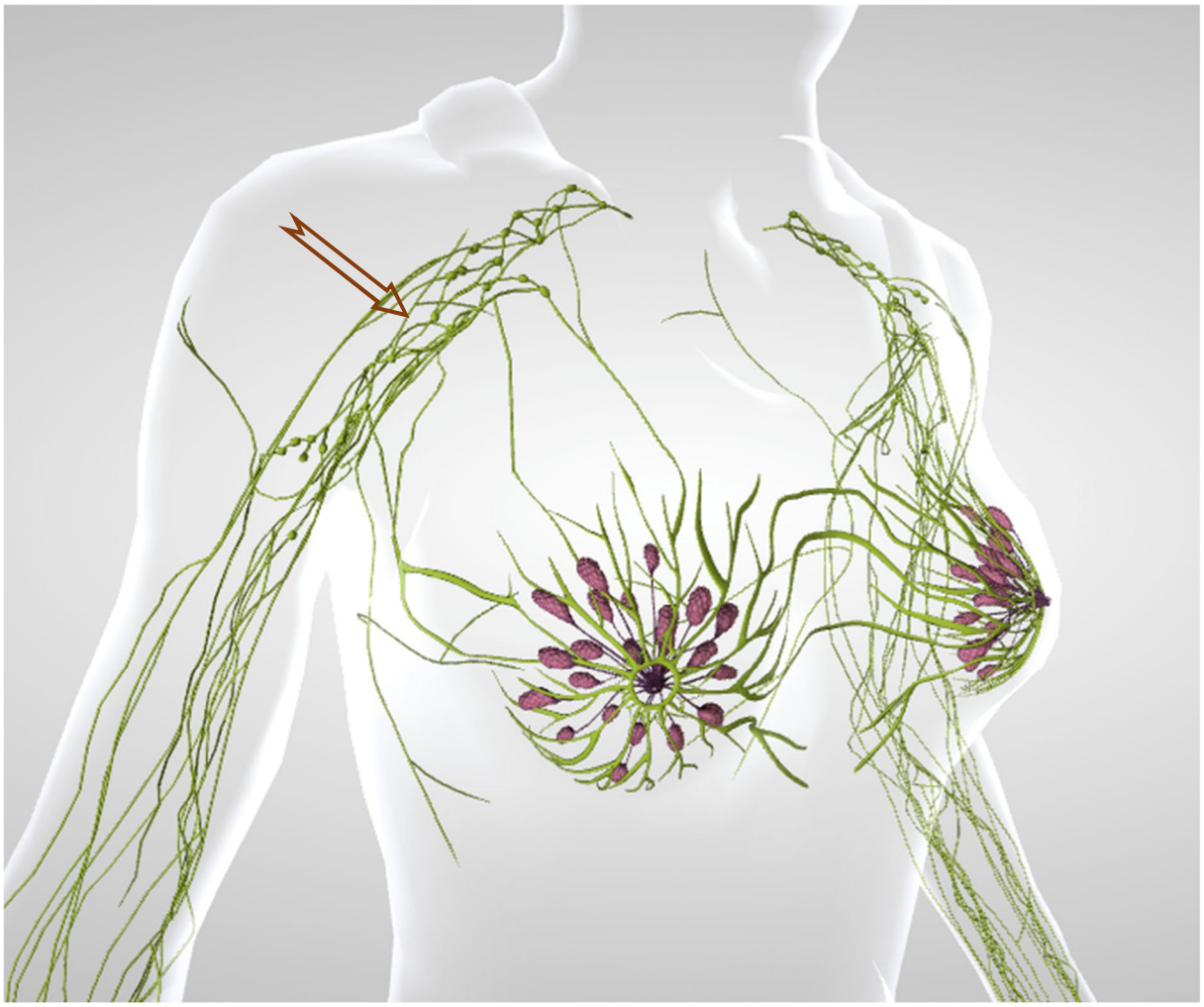

Figure 2. Lymphatics of arm and breast (From https://www.mskcc.org)

Finally, the occurrence of lymphedema, a condition characterized by fluid accumulation in the interstitial space[27], is expected to be minimal after SLNB[28]. However, a SLNB and the additional radiation therapy can cause damage to the lymphatic system. Therefore, transport capacity of the lymphatic system can be compromised, making it vulnerable for the development of lymphedema. Figure 2 shows the lymphatics of the arm and breast. It is clearly demonstrated (see arrow) that there is a confluence of the lymphatics of arm and breast in the axilla. It is possible that a sentinel node is located on lymph pathways of the arm. Therefore, if a sentinel node is removed in this area, it imposes a real risk for developing lymphedema.

Breast edema

Breast edema is a morbidity which is seen after BCS and radiation therapy. In contrast to lymphedema of the arm, breast edema is far less explored in literature. However, in clinical practice, breast complaints in breast cancer patients are common. After BCS, most patients receive adjuvant radiation

therapy. They often receive an extra boost on the tumor site on the breast itself to make sure all remaining cancer cells are destroyed. The combination of this treatment can cause damage to the lymphatic system, which can lead to a compromised transport capacity not only in the arm, but also in the breast. Hereby, the breast size can increase by more than one cup size[29]. However, swelling of the breast is not the only criterion that is associated with breast edema. Besides an increased volume of the breast[30–35], other common criteria found in the literature are pea d'orange[29–31,33–35], heaviness of the breast[31,33,34], redness of the skin[30,31,35], breast pain[29–31,34,35], skin thickening[30,36], hyperpigmented skin pores[35] and a positive pitting sign[30]. Nevertheless, most studies do not describe a definition of breast edema. Delay et al. classified breast edema into different stages[34]. Stage 1 is characterized by thickening of the skin, while the breast volume remains unchanged. In stage 2, breast edema presents as a visible edema which can lead to asymmetry between both breasts. In patients with severe breast edema, the volume of the operated and irradiated breast can sometimes increase up to 300ml. Stage 2 is further characterized by dilated skin pores, which is called peau d'orange, heaviness, pain and pitting edema on the affected breast. Stage 3 of breast edema is similar to stage 2, but in this stage, the pain is more extensive[34] Wratten et al. describes 2 components of breast edema. Firstly, generalized enlargement or swelling of the breast tissue itself may occur, which is referred to as parenchymal breast edema. Secondly, there may be evidence of edematous changes in the epidermis and dermis, which is referred to as cutaneous breast edema. Although cutaneous edema may occur by itself, in many instances, there will be a combination of both parenchymal and cutaneous breast edema[36]. Besides the absence of a clear definition for breast edema, a standardized method to assess breast edema is lacking as well. The most common method found in literature, is the physical examination. However, different studies use different criteria to diagnose breast edema based on physical examination[10,29,30,32,37–52]. Other methods to assess breast edema are the use of a mammogram[46,53], ultrasound[30,36,46], MRI[54] or questionnaire[10,31,39,55]. These differences in assessment methods and standards make it difficult to compare studies.

Despite the benefits of BCS, breast edema can be uncomfortable and is associated with distress[56]. The breast asymmetries due to swelling of the breast may cause an unsatisfactory cosmetic result and patients with breast edema mention changes in clothing habits[34,39]. Because of the significant symbolism of the female breast, breast edema can influence the body image which has a definite impact on the QOL[10,31]. Especially younger patients report changes in body image[39].

OBJECTIVES

The main goal of this thesis is to obtain more insight in the morbidity after breast cancer treatment.

This thesis is divided in 2 parts:

- Part A consists of 3 scientific papers in which arm and shoulder complaints after SLNB are identified and explored.
- In part B, 3 scientific papers are presented concerning breast edema after BCS and radiation therapy.

PART A: Arm and shoulder complaints after sentinel lymph node biopsy

In literature, SLNB and ALND are often compared with beneficial results in favor of the less invasive SLNB. Despite the strong reduction in morbidity after the SLNB procedure, negative aspects may be underestimated. There is still a risk of treatment-related morbidity such as limitations in shoulder ROM, loss of strength, pain, winged scapula, AWS, sensitivity disturbances and lymphedema, among women operated with SLNB[11–13,57]. These negative aspects may cause an unsatisfactory psychosocial outcome, influencing activities of daily living and the QOL[15]. Because of the evolution in the treatment of breast cancer, the survival rate has increased. As a result, the long-term health problems related to breast cancer and its treatment and the QOL are becoming more important. Therefore, arm and shoulder complaints among patients who were defined as sentinel negative and their incidence and time course are investigated **(Chapter 1 and 1bis)**.

To cover all health-related QOL aspects, one should look at the bio-psychosocial framework. The self-reported measures in this study focus on all the domains of ICF. The majority of studies on the morbidities after SLNB have only short follow-up (1-3 years). Knowledge of long-term morbidity is essential since the survival rate is increasing. It is therefore the purpose to inventory impairments involving arm and shoulder complaints in sentinel node negative breast cancer patients and to identify activity limitations and participation restrictions. The secondary aim is to investigate which arm and shoulder complaints are still present in those patients after long-term follow-up **(Chapter 2).**

PART B: Breast edema after breast-conserving surgery

In contrast to arm morbidity, which is thoroughly described in literature, only few studies investigated breast morbidity after breast cancer treatment. In many women, BCS followed by radiation therapy gives besides a good survival also a good cosmetic result[10]. However, in some patients breast edema

of the operated and irradiated breast is reported, causing an unsatisfactory cosmetic result, which has a definite impact on QOL[10,58]. In a systematic review of the literature, the aim is to describe the incidence of breast edema in female breast cancer patients after BCS and radiation therapy and to identify its risk factors **(Chapter 3).**

Currently, there is no consensus on the definition of breast edema and on standardized assessment criteria. Breast edema is largely underdiagnosed in clinical practice because lack of standardized assessment tools. Therefore, it is our aim to develop a questionnaire to diagnose and evaluate breast edema, namely the Breast Edema Questionnaire (BrEQ). Furthermore, the clinimetric properties of this newly developed questionnaire are investigated **(Chapter 4).**

Literature on the longitudinal course of breast edema in breast cancer patients is scarce. However, we found it necessary to inform patients about what to expect in case of breast edema. In a prospective cohort study, it is our purpose to investigate the prevalence and longitudinal course of breast edema among breast cancer patients who underwent BCS and radiation therapy. Currently there is no consensus in literature about risk factors of breast edema. The prognostic value of personal factors like BMI, cup size, menopausal state etcetera and treatment-related factors such as type of axillary surgery, (neo-)adjuvant treatment and radiation parameters remains uncertain, because these factors were only investigated in a limited number of studies. Therefore, the secondary purpose is to identify personal and treatment-related factors which can influence breast edema **(Chapter 5).**

The following research questions are set forth:

- Which arm and shoulder complaints are present in breast cancer patients who are defined as sentinel negative? What is the incidence and time course of these complaints? **(Chapter 1)**

- What is the incidence and time course of lymphedema in sentinel negative breast cancer patients? **(Chapter 1bis)**

- What is the prevalence of scapula alata, AWS, loss of mobility, loss of strength, pain, lymphedema and sensory disturbances in sentinel negative breast cancer patients on the short and long term? Which activity limitations and participation restrictions are present in these patients? **(Chapter 2)**

- What is the incidence of breast edema in female breast cancer patients after BCS and radiotherapy and what are risk factors for breast edema? **(Chapter 3)**

- What are the clinimetric properties of the BrEQ-questionnaire? **(Chapter 4)**

- What is the prevalence and longitudinal course of breast edema in patients who underwent BCS and radiotherapy, measured with the BrEQ? Which personal and treatment-related factors have an influence on breast edema? **(Chapter 5)**

ORGANIZATION OF THE STUDY

The reviews of data were all performed accordingly the Cochrane Collaboration recommendations. A systematic search strategy was performed following the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement. The search strategy was conducted in the databases up until October 18th 2013 **(Chapter 1)**, October 29th 2013 **(Chapter 1bis)** and June 27th 2014 **(Chapter 3).**

The database of the Multidisciplinary Breast Clinic of the Antwerp University Hospital was retrospectively searched to identify breast cancer patients who underwent breast cancer treatment between January 2007 and January 2012. Eligible study participants were contacted by phone between February and April 2014. Patients who gave consent were included in the study and received a survey by mail to assess self-reported arm and shoulder complaints. The study was approved by the ethics committee of the Antwerp University Hospital. Written informed consent was obtained for all subjects **(Chapter 2).**

Patients were recruited from the Multidisciplinary Breast Clinic of the Antwerp University Hospital. Clinimetric properties of the BrEQ-questionnaire were tested at the Radiology Department. Patients underwent an annual ultrasound of both breast and filled in the BrEQ. The study was approved by the ethics committee of the Antwerp University Hospital. Written informed consent was obtained for all subjects **(Chapter 4).**

For the prospective cohort study, patients were recruited from the Iridium Cancernetwork's hospitals which includes AZ Klina, AZ Monica, AZ Nikolaas, AZ Sint-Jozef Malle, GZA Hospitals, UZA and ZNA. A first contact moment took place in the Radiotherapy department of the St-Augustinus Hospital, after the radiotherapy simulation. Afterwards, data were prospectively gathered by postal mail or email. The study was approved by the ethics committees of the Antwerp University Hospital and GZA Hospitals. Written informed consent was obtained for all subjects **(Chapter 5).**

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PART A

Arm and shoulder complaints after sentinel lymph node biopsy

CHAPTER 1

Shoulder and arm morbidity in sentinel node negative breast cancer patients: a systematic review

Published in Breast Cancer Research and Treatment:
Verbelen H, Gebruers N, Eeckhout FM, Verlinden K, Tjalma W. Shoulder and arm morbidity in sentinel node-negative breast cancer patients: a systematic review. *Breast Cancer Res Treat.* 2014 Feb;144(1):21-31. (SCI: 3.940; Q1)

Abstract

Objective: To assess which shoulder and arm impairments are common in sentinel node negative breast cancer patients and to describe the incidence and time course of these impairments.

Data Sources: A systematic literature search was performed using different electronic databases until October 2013.

Study Selection: A first selection based upon title and abstract and a second selection based on the full text was performed by means of predefined inclusion criteria: (1) research studies that included breast cancer patients surgically treated using the sentinel lymph node biopsy (SLNB) technique, (2) sentinel node negative patients and (3) studies that investigated morbidities of shoulder and/or arm. The exclusion criteria were (1) reviews or case studies, (2) patients who have had a SLNB followed by a axillary lymph node dissection (ALND), (3) results of ALND-patients and SLNB-patients were not described separately and (4) no follow-up described.

Data Extraction: Patient characteristics, morbidities and assessment of the morbidities in patients who underwent SLNB alone and who were node negative were described based on the included publications (representing 5448 patients).

Data Synthesis: Thirty articles were included. Shoulder and arm impairments among sentinel node negative patients are loss of mobility, loss of strength, pain, axillary web syndrome and sensory disorders. Within the first month after SLNB the morbidities with the highest incidence are decreased abduction (range:40.8%-100%) and forward flexion of the shoulder (range:37%-100%), pain (range: 3.4%-56.6%) and numbness (range: 2%-64%). Morbidities with the highest incidence after 2 years are pain (range: 5.6%-51.1%), numbness (range: 5.1%-51.1%), loss of strength (range: 0%-57.7 %), decreased internal rotation (44.4%) and decreased abduction (range:0%-41.4%).

Conclusion: Although shoulder and arm impairments are less common after SLNB alone compared to ALND, they cannot be neglected. A considerable number of patients still suffer from those impairments more than 2 years after surgery.

Key words: Breast neoplasms, Sentinel Lymph Node Biopsy, Morbidity, Review

Introduction

Breast cancer is the most common malignancy in women in the Western World and the incidence is still increasing[1]. At some time during their life, breast cancer will be diagnosed in 1 out of every 8 women[2]. In the past, breast surgery was more extensive. Many women underwent and still undergo axillary lymph node dissection (ALND) which can cause arm and shoulder morbidities like numbness, pain, limitation of arm movement and lymphedema[3]. Over the years, surgical techniques have changed dramatically with the introduction of more breast conserving techniques and the sentinel lymph node biopsy (SLNB). SLNB is now widely used as a standard procedure in breast cancer patients. Therefore, the number of patients treated with SLNB is increasing spectacularly. SLNB can reduce unnecessary axillary clearance and therefore we can expect that it results in considerable less arm and shoulder morbidity[4]. In the literature, SLNB and ALND are often compared with beneficial results in favor of SLNB. Despite a strong reduction in morbidity after the SLNB procedure, the negative aspects may be underestimated. There is still a risk of treatment-related morbidity such as limitations in shoulder range of motion, loss of strength, numbness, dysesthesias and pain among women operated with SLNB alone[2,5–7]. These negative aspects may cause an unsatisfactory psychosocial outcome, influencing activities in daily living and the quality of life (QoL)[8].

Because of the evolution in the treatment of breast cancer, the survival rate has increased. As a result, the long-term health problems related to breast cancer and its treatment and the QoL are becoming more important. The purpose and relevance of this systematic review is to identify impairments of the arm and shoulder among patients who were identified as sentinel node negative and received no additional axillary lymph node dissection. The secondary aim is to describe the incidence and time course of these impairments.

Methods

Literature search and selection

To identify arm and shoulder morbidity after SLNB we systematically reviewed the literature addressing following research questions: (1) Which arm and shoulder impairments aside from lymphedema are present in breast cancer patients who are defined as sentinel negative, (2) what is the incidence and (3) time course of these impairments?

The following electronic databases were screened online: PubMed (September 23, 2013), Web of Science (October 18, 2013), Embase (October 10, 2013) and Cochrane clinical trials (September 23, 2013).

To retrieve eligible studies, Medical Subject Headings (Mesh-terms) and key words were combined to describe the patient population, intervention and outcome. The specific search strategy used for PubMed is described in Table 1. An equivalent search strategy was used for the other databases but included a number of modifications because of differences in indexing terms (MeSH for PubMed and Cochrane, EMTREE for EMBASE).

Table 1. Boolean search strategy for PubMed

(Breast Neoplasm[MeSH] OR ”breast cancer”) AND (morbidity AND (arm OR shoulder) OR "Pain, Postoperative"[Mesh]OR ”Range of Motion, Articular”[Mesh]OR ”axillary web syndrome” OR abduction OR elevation OR rotation) AND (SLN OR sentinel OR ”sentinal lymph node biopsy” OR ”Lymph node excision” OR ALND OR ”axillary clearance” OR axillary lymph node dissection) NOT "Lymphedema"[Mesh]

All articles were screened based upon title and abstract in order to decide whether they had to be included for further reading or not. Four raters (H.V., N.G., FM. E., K.V.) screened the selected full-text articles for the inclusion and exclusion criteria. In case the 4 raters had diverging opinions, consensus was sought during a meeting. Inclusion criteria were: (1) research studies that included breast cancer patients who were surgically treated using the SLNB technique, (2) sentinel node negative patients and (3) studies that investigated morbidities of shoulder and/or arm. Exclusion criteria were (1) reviews or case studies, (2) patients who have had a SLNB followed by an ALND, (3) results of ALND-patients and SLNB-patients were not described separately and (4) no follow-up described.

Data-extraction

Data on patient characteristics, morbidities and assessment of the morbidities were independently abstracted by 4 reviewers (H.V., N.G., FM. E., K.V.). Only data from patients who underwent SLNB alone and who were node negative were extracted. The search did not focus on secondary lymphedema as a morbidity of breast cancer surgery because it was expected to be minimally present in node negative patients. Therefore, results on lymphedema were not incorporated in this review. Three articles of Rietman et al. included the same participants with another follow-up[9–11]. Results of these studies are extracted only once.

Quality assessment

The methodological quality of the selected articles was assessed using checklists (http://dcc.cochrane.org/beoordelingsformulieren-en-andere-downloads) for cohort studies and randomized controlled trials (RCT). Four reviewers (H.V., N.G., FM. E., K.V.) independently evaluated the selected articles. Items could be rated by "1", "0" or "?". An item was rated "1" if sufficient information was available and bias was unlikely. An item was rated "0" if sufficient information was available but the article did not meet the criteria. An item was rated "?" if no information was available. If disagreement persisted about the assignment of a score to an item, consensus was sought during a meeting.

Results

Selection of studies

Initially the search yielded 348 citations. After the first screening, 58 non-duplicate abstracts were selected and full texts were retrieved. Four reviewers assessed the full texts and finally a total of 30 studies were included in this review[2,5–33]. The literature search and study selection process are shown in Figure 1.

Methodological quality

The results of the quality assessment are presented in Table 2. Scores for study quality ranged from 3 to 7 out of 8 for cohort studies with a median score of 6. Scores ranged from 5 to 7 out of 9 for RCTs with a median score of 6.

Characteristics of included studies

Six RCTs were selected in this review[7,12,20,29–31] and 24 cohort studies[2,5,6,8–11,13–19,21–28,32,33]. In total, 30 studies recruited 5448 breast cancer patients from 13 different countries who underwent SLNB alone. One study did not report source of participants[17]. Age ranged from 28 years to 90 years and the mean age was 58,2 years. Three studies defined no mean age[5,7,12] and 3 studies defined an overall mean for both SLNB and ALND-patients (59yrs, 55.6yrs and 56.5yrs respectively)[10,22,27]. Studies had different patient groups and used different cancer treatment (breast surgery, radiation therapy, chemotherapy and/or hormonal therapy). Different studies described different morbidities. For a summary see Table 2.

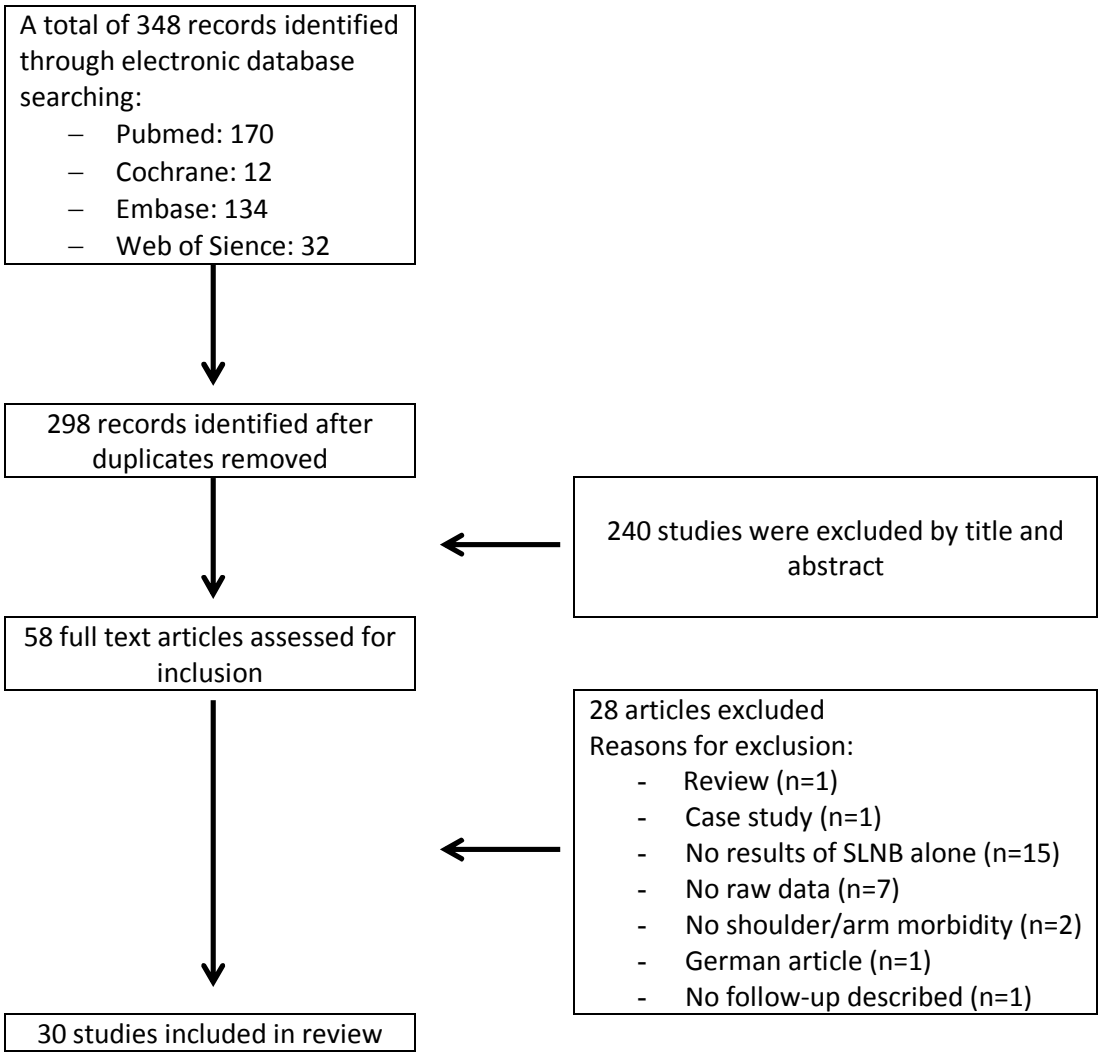

Figure 1. Flow chart of the study selection procedure

Morbidity

The arm and shoulder impairments among breast cancer patients undergoing SLNB found in the literature are loss of mobility[2,6–11,13–15,17,18,20,21,23–25,31–33], loss of strength[2,6,9–12,14,17,18,21], axillary web syndrome[5,24,33], pain[6,9,11,12,14,15,17,20,21,23,24,32] and sensory disorders[6–12,14,15,17,20,21,23,31–33]. Different studies used different methods of assessment. For a summary of the incidence of the morbidities, the longitudinal course and the method of assessment, see Table 3. Of the 30 selected articles, 9 did not describe a specific follow-up, but instead a follow-up range[8,16,19,22,26–28,30,33]. Of these studies, incidence of the morbidities and the method of assessment are presented in Table 4.

Table 2. Study characteristics of 28 selected studies

Reference	Sample size		Treatment of cancer / SLNB					Design	Follow-up	Assessment
	SLNB	ALND	BCS	MTC	RT	CT	HT	Methodological score		
Bergman 2012	58	118	-	-	-	-	-	Cohort (6/8)	45 days	Phys exam: AWS
Aerts 2011	51	38	31	20	35	10	12	Cohort (7/8)	> 2 years	Phys exam: ROM Questionnaire: pain, strength, ROM, numbness
Land 2010	391	356	320	71	309	-	-	RCT (5/9)	36 months	Questionnaire: pain, numbness, strength
Favarao 2009	38	-	-	-	-	-	-	Cohort (3/8)	3 months	Phys exam: ROM
Kootstra 2010	51	121	35	16	35	9	10	Cohort (7/8)	24 months	Phys exam: strength, ROM
Crane-Okada 2008	119	68	119	0	115	43	-	Cohort (4/8)	59 months	Phys exam: ROM, numbness Questionnaire: strength, pain, paresthesia
Langer 2007	449	210	411	38	411	124	355	Cohort (6/8)	>30 months	Phys exam: ROM Questionnaire: pain, numbness
Husen 2006	203	167	147	54	134	35	90	Cohort (5/8)	12-36 months	Questionnaire: pain, numbness, strength, ROM
Schulze 2006	31	103	23	8	19	1	21	Cohort (5/8)	>20 months	Phys exam: ROM, strenght, numbness Questionnaire: numbness, pain, strength, ROM
Rietman 2003, 2004, 2006	57	124	-	-	-	-	-	Cohort (5/8)	24 months	Phys exam: edema, ROM, strength, numbness VAS: pain
Barranger 2005	54	61	54	0	54	15	40	Cohort (7/8)	10-31 months	Questionnaire: pain, ROM, strength, numbness, paresthesia
Fleissig 2006	424	405	393	31	349	144	362	RCT (5/9)	50 months	Questionnaire: pain, numbness, ROM
Rönkä 2005	43	40	35	8	36	6	18	Cohort (6/8)	12 months	Phys exam: ROM, numbness VAS: pain, numbness, strength, ROM
Langer 2004	40	60	0	40	-	-	-	Cohort (3/8)	6-106 months	Phys exam: ROM, paresthesia
Arnaud 2004	113	72	87	26	62	22	56	Cohort (6/8)	12 months	VAS: pain
Peintinger 2003	25	31	25	0	25	5	17	Cohort (6/8)	12 months	Phys exam: ROM Questionnairel: pain
Leidenius 2003	49	36	39	10	-	-	-	Cohort (4/8)	3 months	Phys exam: AWS, ROM
Haid 2002	66	85	-	-	51	18	49	Cohort (3/8)	> 2 months	Phys exam: ROM, strength, numbness Questionnaire: pain, ROM, strength
Haid 2002	57	140	50	7	47	16	43	Cohort (6/8)	5-30 months	Questionnaire: pain, ROM, numbness, paresthesia
Burak 2002	48	48	-	-	-	-	-	Cohort (4/8)	8-29 months	Questionnaire: numbness
Ashikaga 2010	2008	1974	1852	156	1619	786	1353	RCT (6/9)	36 months	Phys exam: ROM Questionnaire: numbness, paresthesia
Purushotham 2005	143	155	133	10	132	43	114	RCT (7/9)	12 months	Phys exam: ROM, numbness, paresthesia Questionnaire: numbness, paresthesia
Helms 2008	57	93	-	-	-	-	-	RCT (6/9)	6-36 months	Phys exam: ROM, strength, numbness Questionnaire: strength, pain, ROM
Mansel 2006	495	496	457	38	-	-	-	RCT (6/9)	18 months	Phys exam: ROM, numbness Questionnaire: numbness
Belmonte 2012	64	29	64	0	58	21	48	Cohort (7/8)	12 months	Phys exam: ROM, winged scapula, numbness
Swenson 2002	169	78	141	28	132	67	119	Cohort (6/8)	12 months	Questionnaire: ROM, pain, numbness
Kootstra 2013	34	76	26	8	26	7	7	Cohort (6/8)	7 years	Phys exam: ROM, strength
Wernicke 2013	111	115	111	0	111	28	60	Cohort (6/8)	10 years	Phys exam: ROM, AWS Questionnaire: paresthesia

Abbreviations: BCS: breast-conserving surgery; MTC: mastectomy; RT: radiation ttherapy; CT: chemotherapy; HT: hormone therapy; phys exam: physical examination; AWS: axillary web syndrome; ROM: range of motion; VAS: visual analogue scale;

Discussion

Shoulder and arm impairments of breast cancer patients with SLNB alone were systematically assessed. Twenty nine out of 30 studies compared SLNB with level I or II ALND and all of them reported that the morbidity after SLNB alone was much lower compared to ALND[2,5–12,14–33]. Although SLNB generates fewer morbidities than ALND, the literature demonstrated that 2 years after breast

Table 3. Morbidities and methods of assessment

Morbidity Number of studies Participants	Method of assessment	Postoperative outcomes									
		0-1 week	**2 weeks**	**1 month**	**6 weeks**	**2 months**	**3 months**	**6 months**	**12 months**	**24 months**	**>24 months**
Loss of mobility	Questionnaire (%)	-	-	4.7%; 24.5%	-	-	2.6%	10.6%; 4%	3.1%; 3.2%; 6.4%	-	31.6%
6	Goniometer (Δ between arms >20°)(%)	26.8%	-	-	-	-	-	-	-	-	3.5%
1305	Inable to raise arm above shoulder (%)	-	-	-	-	-	-	-	-	-	3.4%
Decreased abduction	Goniometer (°)	152°	178°	-	143.4°	-	-	-	162.1°;	162.5°	-
	Goniometer (Δ between arms)(°)	-	-	-	-14.7°	-	-	-6.7°	158.9°	-5.7°	-
14	Goniometer (Δ between arms >10°)(%)	40.8%	20.5%	-	-	-	-	5.7%	-8.4°; -6.6°	-	37.8%
3076	Goniometer (Δ baseline/FU)(°)	-	-	-6.5°	-	-	-1.9°	-1.5°	-	-	-
	Goniometer (Δ baseline/FU>10°)(%)	-	44%	100%	-	76.3%	0%, 10%	7%	-2.5°	-	-
	Goniometer (Δ baseline/FU>20°)(%)	-	-	-	-	-	-	-	-	-	6%
	Not described	-	-	-	-	-	-	-	7%	-	0%,41,4%
Decreased forward flexion	Goniometer (°)	150.6°	176°	-	162.6°	-	-	-	169.8°,154.6°	-	-
	Goniometer (Δ between arms)(°)	-	-	-	-6.5°	-	-	-3.7°	-4.5°; -2.5°	-3.4°	-
	Goniometer (Δ between arms >10°)(%)	-	-	-	-	-	-	-	-	-	28,9%
11	Goniometer (Δ baseline/FU)(°)	-	-	-5.8°	-	-	-2.0°	-2.0°	-2.7°	-	-
926	Goniometer (Δ baseline/FU>10°)(%)	-	37%	100%	-	86.4%	0%; 7%	9%	10%	-	-
	Goniometer (Δ baseline/FU>20°)(%)	-	-	-	-	-	-	-	-	-	0%
Decreased external rotation	Goniometer (°)	-	-	-	65.7°	-	-	-	63.1°	-	-
	Goniometer (Δ between arms)(°)	-	-	-	-0.5°	-	-	-1.2°	-1.2°; -1.8°	-1.8°	-
	Goniometer (Δ between arms >10°)(%)	-	-	-	-	-	-	-	-	-	11.1%
9	Goniometer (Δ baseline/FU)(°)	-	-	-0.7°	-	-	-0.2°	-0.6°	-0.6°	-	-
852	Goniometer (Δ baseline/FU>10°)(%)	-	19%	0%	-	0%	0%; 5%	9%	16%	-	-
	Goniometer (Δ baseline/FU>20°)(%)	-	-	-	-	-	-	-	-	-	1%
Decreased internal rotation	Goniometer (Δ between arms)(°)		-	-	-	-	-	-	-1.3°	-	-
	Goniometer (Δ between arms >10°)(%)		-	-	-	-	-	-	-	-	44.4%
	Goniometer (Δ baseline/FU)(°)		-	-0.4°	-	-	-1.0°	-0.2°	-1.7°	-	-
5	Goniometer (Δ baseline/FU>10°)(%)		2%	0%	-	0%	0%; 0%	3%	0%	-	-
691											
Decreased extension	Goniometer (°)	51,7°	-	-	-	-	-	-	52.2°	-	-
	Goniometer (Δ between arms >10°)(%)	-	-	-	-	-	-	-	-	-	13.3%
3	Goniometer (Δ baseline/FU>10°)(%)	-	-	3%	-	0%	0%	-	-	-	-
114											

Table 3. Continued

Morbidity Number of studies Participants	Method of assessment	Postoperative outcomes									
		0-1 week	**2 weeks**	**1 month**	**6 weeks**	**2 months**	**3 months**	**6 months**	**12 months**	**24 months**	**>24 months**
Decreased	Goniometer (°)	-	-	-	79.9°	-	-	-	82.4°	83.6°	-
Abd/external	Goniometer (Δ between arms)(°)	-	-	-	-4.8°	-	-	-2.5°	-3.9°	-3.1°	-
rotation	Goniometer (Δ baseline/FU>20°)(%)	-	-	-	-	-	-	-	-	-	0%
5											
161											
Decreased	Goniometer (°)	29.4°	-	-	-	-	-	-	35.6°	-	-
hor. add	Goniometer (Δ baseline/FU>10°)(%)	-	-	24%	-	0%	0%	-	-	-	-
1	Goniometer (Δbetween arms 5°-20°)(%)	-	-	-	-	-	-	-	-	-	5%
25	Goniometer (Δ between arms >20°)(%)	-	-	-	-	-	-	-	-	-	0%
Loss of	Questionnaire (%)	28%	9%	-	-	-	-	8%	8%	5%	35.6%, 11%;
strength											47.7%; 6%
5	VAS (%)	-	-	-	-	-	-	-	19%	-	-
635											
Decreased	Yamar (Δ between arms)(kg)	-	-	-	-1kg	-	-	0kg	0.3kg	-0.5kg	-
grip strength	Yamar (Δ baseline/FU)(Nm)	-	-	-	-5.8Nm	-	-	-	0.0Nm	-17.2Nm	-
5	Yamar (Δ baseline/FU>20%)(%)	-	-	-	-	-	-	-	-	-	5%
161											
Decreased	HH dynamometer(Δbetween arms)(Nm)	-	-	-	-0.4Nm	-	-	-5.9Nm	-4.1Nm	-3.1Nm	-
strength	HH dynamometer(Δ baseline/FU)(Nm)	-	-	-	-14.4Nm	-	-	-	-7.5Nm	-	-
elbow flexors	HH dynamometer (Δ baseline/FU>20%)	-	-	-	-	-	-	-	-	-	0%
4	(%)										
161											
Decreased	HH dynamometer(Δbetween arms)(Nm)	-	-	-	-1.2Nm	-	-	-2.2Nm	-7.4Nm	-3.8Nm	-
strength	HH dynamometer(Δ baseline/FU)(Nm)	-	-	-	-15.9Nm	-	-	-	-1.0Nm	-	-
shoulder	HH dynamometer (Δ baseline/FU>20%)	-	-	-	-	-	-	-	-	-	6%
abductors	(%)										
5	Diminution abduction+3kg (%)	-	-	-	-	-	-	-	-	-	15.8%
192											
Winged	Not described	0%	-	-	-	-	-	-	-	0%	-
scapula											
1											
449											

Table 3. Continued

Morbidity Number of studies Participants	Method of assessment	Postoperative outcomes									
		0-1 week	**2 weeks**	**1 month**	**6 weeks**	**2 months**	**3 months**	**6 months**	**12 months**	**24 months**	**>24 months**
Axillary web syndrome **2** **83**	Physical exam	-	-	12.1%	-	-	20%	-	-	-	-
Arm pain **5** **1426**	Questionnaire (%)	9.3%; 22%	22%	9.7%	-	-	3.3%	11%, 6.4%	11%; 3.4%	8%	9.3%;8.1%; 7%
	VAS (%)	-	-	-	-	-	-	-	28%	-	-
Shoulder pain **2** **568**	Questionnaire (%)	9.3%	-	-	-	-	-	-	-	-	9.3%; 8.1%
Axillary/ thoracic pain **2** **568**	Questionnaire (%)	8.2%, 3,4%	-	-	-	-	-	-	-	-	32.2%, 5,6%
Numbness **12** **3870**	Questionnaire (%)	6.6%		18%; 40.6%; 3.7%	-	-	20%; 3%	14.5%; 16%; 30.3%; 3%	16.7%; 12.6%; 11%; 24.9%,	9.9%	51.1%; 10.9%; 26.3%; 8.1%
	Pin-prick method (%)	-		14%	-	-	14%	15%	2.7%	-	-
	Not described (%)	-		31.7%	64%	-	-	42.9%	9%	18%	
									17.2%; 25.5%		10.5%
Arm numbness **3** **553**	Questionnaire (%)	16%	10%	-	-	-	-	8%	9%	7%	6%
	Von Frey filaments	-	2%	-	-	-	0%	0%	0%	-	-
	VAS (%)	-	-	-	-	-	-	-	7%	-	-
	Cotton ball/needle	-	-	-	-	-	-	-	-	-	5.1%
Axillary numbness **2** **434**	Von Frey filaments	-	7%	-	-	-	0%	0%	2%	-	-
	Cotton ball/needle	-	-	-	-	-	-	-	-	-	14.4%
Paresthesia **4** **2269**	Questionnaire (%)	-	-	-	-	-	-	10.4%	9.2%	8.6%	7.5%; 10.2%; 15.8%, 10,8%

Abbreviations:%: percentage of patients; Δ: difference; FU: follow-up; VAS: visual analogue scale; HH: handheld; abduction+3kg: abduction against a resistance of 3kg; hor: horizontal; abd: abduction; add: adduction

Table 4 Morbidities and methods of assessment

Morbidity	Method of assessment	Author, participants, follow-up range (months)								
		Husen, 203 Range: 12-36	Barranger, 54 Range: 10-31	Haid, 66 Range: >2	Haid, 57 Range: 5-30	Burak, 48 Range: 8-29	Langer, 40 Range: 6-107	Helms, 57 Range: 6-36	Belmonte, 64 Range: 1-12	Wernicke,111 Range: 0-24
Loss of mobility	Questionnaire (%)	12%	9.4%	Low morb.	8.8%	-	-	Low morb.	-	-
	Referral to therapy is warranted (%)	-	-	-	-	-	0%	-	-	-
Decreased abd	Goniometer (Δ between arms >10°)(%)	-	-	Low morb.	-	-	-	Low morb.	-	-
Loss of strenght	Questionnaire (%)	18%	17.3%	Low morb.	-	-	-	Low morb.	-	-
	Abd+3kg (Δ between arms >20°)(%)	-	-	Low morb.	-	-	-	Low morb.	-	-
Pain	Questionnaire (%)	16%	-	Low morb.	19.3%	-	-	Low morb.	-	-
Arm/shoulder pain	Questionnaire (%)	-	21.2%	-	-	-	-	-	-	-
Numbness	Questionnaire (%)	6%	5.7%	-	0%	16.7%	-	-	-	-
	Physical exam (%)	-	-	Low morb.	-	-	-	Low morb.	-	-
Paresthesia	Questionnaire (%)	-	5.9%	-	7%	-	-	-	-	-
	Not described (%)	-	-	-	-	-	25%	-	-	-
Winged scapula	Physical exam (%)	-	-	-	-	-	-	-	0%	-
Axillary web syndrome	Physical exam (%)	-	-	-	-	-	-	-	-	0,9%

Abbreviations: %: percentage of patients; Δ: difference; abduction+3kg: abduction against a resistance of 3kg; abd: abduction; morb: morbidity

surgery some patients still suffer from shoulder and/or arm impairments after SLNB alone. Impairments with the highest incidence after 2 years are pain (range: 5.6%-51.1%)[6,12,14,15,17], numbness (range:8.1%-51.1%)[6,7,12,14,15,17], loss of strength (range: 0%-35.6%)[6,12,14,17,18], decreased internal rotation (44.4%)[6] and decreased abduction (range: 0%-37.8%)[6,17,18,33] (see Table 3).

Within the first month after the SLNB the morbidity with the highest incidence was restricted shoulder range of motion (ROM). Mainly abduction and forward flexion were limited. One study demonstrated that all patients had limited abduction and forward flexion of 10° or more at 1 month post operatively[13]. External rotation and adduction were limited to a lesser extent and internal rotation and extension of the shoulder were minimally affected. The longitudinal course of the shoulder ROM showed a decreasing prevalence. One study showed that more than 2 years after surgery a limitation in abduction of 10° or more was still present in 37.8% of patients[6]. Contradictory, another study described an incidence of 0%[17]. This contradiction can possibly be explained by the difference in assessment. For example, shoulder ROM was assessed using a goniometer[2,6–11,13,17,18,21,24,25,27,30,31], questionnaires[16,17,19,20,22,23,26,28,32] or by evaluating the ability to raise the arm above the shoulder[14]. Two studies did not describe the method of assessment for ROM[17,18]. In some studies data were compared between both arms[2,6–8,17], in other between the baseline values and follow-up values[13,18,21,31]. Therefore, the results must be interpreted with caution. Additionally, studies used various ways to describe the outcome: some studies described the incidence and determine a cut-off value. For example a difference of 10° or more in ROM is a loss of mobility[6,7,13,17,21]. Other studies described raw data for example degrees in the case of shoulder ROM[2,8–11,24,25,31].

Other morbidities such as pain, numbness and loss of strength were often present from the first week post operatively and can persist until 2 years after surgery. The highest incidence of pain is described 1 month after surgery (56.6%)[32]. The incidence of paresthesia was 10,4% at 6 months post operatively and it is still present 2 years post operatively, ranging from 7.5% to 15.8%[7,14,17]. The selected literature contained various descriptions of morbidities. For example, when describing a morbidity, some articles made a subdivision by region. For example, for pain a distinction was made between arm pain, shoulder pain, axillary pain and thorax pain. The same distinction was used for numbness. The differences in assessment methods and standards for describing a morbidity made comparison of data difficult.

Winged scapula was reported only in one study. Not a single SLNB patient developed this impairment and only one ALND-patient did[15]. This showed that the expectation of such morbidity is minimal.

The prevalence of axillary web syndrome 1 month after SLNB alone was 12.1%, compared to 37.3% after ALND[5] and 20% after 3 months compared to 72% in ALND patients[24]. One study described an incidence of 0.9%, but this study did not describe a specific moment in time, but instead a follow-up range[33].

Two studies used a summation score to assess shoulder and arm morbidity[27,30]. Four subjective and four objective symptoms were assessed and scores were attributed to the tests. A summary score reflecting severity of shoulder-arm morbidity is calculated from the 8 tests, with higher scores reflecting less severe morbidity. This method made it difficult to obtain data on individual morbidities.

Apart from shoulder morbidity, 7 of the selected studies assessed the incidence of seroma formation[11,14,15,17,25,29,32], 6 studies assessed the incidence of infection[11,14,15,17,25,32] and 4 studies the incidence of hematoma after SLNB[14,15,17,25]. The assessment of seroma formation, infection and hematoma was commonly performed by physical examination[25,29]. In two studies these morbidities were assessed using a questionnaire where patients described their symptoms[14,32]. Unfortunately most studies did not describe the assessment instrument[11,15,17].

The incidence of seroma formation the first month after the SLNB ranged between 1.7% and 12% among the studies[11,14,15,17,25,29]. During the first week post operatively, the incidence varied from 1.7% to 11%[11,14,15,17,29]. One study described an incidence of 12% after 2 weeks[25] and after 1 month the incidence was only 3.9% according to another study[32]. Literature showed that the incidence of seroma after ALND (range 3%-85%) is higher compared to SLNB[34]. The question rises whether the tissue alterations associated with seroma formation have an impact on the development of arm and shoulder impairments.

The incidence of infection ranged between 0.8% and 10% during the first week postoperatively[11,14,15,17]. One study described an incidence of 6% after 2 weeks[25], and another study an incidence of 6.3% after 1 month[32].

During the first postoperative week, the incidence of hematoma after breast surgery using the SLNB ranged between 1.8% and 4.2%[14,15,17]. One study reported that the incidence of hematoma is 8%, two weeks after surgery[25].

Although the literature search did not focus on secondary lymphedema of the arm as a morbidity of breast cancer surgery, several of the selected articles described it[2,6–12,14,15,17,18,20–23,26–33]. When lymphedema of the arm was assessed objectively by means of circumference measurements or a water displacement method, after 6 months the incidence was 9% for SLNB-patients[7]. After 12

months the incidence ranged between 2% and 8.6%[7,21] and after 24 months it was 8.2%[7]. More than 2 years after breast cancer surgery the incidence ranged between 0% and 27.3%[6,7,14,15,17,18,33]. Although all studies found that the incidence of secondary lymphedema was lower after SLNB compared to ALND, it cannot be neglected and it is an indication for further investigation.

In the next paragraph the limitations present in this systematic review are discussed. Many limitations relate to methodological differences in the assessment of the reported outcomes, making comparison of results difficult. As mentioned earlier there are no uniform standardized assessment criteria for assessing the upper limb in breast cancer patients. Studies used various methods and standards, which made it difficult to compare data among studies. Different assessment methods may partly explain the variation in incidence of the morbidities. A consensus on standardized assessment criteria is needed among researchers and clinicians. Studies have different patient groups and use different cancer treatment, which may also contribute to the differences in incidence of the arm and shoulder impairments. There were only 6 RCTs in our study because few publications were conducted in a randomized approach[7,12,20,29–31].

From a total of 29 eligible studies that compared SLNB and ALND, all of them reported much lower morbidity after SLNB alone; for a summary see Table 5. Increased morbidity can be associated with less QoL[6]. Long term health problems related to breast cancer treatment and the QoL afterwards are becoming more important, therefore information on arm and shoulder impairments in sentinel node negative patients should be used to improve the rehabilitation of these patients.

Table 5 Incidences of arm and shoulder impairments according to type of surgery

Morbidity	ALND	SLNB
Numbness	3%-86,8%	6,6%-51,1%
Paresthesia	13,5%-73,3%	7,5%-15,8%
Pain	57,5%-78,8%	15,8%-56,6%
Loss of mobility	Up to 100%	Up to 100%
Loss of strength	42%-60,5%	5%-35,6%
Axillary web syndrome	37,3%-72%	12,1%-20%

Conclusion

Compared with ALND, SLNB is a minimally invasive procedure. Arm and shoulder morbidities including loss of mobility, loss of strength, pain, sensory disorders, axillary web syndrome and winged scapula are less common or absent after SLNB alone compared to ALND. However, shoulder

morbidities in sentinel negative patients are not negligible and have an impact on the QoL. Some patients still suffer from those impairments more than 2 years after breast surgery. Further research, determining predictors of morbidity in SLNB patients is needed so risk factors can be taken into account in clinical practice. More long-term prospective studies with standardized measurements are warranted to investigate the relationship between arm and shoulder impairments and quality of life.

Conflict of interest

The authors declare that they have no conflict of interest.

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CHAPTER 1bis

Incidence and time path of lymphedema in sentinel node negative breast cancer patients: a systematic review

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Abstract

Objective: To systematically assess the incidence/prevalence and time path of lymphedema in sentinel node negative breast cancer patients.

Data sources: A systematic literature search was performed using four different electronic databases (Pubmed, Embase, Cochrane Clinical Trials, WoS) until November 2013.

Study selection: Inclusion criteria were: 1) research studies that included breast cancer patients who were surgically treated using the sentinel lymph node technique (SLNB), 2) sentinel node negative patients, 3) studies that investigated lymphedema as a primary or secondary outcome, 4) data extraction for incidence or time path of lymphedema was possible and 5) publication date starting from 1st January 2001. Exclusion criteria were (1) reviews or case studies, (2) patients who have had a SLNB followed by an axillary lymph node dissection (ALND), (3) results of ALND-patients and SLNB-patients were not described separately and (4) studies not written in English.

Data extraction: after scoring the methodological quality of the selected studies, the crude data concerning the incidence of lymphedema were extracted. Data concerning the time points and the incidence of lymphedema were also extracted.

Data synthesis: 28 articles were included, representing 9,588 SLNB negative patients. The overall incidence of lymphedema in sentinel node negative breast cancer patients ranged from 0% to 63.4%. The studies that have assessed lymphedema at predefined time points, instead of a mean follow-up time, demonstrated an incidence range at ≤3, 6, 12, 18 or > 18 months post-surgery of 3.2-5%, 2-10%, 3-63.4%, 6.6-7% and 6.9-8.2% respectively.

Conclusion: In SLNB-patients there is still a problem of lymphedema, if so it mostly occurs 6 to 12 months after surgery. Due to different assessments and criteria there is a wide range in incidence. Clear definitions of lymphedema are absolutely necessary to tailor therapy.

Key words: Lymphedema**,** Breast neoplasms, Sentinel Lymph Node Biopsy, Systematic Review

Introduction

Breast cancer is known as the most common malignancy in women in the Western World. Unfortunately, the incidence is still increasing[1]. At some time during their life, breast cancer will be diagnosed in 1 out of every 8 women[2]. In the past breast surgery was very extensive; present-day surgical procedures have become more refined. Many women underwent and still undergo axillary lymph node dissection (ALND) which can cause several arm and shoulder morbidities like numbness, pain, limitation of arm movement, also including lymphedema [3]. Over the years, surgical techniques have changed dramatically with the introduction of breast conserving techniques and the sentinel lymph node biopsy (SLNB). SLNB is widely used as a standard assessment procedure in breast cancer patients. The number of patients treated with SLNB is increasing since women with limited SLN involvement are no longer treated with ALND[4]. SLNB can reduce unnecessary axillary clearance; therefore it is expected to substantially decrease arm and shoulder morbidity, including upper limb lymphedema [5]. In the literature SLNB and ALND patients are often compared, with beneficial results in favor of SLNB[6]. Despite a strong reduction in morbidity after the SLNB procedure, the complication rate may be underestimated. The occurrence of lymphedema, a condition characterized by fluid accumulation in the interstitial space[7], is expected to be minimal in SLNB [8]. However, a recent systematic review by Verbelen et al. demonstrated that lymphedema might be a morbidity in SLNB negative patients to take into account [9]. The aim of this systematic review is to provide answers concerning the following questions: 1) what is the incidence/prevalence of lymphedema related to breast cancer surgery in sentinel node negative patients, 2) what is the time path of this lymphedema?

Methods

The literature was systematically reviewed, based upon the PRISMA guidelines, addressing the following research questions: 1) what is the incidence of lymphedema related to breast cancer surgery in sentinel node negative patients, 2) what is the time path of lymphedema in SLN negative patients? Four electronic databases were screened online to identify eligible studies: PubMed (October 14, 2013), Web of Science (October 22, 2013), Embase (October 23, 2013) and Cochrane clinical trials (October 29, 2013). In order to retrieve eligible studies, Medical Subject Headings (Mesh-terms) and key words were combined in a Boolean search strategy to describe the patient population (P: breast cancer), the intervention (I: SLNB) and the outcome (O: Lymphedema). We did not define any comparison (C: /) nor study design (S:/) and all papers had to be written in Dutch or English. The specific search strategy used for PubMed is shown in detail in Table 1. An equivalent search strategy was used for the other three databases but included a number of modifications regarding the differences in the use of indexing terms (MeSH for PubMed and Cochrane, EMTREE for EMBASE).

Table 1. Boolean search strategy performed in Pubmed

"Lymphedema"[MeSH] OR "Lymphedema"[All Fields] OR "lymphoedema" [All Fields]) AND ("Breast Neoplasms"[MeSH] OR "Breast Neoplasms"[All Fields] OR "breast cancer" [All Fields]) AND ("Sentinel Lymph Node Biopsy"[MeSH] OR "Sentinel Lymph Node Biopsy"[All Fields] OR "Sentinel"[All Fields] OR "Sentinel lymph node" [All Fields] OR "Sentinel lymph node dissection" [All Fields] OR " lymph node excision" [MeSH] OR " lymph node excision"[All Fields]) NOT review NOT case report

Abbreviation: MeSH, Medical Subject Heading

All references were screened by title and abstract in order to decide for further reading or not (first screening). Three raters (G.N., D.T., C.D.) screened the selected full-texts, based upon predefined inclusion and exclusion criteria (second screening). In case the three raters had diverging opinions, consensus was sought during a meeting. The inclusion criteria used during both screenings were: 1) research studies that included breast cancer patients who were surgically treated using the SLNB technique, 2) sentinel node negative patients, 3) studies that investigated lymphedema as a primary or secondary outcome and 4) data extraction for incidence or time path of lymphedema was possible. Exclusion criteria were 1) reviews or case studies, 2) patients who had a SLNB followed by an ALND, 3) results of ALND-patients and SLNB-patients were not described separately and 4) studies not written in English or Dutch .

Data on patient characteristics, method of assessment, definition of lymphedema, incidence of lymphedema and time path of lymphedema were independently abstracted by three reviewers (G.N., D.T., C.D.). In case of diverging opinions, a consensus meeting was held.

Quality assessment

The methodological quality of the selected articles was assessed using checklists for cohort studies, cross-sectional studies and randomized controlled trials (http://dcc.cochrane.org/beoordelingsformulieren-en-andere-downloads). Three reviewers (G.N.., D.T., C.D.) evaluated the selected articles independently. Items could be rated by "1", "0" or "?". An item was rated "1" if sufficient information was available and bias was unlikely. An item was rated "0" if sufficient information was available but the article did not meet a specific criterion. An item was rated "?" if no information was available. If disagreement persisted about assigning a score to an item, consensus was sought during a meeting. Nine items were scored for RCT and cohort studies, while only five items were scored for the cross-sectional studies.

Results

Initially the search yielded 635 citations. After the first screening and removal of duplicates, 96 full text articles were retrieved. After the final screening based upon the full-texts, 28 studies were found eligible and included in this review[6, 8, 10-35]. The results of this systematic review are based on 21 cohort studies[8, 14-20, 22-30, 32-35], 3 RCT's[6, 12, 21] and 4 cross-sectional studies [10, 11, 13, 31]. Four studies[16, 17, 24, 25] reported from the same sample of patients, these data were extracted only once. Consequently, the selected studies represent a total of 9,588 SLNB negative patients. The literature search and study selection process are shown in Figure 1.

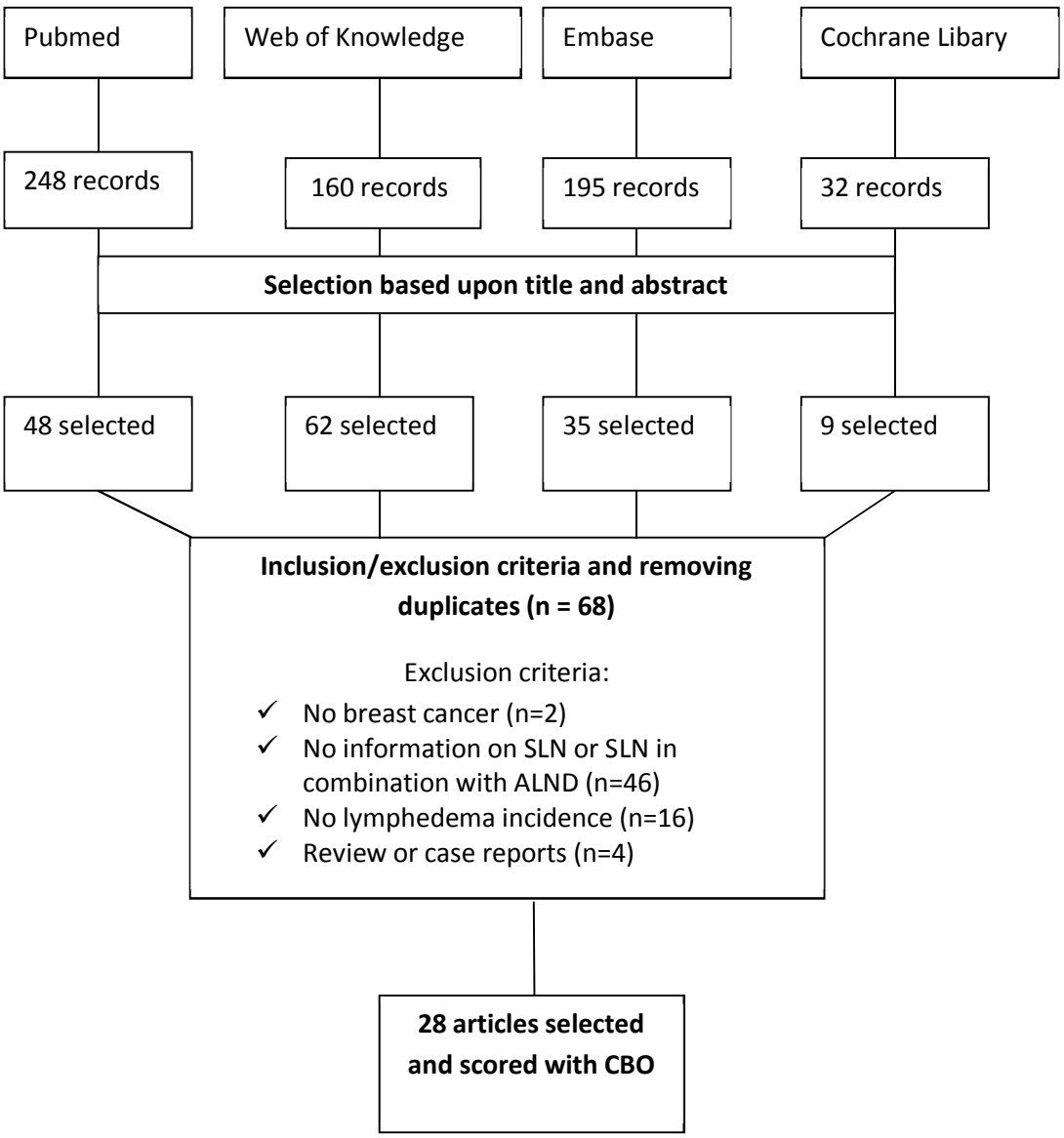

Figure 1. Flow chart of the study selection procedure

Table 2. Summary of lymphedema incidence/prevalence and time path of the selected studies

Reference (author, year) Design (methodological score) n (n° of SLNB negative patients)	Lymphedema assessment method definition used	Incidence of lymphedema in SLNB (percentages are in bold)	Time points/follow-up
Armer et al., 2004 Cross-sectional (5/9) n=9	Circumference measurements >2 cm of difference between sides	2/9 patients or **22.2%**	4-14 months after surgery; median 8.5 months after surgery
Ashikaga et al., 2010 RCT (6/9) n=2008	Water displacement <5% diff /5-10% diff/>10% diff	**16.7%** of 1151 patients have excess volume after 3 year of follow-up (Pts with >5% diff who had <5% diff at baseline). >10% between **7-9%**	>10% diff at Baseline, 6-12-18-24-30-36 months follow-up are respectively 8%-9%-8.6%-6.6%-8.2%-6.9%-7.5%
Blanchard et al., 2003 Cross-sectional (6/9) n=685	Questionnaire	39/683 patients or **6%**	Mean follow-up was 2.4y (sd = 0.9y)
Celebioglu et al., 2007 Cohort (6/9) n=30	Water displacement >10% diff between arms	0/30 patients or **0%**	Follow-up: baseline- 1-2-3y
Goldberg et al., 2010, 2011 Cohort (6/9) n=600	Circumference measurements Difference of >2cm = presence of edema Difference of >5cm = severe edema Interview	**5%** (31/600) had edema of which 3/600 had severe edema **3%** (18/600) reported edema	Median follow-up was 5y (2.7-8y)
Golshan et al., 2003 Cohort (3/9) n=77	Circumference measurements Difference of >3cm between arms	2/77 or **2.6%**	Minimum 1y post-op
Haid et al., 2002 Cohort (5/9) n=57	Circumference measurements Difference of >2cm between arms	2/57 or **3.5%**	mean follow-up time was 25 (range 14–60) months
Langer et al., 2007 Cohort (7/9) n=449	Circumference measurements Difference of >2cm between arms	15/431 or 3.5%	Mean follow-up time was 31.0 (range 11-62)months
Leidenius et al., 2005 Cohort (4/9) n=92	Circumference measurements Difference of >2cm between arms	1/92 or **1%**	3 years post-operative
Lucci et al., 2007 RCT (6/9) n=446	Circumference measurements Difference of >2cm between arms	Range = **5.5% - 7.7%**	Subjective assessment: 6 months 19/339 or 5.6% 12months 16/268 or 6% >12 months 14/253 or 5.5%

			Objective assessment: 30 days 17/272 or 6.3% 6 months 21/271 or 7.7% 12 months 14/226 or 6.2%
Lumachi et al., 2009 Cohort (5/9) n=54	Circumference measurements Difference of >2cm between arms	2/54 or **3.7%**	median follow-up was 22 months (range 18-28 months)
Madsen et al., 2008 Cohort (6/9) n=164	Water displacement Questionnaire	Range **7-10%** (questionnaire)	6 months 10% (questionnaire) 18 months 7% (questionnaire)
Mansel et al., 2006 RCT (8/9) n=478	Circumference measurements Self-assessment	**3.2% - 5%** (self-assessment)	1 month 3.2% 3 months 5% 6 months 4.5% 12 months 5%
Mc Laughlin et al., 2008 (x2) Cohort (6/9) n=600	Circumference measurements Difference of >2cm = presence of edema Difference of >5cm = severe edema Interview	**5%** (31/600) had edema of which 3/600 had severe edema **3%** (18/600) reported edema	Median follow-up time was 5y (range 2.7-8y)
McLaughlin et al., 2013 Cohort (5/9) n=67	Circumference measurements 10% or more increase in volume Questionnaire Interview	2-3% 5-6% 6-11%	6 months: 2% (1/67) had measured edema 5% (3/67) had edema based upon the questionnaire 11% had perceived edema based upon the interview 12months: 3% (2/67) had measured edema 6% (4/67) had edema based upon the questionnaire 6% had perceived edema based upon the interview
Ozcinar et al., 2012 Cohort (8/9) n=80	Circumference measurement >2cm of difference between arms	**1.9-8%**	Mid-term (9-12 months post-op) 8% Late-term (> 12-64 months post-op) 1.9%
Rodriguez Paim et al., 2008 Cross-sectional (3/5) n=48	Circumference measurement >1cm of difference between arms	**4.2%** (2/48)	Mean 23 months post-op (6-60 months)

Rönka et al., 2005 Cohort (7/9) n= 43	Circumference measurement Increase in limb volume of 5% or more Self-reported lymphedema (VAS-score)	**12%** (5/43) Mild **9%** Moderate **3.5%**	1 year after surgery
Roumen et al., 2001 Cohort (4/9) N=90	Questionnaire	**0%**	Median 24 (16-40) months
Schijven et al., 2003 Cohort (6/9) n=180	Questionnaire	**1.1%**	<1y – 3y post-op
Schulze et al., 2006 Cohort (7/9) n=31	Circumference measurement for the arm in combination with a water displacement for the volume of the hand >10% difference Questionnaire	15.8% (3/19) 10.5% (2/19)	Both incidence percentages are presented for long-term morbidities (>20 months post-op; mean 49 months for SLNB)
Velloso et al., 2011 Cross-sectional (3/5) n=45	Circumference measurements 10% or more increase in volume	**4.4%(**2/45)	Mean 21.3 (range 10-42) months
Wernicke et al., 2013 Cohort (7/9) n=111	Circumference measurement >1cm of difference between arms Self-assessment by patients	**5.4%** (6/111) **9.1%** (10/111)	Mean 9.4y after surgery (range: 8.3-15.3y)
Wilke et al., 2006 Cohort (6/9) N=4069	Circumference measurement >2cm increase in comparison with baseline measurement	**0-7%**	0% at 30d of follow-up (n= 4069) 7% at 6month follow-up (n = 2904)
Yen et al., 2009 Cohort (6/9) n=319	Self-assessment by telephone survey	**7%**	Median 48 months post-surgery
Francis et al., 2006 Cohort (6/9) n=41	Circumference measurements >5% difference in comparison with pre-operative volume	**63.4%** (26/41)	1 year post-surgery: >5% difference (17/41 or 41%) ≥10%difference (9/41 or 22%)

Overall, including all methods of assessment and all definitions used, the incidence/prevalence of lymphedema is very broad, ranging from 0% to 63.4% (see table 2). When the included studies were divided based upon the assessment methods, the following incidences were demonstrated. For the studies that used a circumference measurement, the incidence varied between 1% and 63.4% (table 2)[8, 10, 11, 15-27, 30-33]. When a water displacement method was used, the incidence varied from 0% to 15.8% (table 2)[12, 14, 30]. Water displacement and circumference measures are both objective assessments whereas questionnaires and interviews are subjective tools. When looking at the studies that have used these subjective tools, the incidence varied from 0% to 11% (table 2)[6, 13, 17, 23, 25, 28-30, 32, 34, 35].

In the above described results, no distinction was made based upon the different follow-up times or measuring intervals. Next, the incidence at specific time-points will be described (see table 3). These results were extracted from the studies that specifically reported the incidence at pre-defined time points. Most commonly, lymphedema assessment was done at 3, 6, 12, 18 or >18 months post-surgery. The longest follow-up time was 9.4 years in the study of Wernicke et al.[32] The studies that have assessed the lymphedema at predefined time points, instead of a mean follow-up time, demonstrated an incidence range at ≤3, 6, 12, 18 or > 18 months post-surgery of 3.2-5%, 2-10%, 3-63.4%, 6.6-7% and 6.9-8.2% respectively[6, 12, 15, 21, 23, 33, 35].

Combining the information about the diagnostic criteria and the defined time points, an informative overview can be presented (see table 3). Table 2 clearly presents that the incidences' change with regard to the chosen definition; and that lymphedema is most common between 6 and 12 months of follow-up. Also, the long-term incidence is not negligible. Incidences are within narrow ranges when compared to the range presented among all studies (table 2).

Discussion

The results of our systematic review clearly demonstrate that lymphedema is a non-negligible complication in SLNB negative breast cancer patients. The overall range of the lymphedema incidence is very broad, namely 0 to 63.4%. Two studies are mainly responsible for this broad range [11, 15]. Both studies have clear limitations, their results should be appraised critically with regard to the incidences found. Armer et al, reported from a very low number (n=9) of SLNB patients, of which two (22%) were diagnosed with edema [11]. Francis et al have used a very liberal definition, namely 5% volume difference between preoperative and postoperative arm volumes. Additionally, weight alterations were only corrected when patients' weight changed with 10 pounds or more. Therefore, this approach is totally different and incomparable with the other studies[15]. If both studies (Armer et al. and Francis et al.) were to be discarded from the results, the incidence range would be 0-15.8%. The aforementioned

Table 3. Overview of the incidence ranges at predefined time points with regard to the diagnostic definition used.

Definition used	≤ 3 months FU	6 months FU	12 months FU	≥ 18 months FU	References used*
Water displacement ≥ 5% difference		22.4%	12% -21.6%	19.6%	12; 27
Water displacement ≥ 10% difference		2% - 9%	0% - 8.6%	0% -8.2%	12; 14; 23; 27
Circumference measurement ≥ 2cm difference	0% - 6%	7% - 8%	6%-8%	1%	20; 21; 26; 33
Questionnaires/ subjective assessments		5% - 10%	2% - 6%	6% - 7%	21; 23; 35

*only the studies that provided data on predefined time points were used to create this table. Studies with an mean or median follow-up were omitted because of the potential bias that is created by mixing different follow-up times.

incidence rate is less in comparison with lymphedema after ALND with a reported range of 13.5% to 28.2% [36]. The response to our first research question is that lymphedema is less incident in SLNB than ALND. However, clinicians and/or therapists should still be aware of the possibility of lymphedema formation in SLNB. Mostly, the lymphedema in SLNB negative patients has a mild character. Untreated, this lymphedema will progress to a more severe lymphedema. The results of our review reveal that severe lymphedema (≥ 10% diff. or >5cm diff.) was encountered significantly less in SLNB than in ALND. However, severe lymphedema was diagnosed in 0.2-9% of the SLNB patients with lymphedema[6, 12, 13, 15-17, 20, 24, 27, 30].

Several limitations among the selected studies need to be discussed. Not surprisingly, a wide variation of assessments and accompanying measuring protocols were used by the different research groups. Four studies relied totally on subjective assessments as for example a questionnaires or an interview (incidence of lymphedema 0-7%) [13, 28, 29, 34]. Since lymphedema is a complex morbidity; it is doubtful that a patient is able to correctly answer questions regarding the presence or absence of lymphedema. Therefore, objective assessment methods like the water displacement or circumference measures are recommended. However, we also found that the objective assessments used in the selected studies had a number of limitations. In case of the circumference measurements and water displacement

method, a wide variety of definitions is used (e.g. >1cm difference, 2cm difference, >2cm difference, 5% difference, >10% difference). It is clear that when a higher difference is needed to diagnose edema, the incidence will decrease. On the contrary, a limited difference in circumference (e.g. >1 or 2cm difference) can also be found in perfectly healthy subjects. The latter is very well demonstrated in two studies that compared the incidence based upon common lymphedema definitions[37, 38]. In the same sample of breast cancer patients, the incidences varied between 21% and 70%[37] or 41% and 94%[38] based upon the chosen definition to diagnose lymphedema. It is essential that international consensus among clinicians/therapists is established concerning the definition of lymphedema. In 2007 we have proposed to use prediction formulas based upon water displacement to diagnose edema/lymphedema[39]. Another apparent limitation, none of the selected studies have mentioned to take into account the patient's arm dominance when defining the lymphedema volume. In case of unilateral edema, most researchers use the contralateral limb for comparison, stating that both limbs have the same volume. Unfortunately, both arms are not identical. It was demonstrated that the dominant arm of a healthy person is 3.3% (sd 3%) larger than the non-dominant arm[39-42]. Based upon these findings, prediction formulas for the upper limbs were presented to cope with dominance in unilateral edema[39]. We suggest taking into account these volume difference when assessing the edema volume in patients. Since none of the studies corrected for dominance, it is plausible that the lymphedema incidences presented in this review might still be underestimated.

Concerning the second research question regarding the time path of lymphedema after SLNB, diverging results were found (see table 2). Again, if we omit the studies of Armer et al.[11] and Francis et al.[15] a more focused result can be displayed and discussed. Until three months post-surgery, lymphedema after SLNB is relatively low (range 3.2% to 5%)[6]. At 6 months post-surgery an increase in lymphedema incidence is demonstrated (range 2% to 10%)[6, 21, 23]. The most common follow-up period to assess lymphedema in SLNB was 12 months post-surgery with incidences between 3% and 12%[6, 21, 23, 27]. Follow-up periods of 18 months and longer resulted in incidences between 6.9% to 8.2%. A follow-up of 5 years or longer was only seen in five studies[16, 17, 24, 25, 32] of which four[16, 17, 24, 25] reported from the same cohort. Long term (≥ 5y) incidence was 5% to 5.4% [17, 32].

Clinicians and therapists need to be aware that lymphedema remains a complication to take into account when assessing SLNB patients. As demonstrated by the different studies, 6- 12 months after surgery is a critical moment in follow-up to assess the presence of lymphedema in SLNB.

Overall, we have found that the incidence of lymphedema in SLNB is less when compared to ALND. This can be well explained by the less-invasive surgery that needs to be performed. Nevertheless, lymphedema does occur in SLN-negative patients. Therefore, new techniques are tested and

implemented by surgeons to further reduce the risk of breast cancer related lymphedema; for instance the use of axillary reverse mapping (ARM), a technique first described in 2007[43]. ARM provides a way to visualize the lymphatic routing of the arm, breast and axilla. This way, surgeons are able to preserve as much as possible the normal lymph pathways. The evidence on ARM is not yet conclusive[43]; however in SLNB patients the results are very promising[44-47]. We have found no evidence that ARM was used in one of the studies presented in the current review of the literature. However, ARM studies have also demonstrated that about 20% of the SLNB patients have a lymphatic route from the upper limb that passes the same (sentinel) nodes. Sakurai et al, have demonstrated that only these patients were at risk of developing lymphedema. Additionally, they demonstrated that 5 out of 76 patients (6.6%), who had a lymphatic route from the upper limb involving the sentinel, developed lymphedema. On the contrary, none of the patients with an alternative route from the upper limb experienced lymphedema[45]. This evidence demonstrates that in some patients it is almost inevitable to prevent lymphedema after surgery.

The current systematic review reveals that lymphedema after breast cancer therapy remains a complication even in SLNB-negative breast cancer patients. Lymphedema after breast cancer is a complication that needs life-long attention[48]. It is essential to treat the lymphedema, not only to improve the QoL[49, 50], but also to prevent the worsening and additional complications related to lymphedema[50, 51]. Physicians and therapists need to be aware that lymphedema is a possible complication in SLNB-negative breast cancer patients. The real problem exposed by the current review is the lack of a uniform diagnostic definition of lymphedema. We have found subjective as well as objective assessments. The incidence found by both assessments differ within a same sample of patients; this can be explained by the fact that some patients will have complaints related to lymphedema without the objective volume difference. Vice versa, some patients will demonstrate a significant volume difference without complaining from the lymphedema. Therefore, the authors suggest combining an objective assessment with a subjective assessment. We suggest the water displacement method with correction for hand dominance as objective assessment[39]. The subjective assessment should be a questionnaire that relates to the limitations based upon the ICF-criteria, for instance the LYMPH-ICF questionnaire[52]; none of the selected studies have used such an approach. Patients with a volume difference between 5-10% and limited complaints on the questionnaire are instructed to self-management of their lymphedema whereas patients with severe complaints or severe volume increase receive full treatment based upon compression, manual drainage and exercise[53]. Not only therapists but also the patients should be attentive to all possible complications, including lymphedema, that could arise after breast cancer treatment, enhancing the early detection

of these complications[9]. Therefore, providing sufficient information, not only about lymphedema but all possible complications[9, 54] after breast cancer treatment, is essential.

Study limitations

Very few RCT's could be included in the current review; due to the randomization process the results concerning the SLNB negative patients were not depicted separately. Due to a great variety in assessments and definitions used for lymphedema it is difficult to make a general conclusion concerning the incidence of lymphedema. We do suggest an alternative diagnostic approach.

Conclusion

In SLNB-patients there is still a problem of lymphedema, if so it mostly occurs 6 to 12 months after surgery. Due to different assessments and criteria there is a wide range in incidence. Clear definitions of lymphedema are absolutely necessary to tailor therapy.

Conflict of interest

The authors have no conflict of interest to declare.

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CHAPTER 2

Long-term morbidity after a negative sentinel node in breast cancer patients

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Abstract

Morbidity after sentinel lymph node biopsy is often underestimated. The aim of this study is to inventory arm and shoulder complaints in sentinel node negative breast cancer patients post-surgery after long-term follow-up. Sentinel-node-negative breast cancer patients with at least 2 years of follow-up after surgery were included in this study. Self-reported arm and shoulder morbidities were assessed using a survey. Patients (n=126) were asked if they ever developed complaints, if these complaints were still present and whether they were ever treated for these complaints. After a mean follow-up of 55.5 months (range 25-86 months) the prevalence of the self-reported arm and shoulder complaints was 25.8% for pain, 12.0% for numbness, 6.4% for paresthesias, 7.1% for lymphedema, 8.0% for axillary web syndrome, 26.2% for loss of strength and 19.5% for limitations in range of motion. 38.1% of the patients were treated by a physical therapist concerning the experienced complaints after SLNB. Up to 7 years post-surgery a considerable amount of sentinel negative patients still suffer from arm and shoulder complaints. These complaints affect the activities of daily living. Therefore, more research is needed regarding the value of early detection and treatment of these complaints.

Key words: Breast Neoplasms, Sentinel lymph node biopsy, Morbidity, Survey

Introduction

In scientific literature a distinction is made between an axillary lymph node dissection (ALND) and a sentinel lymph node biopsy (SLNB) in the treatment of breast cancer. The less invasive SLNB results in considerably less arm and shoulder morbidity[1]. However, the negative aspects of the SLNB should not be underestimated. Our systematic review in sentinel node negative patients demonstrated that a large group of patients developed arm and shoulder complaints post-treatment like pain, numbness, paresthesias, lymphedema, axillary web syndrome, loss of strength and loss of mobility[2]. Due to the evolution in breast cancer treatment, survival has increased significantly[3]. As a result, treatment-related health problems and post-cancer functioning are becoming more important[4]. To cover all health-related aspects, one should look at the bio-psychosocial framework. The International Classification of Functioning Disability and Health (ICF) is an extensively used framework to describe the health condition of a patient within this bio-psychosocial context (www.who.int/classifications/icf/en). The ICF covers all domains of disability. Disability involves dysfunctioning at one or more levels: impairments in body functions or structures, activity limitations and participation restrictions. The self-reported measures in this study focus on all the domains of the ICF. The majority of studies on the morbidities after SLNB have only a short follow-up (1 to 3 years)[4–23]. Although an abundance of previous research is available on morbidity after SLNB, the follow-up period is often short and self-reported measures focus on a specific domain of dysfunctioning. Understanding morbidity and its timeline is essential to organize adequate health care. Therefore, the aim of this study is to inventory impairments involving arm and shoulder complaints in sentinel node negative breast cancer patients and to identify activity limitations and participation restrictions. The secondary aims are to investigate which arm and shoulder complaints are still present in those patients after long term follow-up and to investigate if patients with these complaints were treated and what treatment they received.

Materials and methods

Study population

In this cross-sectional study, breast cancer patients who have had breast cancer treatment between January 2007 and January 2012 in the Multidisciplinary Breast Clinic of the Antwerp University Hospital were identified in the Clinic's database (MOCA, Medical Oncology Center Antwerp). Primary surgery consisted of breast-conserving surgery or mastectomy. Patients were eligible if they were surgically treated using the sentinel-procedure only and if the sentinel node was negative. If indicated, post-operative adjuvant treatment consisted of radiation therapy, chemotherapy, Herceptin® and/or hormonal therapy. Patients who have had a sentinel lymph node biopsy followed by an axillary lymph

node dissection and patients who were unable to fill out a Dutch survey were excluded. Eligible participants were contacted by phone between February and April 2014. Patients who gave written consent were surveyed by mail. Patients were asked to reply within 14 days. If after three weeks no survey was received, a reminder was sent to these patients. The survey was approved by the Ethical Committee of the Antwerp University Hospital (registration: B300201317503).

Data collection

Self-reported arm and shoulder morbidities were assessed by means of a survey. The survey was developed, based upon the results of our systematic review, to collect information on the following morbidities: loss of strength, loss of mobility, numbness, paresthesias, lymphedema, axillary web syndrome and pain[2]. Patients were 1) asked if they ever developed these complaints, 2) if these complaints are still present and 3) whether they were ever treated for one of these complaints. Data was collected retrospectively, however data concerning long-term morbidities were collected at the time patients filled out the survey. Several activity limitations and participation restrictions were scored on a 11-point Likert scale. A score of 0 was given when an activity was not limited at all, a score of 10 was given when an activity was impossible to execute. Current personal data like age, menopausal status, preoperative bra cup size and body mass index were also collected by the survey. In addition, medical information e.g. type of surgery, the date of surgery and the adjuvant therapies was extracted from the electronic medical file of the patients.

Data analysis

Data from the survey and the electronic medical file of the study participants were processed using 'Open Clinica', an open source clinical trial software for electronic data capture and clinical data management. The Statistical Package for the Social Sciences (SPSS) version 22 was used to analyze results. Socio-demographic and clinical variables were analyzed using descriptive statistics as frequencies, means, standard deviations and percentages. Additionally, Chi-square and t-test statistics were performed to analyze the relationship between arm & shoulder complaints to the type of surgery and adjuvant therapy.

Results

Respondents and their characteristics

A total of 126 sentinel negative breast cancer patients were enrolled in this descriptive cross-sectional study. A response rate of 83% was accomplished. For a detailed overview of the participant selection

process, see Figure 1. In all patients a radioactive isotope was the only method used to detect the sentinel node. Between 1 and 3 lymph nodes were removed, with a median of 2 lymph nodes. The characteristics of the study population are shown in Table 1.

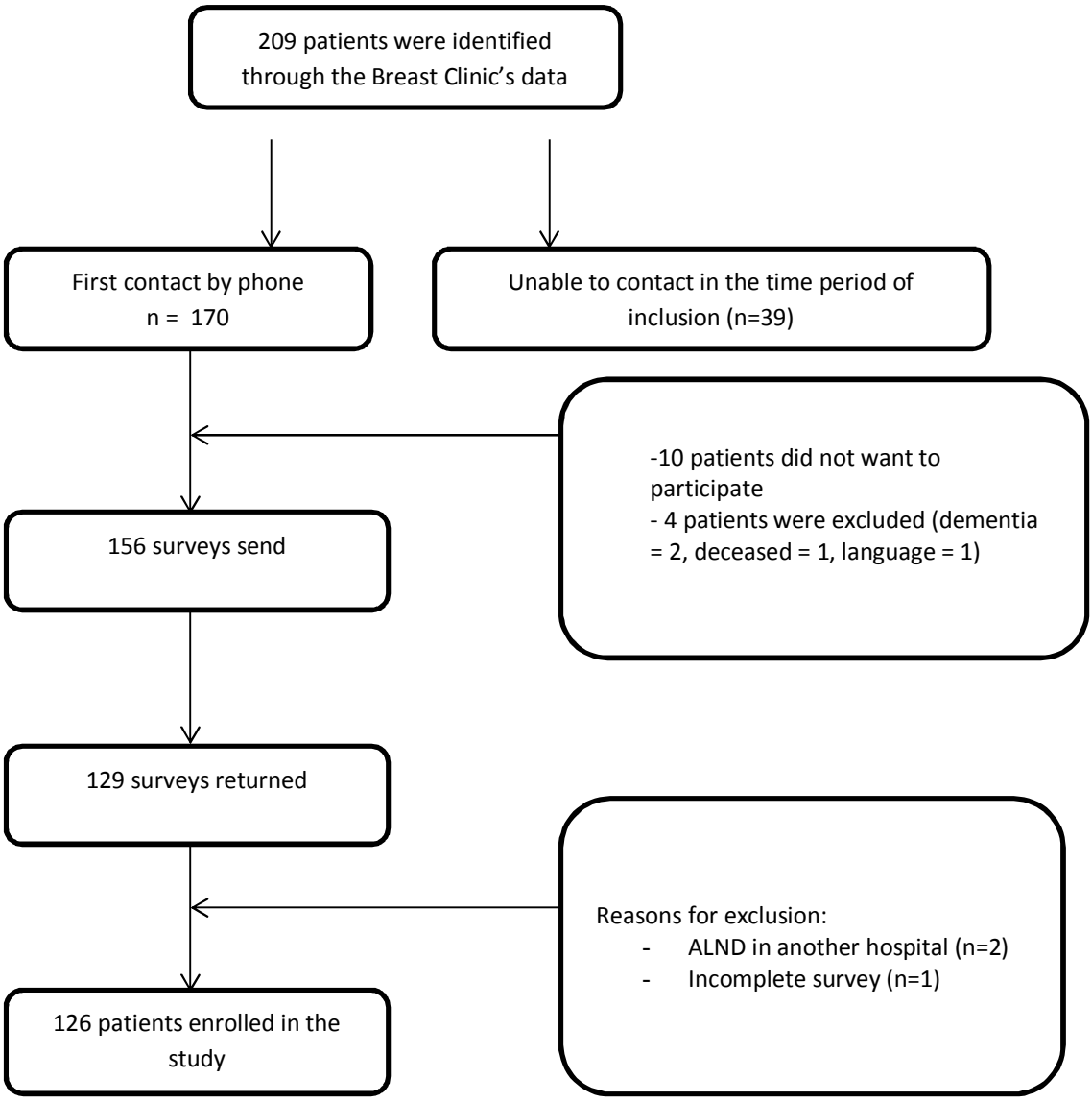

Figure 1. Selection process of the participating patients

Impairments; Arm and shoulder complaints

Many sentinel negative patients have reported post-surgery complaints (see Figure 2a). The results are presented in 2 categories. First, "Prevalence post-surgery" applies to the percentage of patients who have ever experienced complaints following surgery. For pain, 43.5% of patients developed this complaint, 22.4% for numbness, 12.3% for paresthesias, 7.1% for lymphedema, 14.6% for axillary web syndrome, 43.2% for loss of strength and 53.7% for limitations in range of motion. Second, "Prevalence

2 to 7 years post-surgery" applies to the percentage of patients who indicated that they still had complaints at the moment they filled out the survey. In this study women were on average 55.5 months post-surgery. Exploring the impairments; 25.8% reported pain, 12.0% numbness, 6.4% paresthesias, 5.6% lymphedema, 8.0% axillary web syndrome, 26.2% loss of strength and 19.5% limitations in range of motion.

Table 1. Characteristics of the surveyed sentinel node negative breast cancer patients (n=126)

Age (years) mean (SD)	64.3 (SD±9.5)
Time between SLNB and data collection (months) mean (SD)	55.5 (SD±17.0)
BMI mean (SD)	25.7 (SD±4.1)
	n (%)
Sex	
Male	2 (1.6%)
Female	124 (98.4%)
Breast surgery	
BCS	82 (65.1%)
Mastectomy	44 (34.9%)
Surgery on dominant side	53 (42.1%)
Preoperative bra cup size	
A	11 (8.7%)
B	31 (24.6%)
C	44 (34.9%)
D	13 (10.3%)
E	6 (4.8%)
F	0 (0%)
G	1 (0.8%)
H	1 (0.8)
Unknown	19 (15.1%)
Radiation therapy	89 (70.6%)
Chemotherapy	23 (18.3%)
Hormonal therapy	101 (80.2%)
Post-menopausal	79 (62.7%)

SD standard deviation, *SLNB* sentinel lymph node biopsy, *BMI* body mass index, *BCS* breast-conserving surgery

Figure 2b gives an overview of the prevalence of the arm and shoulder complaints according to the type of surgery using Chi-squared tests. Post-surgery, numbness (p=0.001), lymphedema (p=0.005) and loss of mobility (p=0.016) are shown to be significantly more present after mastectomy. Two to 7 years post-surgery, only numbness (p=0.005) and lymphedema (p=0.037) are significantly more present after mastectomy. Of the patients who received breast-conserving surgery, 92.7% received radiation therapy versus 29.5% for the mastectomy-patients. From this point of view, the prevalence of arm and shoulder complaints were analyzed related to the adjuvant treatment using Chi-squared tests. Our analyses showed that patients who received radiation therapy had significantly more

numbness compared to patients who did not receive radiation therapy (p=0.027). For the other complaints, no significant differences were found.

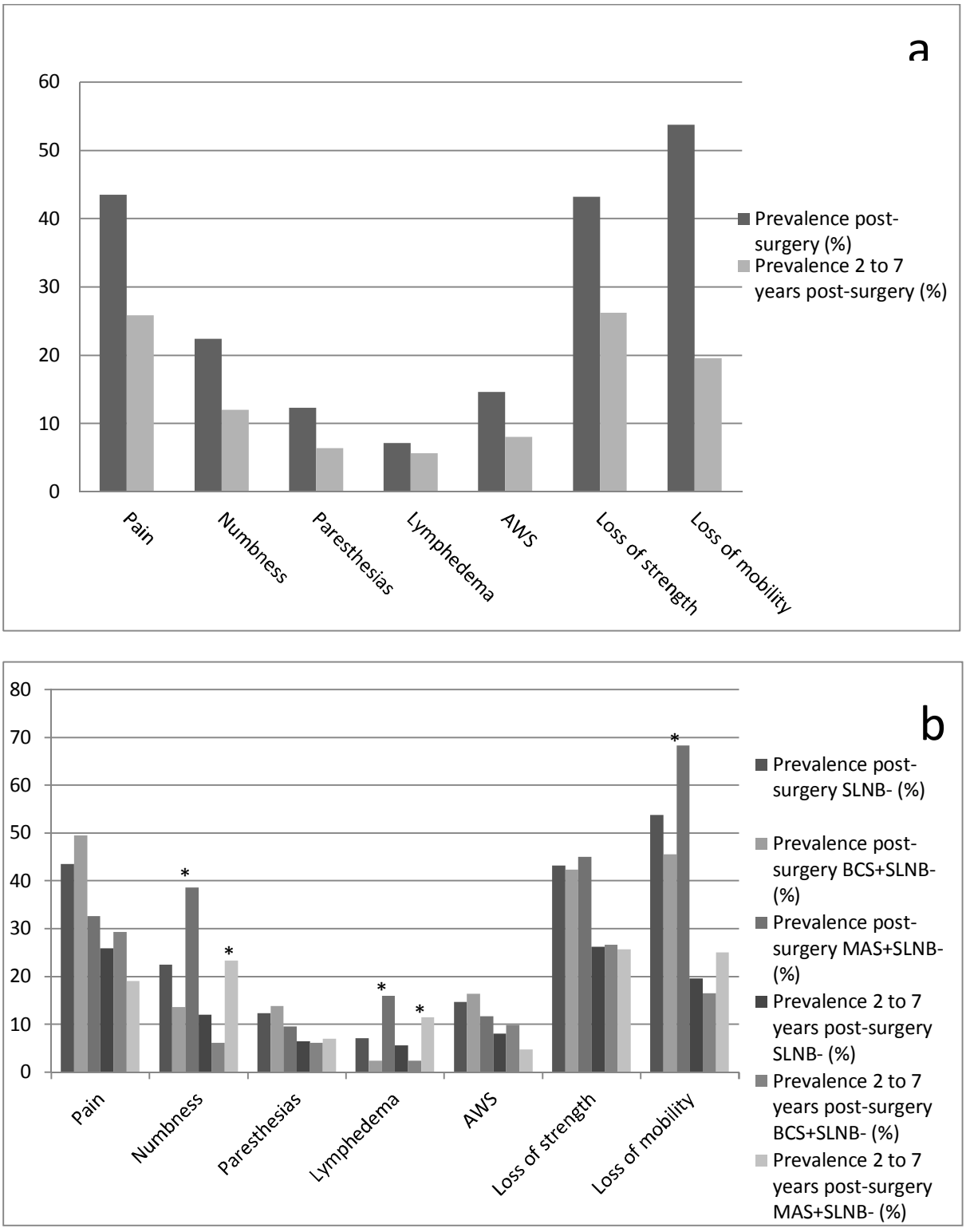

Figure 2. The prevalence of arm and shoulder complaints in sentinel negative patients. **a**: Prevalence in all sentinel node negative patients. **b**: Prevalence according to type of surgery.

Activity limitations and participation restrictions

The activity limitations with the highest prevalence are putting on a bra (58.7%), getting dressed (57.9%), wearing a bra (50.8%), sleeping (50.0%), sports (48.4%) and driving (35.7%). For an overview of the prevalence of all the activity limitations, see Table 2. Other activity limitations reported by the participants were combing hair, lifting heavy objects and hugging. The prevalence of the participation restrictions was 55.5% for household and 39.7% for work.

Table 2. Percentages of activity limitations and participation restrictions in sentinel negative patients

Activity limitations	
Putting on a bra	58.7%
Getting dressed	57.9%
Wearing a bra	50.8%
Sleeping	50.0%
Sports	48.4%
Driving	35.7%
Walking	27.0%
Reading/craft work/TV	26.2%
Sitting	23.0%
Participation restrictions	
Household	55.5%
Work	39.7%

Treatment of arm and shoulder complaints

38.1% of all participants reported that they were treated by a physical therapist concerning their arm and shoulder complaints. Several physical therapy modalities were reported: passive mobilization, massage, exercise therapy, myofascial therapy, trigger point therapy, bandaging, manual lymph drainage, fango therapy and scar tissue treatment. 72.2% of patients who were treated, indicated that their complaints improved after treatment, 11.1% noticed no difference after physical therapy and 16.7% indicated that their complaints completely resolved.

Discussion

This retrospective study revealed that a large proportion of sentinel negative patients reported arm and shoulder complaints post-surgery with a severe impact on activities of daily living. Loss of mobility, loss of strength and pain were the most common morbidities. In the literature SLNB is often compared with ALND with beneficial results in favor SLNB concerning arm and shoulder morbidity[2]. However, in a systematic review it was demonstrated that arm and shoulder complaints after SLNB should not be

underestimated[2]. The data of the current study are well within the range of the prevalences found in the literature (see Table 3)[2,24]. However, the prevalence of paresthesia and loss of strength are higher in the present study. In the literature many different assessment methods are used, which makes comparison of data among studies difficult. Studies use different criteria to define a morbidity, which partially explains the wide variation in prevalence. The literature showed that mainly abduction and forward flexion were limited. Our survey did not make a subdivision based on the movement direction. We assessed loss of mobility by asking whether the patients were able to raise the arm above the shoulder. The same can be applied for loss of strength where in the literature a subdivision is often made between shoulder abductors, elbow flexors and grip strength[7,11–13,26]. Our survey evaluated loss of strength by evaluating the ability to lift heavy objects. Therefore, the results should be interpreted with caution.

Table 3. Prevalence of arm and shoulder complaints in the present study compared to the prevalence found in the literature

	Prevalence in present study (%)	Prevalence in literature* (%)
Pain	43.5	3.3-56.6
Numbness	22.4	2.7-64.0
Paresthesias	12.3	8.6-10.4
Lymphedema	7.1	0-15.8
AWS	14.6	11.7-20.0
Loss of strength	43.2	5.0-28.0
Loss of mobility	53.7	0-100

AWS Axillary web syndrome; * based upon the systematic review of Verbelen et al, 2014 BCRT

The long-term follow-up of patients who underwent SLNB showed that arm and shoulder complaints can persist for many years after initial treatment. Literature concerning long-term consequences of SLNB on shoulder and arm function is scarce. Kootstra et al. investigated arm and shoulder complaints in breast cancer survivors 7 years after diagnosis. Seven years after a SLNB 18% of patients had limited abduction measured using a goniometer[27]. These results are similar to the percentages found in our study (19.8%), although the follow-up in our study is between 2 and 7 years. Regarding loss of strength, the long-term prevalence in our study (27.1%) is slightly higher than in the study of Kootstra et al. (18%). Strength of the shoulder abductors was measured using a hand-held dynamometer[27]. None of the patients had lymphedema measured using circumference measurements, compared to 7.1% in the current study[27]. A possible explanation is that in the study of Kootstra lymphedema is defined as a difference of ≥200ml in arm volume, whereas in the present study the presence of lymphedema is self-reported.

This study reported on the prevalence of arm and shoulder complaints in patients who underwent SLNB in addition to breast surgery. It is possible that the reported outcomes are related to the SLNB or to other potential factors such as the breast surgery itself; whether the patients underwent breast-conserving surgery or mastectomy. As depicted in figure 2b; post-surgery numbness (p=0.001), lymphedema (p=0.005) and loss of mobility (p=0.016) are significantly more present after mastectomy. Two to 7 years post-surgery, only numbness (p=0.005) and lymphedema (p=0.037) are significantly more present after mastectomy. Nevertheless, these results have to be interpreted with caution because patients who underwent breast-conserving surgery received significantly more radiation therapy compared to the patients who underwent a mastectomy. Of the patients who received breast-conserving surgery, 92.7% received radiation therapy versus 29.5% for the mastectomy-patients. From this point of view, patients who received radiation therapy had significantly more numbness compared to patients who did not receive radiation therapy (p=0.027). For the other complaints, no significant differences were found. However, we did expect that radiation therapy would provoke lymphedema as well. According to a systematic review of Disipio et al. radiation therapy is a risk factor for lymphedema that is lent support by a moderate level of evidence[28]. However, this is not the case in our study. Furthermore, in the current study, none of the complaints were related to chemotherapy and hormonal therapy.

Although the prevalence of arm and shoulder complaints are relatively high, only 38.1% of patients were treated for their complaints. Oddly, only 7.1% of the patients developed lymphedema but more than double (15.1 %) of the patients received manual lymphatic drainage. It is well known that manual lymphatic drainage in addition to information and exercise therapy is unlikely to reduce the prevalence of arm lymphedema[29]. It appears that patients often receive manual lymphatic drainage as a prevention therapy and not as a treatment for lymphedema. Despite the fact that impairments in body functions and activity limitations are very common, few patients received adequate therapy. What is the main reason behind this? Was it because they didn't seek for help, or because they were not referred properly by the health care workers? Health care providers should be aware of the possible complaints and their treatments; and therefore, refer patients to a specialized physical therapist for tailored therapy more quickly.

This study demonstrates that many patients still suffer from arm or shoulder complaints months and even years after their cancer treatment. The arm and shoulder complaints influence the activities of daily living and quality of life[4,5,17,30,31]. From this point of view, it is important to include early detection of morbidities and referral for an appropriate treatment. According to the literature; passive mobilization, exercises, and the combination of manual stretching and general exercises are effective for the improvement of shoulder range of motion after breast cancer surgery[32–38]. Exercise is also

effective for treatment of postoperative pain of the upper limb[36,38]. However, high-quality studies are necessary to prove the effectiveness of passive mobilization, stretching, and myofascial therapy as part of the multifactorial treatment[38]. In addition, the appropriate timing and content of the exercise programs need to be further investigated. Self-assessment using a checklist or annual evaluation during follow-up are both feasible approaches.

Study limitations

Data were collected via a self-administrated survey. Some items from the survey remained blank. It is possible that patients did not fill in all questions because the complaint was not present, the question was not clear, or the question was not applicable (e.g. bra cup size or menopause in male patients). If we collected our data via a face-to-face interview, we could clarify items who were not clear for some patients. Study participants were treated between 2 and 7 years ago. The researchers are aware of the risk of recall bias due to the retrospective character of the data collection. However, we strongly believe that the current study has provided useful information about long-term morbidity that has been collected prospectively. Long-term arm and shoulder complaints of sentinel negative patients were not collected retrospectively, but at the time the patients filled out the survey. Patients were asked if the arm and shoulder complaints were currently present. Furthermore, the results of this study are within the range of the prevalence found in the literature (see Table 3). Another limitation of this study is that arm and shoulder complaints are self-reported. The researchers are aware of the limitations of this type of data gathering, however, it is an efficient way to collect information about the history of a large sample. The response rate is often a difficult aspect when using a survey. We have anticipated this difficulty by contacting the participants by phone before sending the survey. Using this methodology, we managed to achieve an excellent response rate of 83%.

Conclusion

Long-term health problems related to breast cancer treatment and the quality of life are becoming more important as the life expectancy is increasing. Up to 7 years post-surgery a considerable percentage of sentinel negative patients still suffer from arm and shoulder complaints. These complaints affect the activities of daily living. Therefore, more attention for early detection and treatment of these complaints is warranted.

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PART B

Breast edema after breast-conserving surgery

CHAPTER 3

Breast edema in breast cancer patients following breast-conserving surgery and radiotherapy: a systematic review

Published in Breast Cancer Research and Treatment:
Verbelen H, Gebruers N, Beyers T, De Monie AC, Tjalma W. Breast edema in breast cancer patients following breast-conserving surgery and radiotherapy: a systematic review. *Breast Cancer Res Treat.* 2014;147(3):463-71. (SCI: 3.940, Q1)

Abstract

Purpose: Breast-conserving surgery (BCS) is commonly used in breast cancer treatment. Despite its benefits, some women will be troubled by breast edema. Breast edema may cause an unsatisfactory cosmetic result, influencing the quality of life (QoL). The purpose of this systematic review is to investigate the incidence of breast edema and to identify risk factors of breast edema in breast cancer patients following BCS and radiotherapy.

Methods: A systematic literature search was performed using different electronic databases (PubMed, Web of Science, Cochrane, Embase) until June 2014. Inclusion criteria were: (1) research studies that included female breast cancer patients who were treated with BCS and radiotherapy and (2) studies that investigated the incidence of breast edema and/or risk factors of breast edema. Exclusion criteria were (1) reviews or case studies and (2) studies published before 1995.

Results: We identified in total 28 papers which represented 4011 patients. There was a great variation in the incidence of breast edema (0%-90.4%). We identified several possible risk factors for breast edema namely increasing irradiated breast volume, increasing boost volume, the use of a photon boost, increasing breast separation, a higher density of the breast tissue, a large tumor, a higher specimen weight, postoperative infection, acute postoperative toxicity and diabetes mellitus. However, their prognostic value remains uncertain.

Conclusion: Breast edema is a common complaint after BCS and radiotherapy. A number of possible risk factors associated with breast edema was identified, but further research is warranted.

Key words: Breast Neoplasms, Breast-Conserving Surgery, Radiotherapy, Breast Edema, Systematic Review

Introduction

Breast-conserving surgery (BCS) followed by radiotherapy is a safe and effective procedure to treat patients with early stage breast cancer[1]. In many women this type of treatment gives besides a good survival also a good cosmetic result[2]. However, some patients will be troubled by breast edema. Hereby the breast size can increase by more than one cup size[3]. In contrast to arm morbidity, which is thoroughly described in literature, only a few studies investigated breast morbidity after breast cancer treatment. Currently, there is no consensus on the definition of breast edema and on standardized assessment criteria. Common criteria found in literature are an increased volume of the breast[4–10], peau d'orange[3–5,7–9], heaviness of the breast[5,8,9], redness of the skin[4,5,7], breast pain[3–5,7,9], skin thickening[4,10,11], hyperpigmented skin pores[7] and a positive pitting sign[4]. However, most studies do not describe the definition of breast edema. Despite the benefits of BCS, breast edema can be uncomfortable and is associated with distress[12]. The breast asymmetries due to swelling of the breast may cause an unsatisfactory cosmetic result and patients with breast edema mention changes in clothing habits[9,13]. Because of the significant symbolism of the breast, breast edema can influence the body image which has a definite impact on quality of life (QoL)[2,5]. Especially younger patients have reported changes in body image[13]. Because of the evolution in the treatment of breast cancer, the survival rate has increased significantly over years. As a result, the long-term health problems, including QoL, related to breast cancer and its treatment are becoming more important. The aim of this systematic review is to describe the incidence of breast edema in female breast cancer patients after BCS and radiotherapy and to identify risk factors that influence the development of breast edema.

Methods

Literature search and selection

The literature was systematically reviewed addressing the following research questions: (1) What is the incidence of breast edema in female breast cancer patients after BCS and radiotherapy and (2) what are risk factors of breast edema?

The following databases were screened online: PubMed (June 27, 2014), Web of Science (June 27, 2014), Embase (November 7, 2013) and Cochrane clinical trials (October 17, 2013).

In order to retrieve eligible studies, Medical Subject Headings (Mesh-terms) and key words were combined to describe the patient population and outcome. The specific search strategy used for PubMed is described in Table 1. For the other databases an equivalent search strategy was used which included a number of modifications because of differences in indexing terms (MeSH for PubMed and Cochrane, EMTREE for EMBASE).

Table 1. Boolean search strategy for PubMed

("Breast Neoplasms"[Mesh] OR "breast neoplasms" OR "human mammary carcinoma" OR "breast tumor" OR "breast cancer") AND ("breast edema" OR "breast oedema" OR "lymphoedema of the breast" OR "lymphedema of the breast")

All articles were screened by title and abstract in order to decide whether they had to be included for further reading or not. Three raters (H.V., T.B., AC. D.) screened the selected full-text articles for the inclusion and exclusion criteria. In case the 3 raters had diverging opinions, consensus was sought during a meeting. Inclusion criteria for both screenings were: (1) research studies that included female breast cancer patients who were treated with BCS and radiotherapy, (2) studies that investigated the incidence of breast edema and/or risk factors of breast edema. Exclusion criteria were (1) reviews or case studies and (2) studies published before 1995. The study of Fisher et al. was used as a benchmark to include studies published since 1995. This study demonstrated that BCS followed by breast irradiation is an appropriate therapy for women with stage I and II breast cancer[14].

Data-extraction

Data on patient characteristics, breast edema, assessment of breast edema and risk factors associated with breast edema were independently abstracted by three reviewers (H.V., T.B., AC. D.).

Quality assessment

The methodological quality of the selected articles was assessed using checklists (http://dcc.cochrane.org/beoordelingsformulieren-en-andere-downloads) for cohort studies, cross-sectional studies and randomized controlled trials (RCT). Three reviewers (H.V., T.B., AC. D.) independently evaluated the selected articles. Items could be rated by "1", "0" or "?". An item was rated "1" if sufficient information was available and bias was unlikely. An item was rated "0" if sufficient information was available but the article did not meet a specific criterion. An item was rated "?" if no information was available. If disagreement persisted about the assignment of a score to an item, a consensus meeting was held.

Results

Selection of studies

Initially the search yielded 446 citations. After the first screening, 56 non-duplicate abstracts were selected, and full texts were retrieved. Four reviewers assessed the full texts and finally a total of 28 studies were included in this review[2–6,11,13,15–35]. The literature search and study selection process are shown in Figure 1.

Methodological quality

The results of the quality assessment are presented in Table 2. Scores for study quality ranged from 4 to 7 out of 8 for cohort studies with a median score of 5, scores ranged from 5 to 7 out of 9 for cross-sectional studies with a median score of 6 and for RCTs cores ranged from 4 to 7 out of 9 with a median score of 5.

Characteristics of included studies

There were 6 RCT's[2,3,6,18,20,25], 10 cross-sectional studies[5,16,21,24,27,29,30,32,33,35] and 12 cohort studies[4,11,13,15,17,19,22,23,26,28,31,34] selected for the current review. In total, the 28 included studies recruited 4011 female breast cancer patients from 12 different countries who underwent BCS and radiotherapy. Age ranged from 23 years to 93 years and the mean age was 58,4 years. Four studies defined no mean age[18,30,33,35].

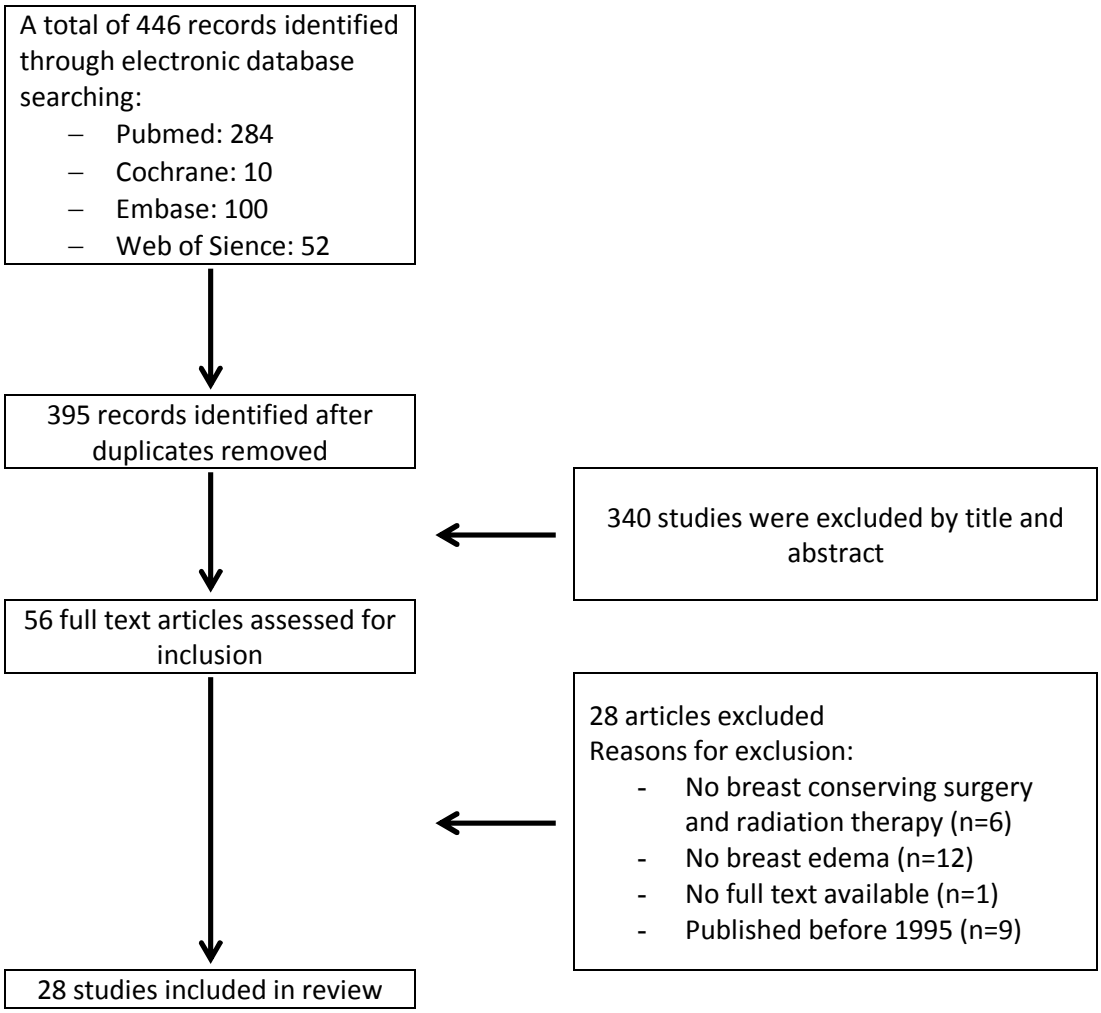

Figure 1. Flow chart of the study selection procedure

The incidence of breast edema

Based on the selected studies the overall incidence of breast edema in breast cancer patients who underwent BCS and radiotherapy ranged between 0% and 90.4%. This range included all kinds of assessment methods and definitions of breast edema and is therefore very broad. What follows is a synthesis of the incidences of breast edema per assessment method. For an overview see Table 2. Most studies used a physical examination to assess breast edema by observing and palpating the breast[3,4,6,15,17–19,21–27,31,32,34]. Some of these studies used additional photographs to evaluate the breast[6,18,25]. In most studies breast edema was divided into categories according to the severity[3,6,15,17–19,21–23,25,27,31,32,34]. For grade 1 or mild breast edema, the incidence varied between 0% and 27%, for grade 2 or moderate breast edema it ranged between 0% and 28% and for ≥ grade 3 or severe breast edema it ranged between 0% and 6% when assessed with a physical examination.

Three studies did not make this subdivision[4,24,26]. The incidence of these three studies ranged between 2% and 43.8%.

In 2 studies breast edema was evaluated by the patient using a questionnaire[5,16]. When using this type of assessment, the incidence for mild, moderate and severe breast edema was 7%-61.8%, 1%-12.2% and 1%-1.5%, respectively. Two studies used the summation score of both a physical examination and a questionnaire to evaluate breast edema[2,13]. The incidences found in those 2 studies ranged between 2.6% and 24.9% for mild breast edema, between 0% and 4% for moderate breast edema and between 0% and 0.5% for severe breast edema.

Objective assessment tools used in the selected studies were MRI, mammogram, high frequency ultrasound (HFUS) and ultrasound elastography. The incidence of breast edema measured with MRI was 64.1%[35]. Wratten et al. used HFUS to assess parenchymal breast edema and described an incidence that varied between 32% and 69%[11]. The same study also measured the skin thickness to evaluated cutaneous breast edema, but no incidence was given. In another study that used ultrasound the incidences were 19%, 2% and 0% for mild, moderate and severe breast edema, respectively[24]. Two studies used a mammogram to evaluate breast edema after BCS and radiotherapy. These studies described an incidence of 21.9% and 23.5% for minimal breast edema, 2% and 31.2% for moderate breast edema and 0% and 15.6% for marked breast edema[20,24]. The study of Vuorela et al. used a physical examination as well as a mammogram to assess breast edema. Seventy nine percent of patients had a solid consistency of the breast as well as radiological edema and 6% had a severe edema[10]. One study used HFUS, US elastography, a questionnaire and a physical examination to assess breast edema[4]. In 43.8% of patients a subjective swelling was found. Sonographic findings of breast edema were an increased interstitial fluid accumulation (72.2%), skin thickness over 2 mm (100%), increased echogenicity of the subcutis (89.5%) and decreased visibility of the echogenic line (100%). Making a combination of the four breast edema criteria, measured with HFUS the incidence of breast edema was 90.4%. In 88.9% of patients breast edema was present when they had an increased elasticity ratio of the subcutis measured with US elastography[4].

Three studies did not describe their assessment method; the incidence of breast edema in these three studies ranged between 0% and 17.2%[28,30,33]. In the study of Grann et al. the assessment method is also not clear. Cosmesis was evaluated by a physician or by a patient interview. The incidence in this study was 72% for mild breast edema. None of the patients had pitting edema[29].

Table 2. Study characteristics of 28 selected studies

Reference	Sample Size	Design (Methodological score)	Follow-up	Assessment	Breast edema (%)
Adriaenssens 2012[5]	131	Cross-sectional (6/9)	0-5 years	Questionnaire	Mild: 61.8% Moderate: 12.2% Severe: 1.5%
Adriaenssens 2012[4]	29	Cohort (4/8)	/	Phys exam HFUS US elastography	43.8% 90.4% 88.9%
Dragun 2013[15]	42	Cohort (4/8)	3-6 weeks	Phys exam	Grade 2: 2.4%
Formenti 2012[16]	98	Cross-sectional (6/9)	2-125 months	Questionnaire	Grade 1: 7% Grade 2: 1% Grade 3: 1%
Chadha 2012[17]	124	Cohort (6/8)	8 weeks	Phys exam	Grade 2 or more: 0-1.4%
Kelemen 2012[13]	198	Cohort (5/8)	1.2-5.9 years	Phys exam, questionnaire	Grade 1: 7.1% Grade 2: 4.0% Grade 3: 0.5%
Li 2011[32]	48	Cross-sectional(6/9)	5-49 months	Phys exam	Grade 1: 45.7% Grade 2: 2.1%
Barnett 2011[18]	1021	RCT (5/9)	2 years	Phys exam, photographs	Mild: 26%-27% Moderate: 12%-14% Severe: 3%-6%
Berrang 2011[19]	104	Cohort (5/8)	0.25-49.4 months	Phys exam	Grade 1: 6%-31% Grade 2: 0%-5%
Kuzmiak 2009[20]	64	RCT (5/9)	1 year	Mammogram	Minimal: 21.9% Moderate: 6.2%-31.3% Marked: 9.4%-15.6%
Constantine 2008[21]	59	Cross-sectional(6/9)	5-53 months	Phys exam	Grade 1: 16.9% Grade 2: 0%
Wenz 2008[22]	48	Cohort (5/8)	30-56 months	Phys exam	Grade 1: 9% Grade 2: 2% Grade 3: 0%
Vicini 2007[23]	91	Cohort (5/8)	24 months	Phys exam	Grade 1: 24% Grade 2: 7% Grade 3: 0%
Harsolia 2007[3]	172	RCT (4/9)	Median: 4.7 years	Phys exam	Grade 2 or more: 1%-28%
Wratten 2007[11]	54	Cohort (5/8)	24 months	HFUS	32%-69%
Mussari 2006[24]	47	Cross-sectional (6/9)	36-63 months	Phys exam Mammogram US	2% Mild: 23.5% Moderate: 2% Severe: 0% Mild: 19% Moderate: 2% Severe: 0%
Toledano 2006[6]	214	RCT (5/9)	4.3-9 years	Phys exam, photographs	Grade 1: 5.5%-7.5% Grade 2: 0%-1% Grade 3: 0%
Marcenaro 2004[25]	58	RCT (5/9)	7-46 months	Phys exam, photographs	Grade 2: 7%-10%
Mayo 2004[33]	120	Cross-sectional (5/9)	1-12 months	Not described	0%
Back 2004[26]	223	Cohort (5/8)	1-4 weeks	Phys exam	8%-20.5%
Hoeller 2003[27]	259	Cross-sectional (6/9)	4.7-18 years	Phys exam	Grade 1: 3% Grade 2: 1%
Forrai 2001[35]	53	Cross-sectional (6/9)	6-166 months	MRI	64.1%
Lamb 1999[28]	169	Cohort (7/8)	Median: 53 months	Not described	17.2%
Grann 2000[29]	56	Cross-sectional (7/9)	16-81 months	Phys exam or interview	Mild edema: 72% Pitting edema: 0%
Fung 1997[30]	55	Cross-sectional (5/9)	0.8-13.7 years	Not described	Mild: 5% Moderate: 3%
Olivotto1996[2]	184	RCT (7/9)	6.7 years	Phys exam, questionnaire	Mild:2.6%-24.9% Moderate/severe: 0%-1.7%
Kuptsova 2008[31]	390	Cohort (5/8)	2.9-6.2 years	Phys exam	Grade 1: 15.0% Grade 2: 1.6% Grade 3: 0% Grade 4: 0%
Goyal 2013[34]	34	Cohort (6/8)	22.1-53.4 months	Phys exam	Grade 1: 0% Grade 2: 0% Grade 3: 3%

Abbreviations: Phys exam: physical examination; US: ultrasound; HFUS: high frequency ultrasound

Risk factors of breast edema

In the present review we identified several possible risk factors for breast edema associated with BCS and radiotherapy. These risk factors are grouped into categories related to (1) radiotherapy, (2) systemic therapy, (3) surgery, (4) tumor characteristics and (5) personal factors.

An increase in irradiated breast volume[13], an increase in boost volume[13,18] and the use of a photon boost were identified as risk factors for breast edema[13]. Breast edema was also more frequent with increasing breast separation, i.e. the distance between the points at which the tangential fields entered the body[13]. There was no association found between breast edema and nodal irradiation[13]. The time interval between the BCS and the start of the radiotherapy is not significantly correlated with the occurrence and degree of breast edema[4].

Several studies compared the presence of breast edema after different types of radiotherapy[3,17,20,25]. There is no significant difference in the incidence of breast edema between whole breast irradiation using a 3-week accelerated schedule with concomitant boost and the 6.5-week conventional schedule with sequential boost[17]. There is also no difference between conventional fractionation (50 Gy in 25 daily fractions in five weeks) and a hypofractionated schedule (45 Gy in 15 fractions in 5 weeks, 3 fractions per week)[25]. Kuzmiak et al. compared whole-breast radiation therapy (WBRT) with intraoperative radiation therapy (IORT) and it showed that breast edema is significantly more present in the WBRT-group[20]. One study compared intensity-modulated radiotherapy (IMRT) with conventional wedge-based radiotherapy. It shows that IMRT is associated with significantly less acute and chronic ≥ grade 2 breast edema[3]. When conventional external beam radiation therapy (EBRT) was combined with IORT, the time interval between both radiation types was significantly correlated with the incidence of breast edema[22]. The incidence of breast edema was significantly higher when the time interval was shorter[22].

Adriaenssens et al. showed that patients who received chemotherapy had a significantly higher degree of breast edema[5]. In contradiction, another study demonstrated that chemotherapy decreases the risk of acute breast edema after irradiation[18]. One study concluded that adjuvant chemotherapy is not significantly correlated with the incidence of breast edema[18]. Chemotherapy was not a significant risk factor for the increase of the elasticity ratio of the subcutis, except for the lower inner quadrant[4].

On the one hand, a study showed that patients who received anti-hormone therapy had a significantly lower degree of breast edema[5]. On the other hand, one study showed that the use of tamoxifen increases the risk for the development of breast edema[18] and another study demonstrated

that anti-hormone therapy is not correlated with de presence of breast edema 2 years after treatment[18].

Wratten et al. compared the degree of breast edema between an axillary lymph node dissection (ALND) and a sentinel lymph node biopsy (SLNB). The average epidermal thickness for patients with a SLNB is lower than in patients with an ALND[11]. There is no difference in skin thickness between a SLNB or no axillary procedure[11]. Other studies showed the type of axillary node surgery is not associated with breast edema[4,5]. A postoperative infection and the presence of acute toxicity increases the risk of late breast edema at 2 years postoperatively[18]. The same study did not show a significant association between the development of postoperative hematoma and breast edema[18]. An operation at the dominant side was not reported as a significant risk factor for breast edema[4,5].

One study demonstrated that a large tumor (≥ 1.9 ± 1.4 cm) increases the risk of developing breast edema[13]. The location of the tumor[5] did not correlate with breast edema, instead a higher specimen weight was found to be associated with the development of breast edema[18].

On the one hand three studies demonstrated that a larger breast volume is associated with breast edema[3,18]. On the other hand studies did not confirm the correlation between the preoperative bra cup size and breast edema[3,5]. Kuzmiak et al. evaluated breast edema with a mammogram. This study stated that the severity of edema was lower with decreasing breast density[20].

Two studies investigated the relation between age and breast edema[5,18]. One study found a negative correlation between the degree of breast edema and age[5]. The other studies demonstrated that older age was significantly associated with an increased risk of breast edema[18].

Adriaenssens et al. found a significantly positive correlation between the degree of breast edema and BMI of patients with breast edema[5]. Other studies stated that body weight[8], BMI[4] and preoperative obesity[4] are not associated with breast edema.

One study found a significant correlation between breast edema and diabetes mellitus[18]. The same study investigated the relation between breast edema and cardiovascular disease, but there was no correlation found.

Other factors which were investigated were smoking history[18], the use of aspirin[2] and genetic factors[31]. None of these factors correlated with breast edema.

Discussion

The results of our systematic review clearly demonstrate that breast edema is a common morbidity in women who underwent BCS and radiotherapy. The breast edema incidence is very broad, namely 0% to 90.4%. Several factors are responsible for this broad range such as no standard assessment method, no uniform definition of breast edema, different types of radiotherapy and different follow-up times or measuring intervals.

All studies have reported various methods and standards for assessing breast edema. The most common assessment method is the physical examination. However, different criteria were used to assess the breast for example the LENT/SOMA criteria[6,22,25,27,31], the National Cancer Institute Common Toxicity Criteria[15,17,19,32,34,] the Modified System of Johansen et al.[13], the RTOG/EORTC criteria (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer)[18,19,23,24,26,27,31] and the Harvard Criteria[3,23]. The use of different criteria can partly explain the variation in incidences. The lack of a transparent definition of breast edema can also be responsible for this variation, making it difficult to find suitable criteria for measuring breast edema or to find a suitable questionnaire. Therefore, a clear definition based upon a standardized assessment is warranted. Therefore, consensus among clinicians and researchers needs to be reached urgently. It can be suggested to evaluate different aspects or symptoms of breast edema using a combination of subjective and objective assessment tools and to make a summation score. For instance, a combination of a questionnaire and ultrasound can be used.

The selected articles report from different types of radiotherapy and different radiation parameters were discussed. Based upon the results of the current review the fractionation dose could not be determined as a risk factor for breast edema. However, Haviland et al. compared the effect of different doses on the development of breast edema. They showed that breast edema was significantly less common in the 40 Gy group (7.0%) than in the 50 Gy group (12.7%)[36]. This study was not included in the current review, because it didn't meet the inclusion criteria (results of BCS and mastectomy were not discussed separately). However, it can be used as a benchmark because it is demonstrated that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early stage breast cancer, regardless the type of surgery. Differences in other radiation parameters like the time interval between surgery and radiotherapy and the extent of lymphatic irradiation can also explain the broad incidence range. Not all studies investigated the effect of these parameters on the incidence and the degree of breast edema. Therefore, the prognostic value of radiation parameters remains unclear.

In the above described results, no distinction was made based upon the different follow-up times or measuring intervals. The incidence at specific time points are described in Table 3. Most studies showed that the incidence of breast edema diminishes over time. However, some patients still suffer from this complaint years after their treatment. Several studies investigated the incidence of breast edema prior to radiotherapy (range: 0%-32%)[2,19,26,34]. The onset of breast edema can occur postoperatively by disturbance in lymphatic circulation. Wratten et al. described the time course of cutaneous edema based on the increase in epidermal thickness. The epidermal thickness increases to a minor extent during radiotherapy itself in most cases, but more significantly in the post treatment period. Epidermal thickness measures usually peak at 4–6 months post treatment and in most instances show signs of returning to baseline levels by 12 months post-treatment. The time course of parenchymal edema assessed visually is about the same[11].

Table 3. Time course of breast edema

Reference	Follow-up	Breast edema
Adriaenssens 2012[5]	0-3 months postoperative	93.3%
	3-6 months postoperative	73.3%
	6-12 months postoperative	82.4%
	12-24 months postoperative	80.6%
	24-60 months postoperative	65.4%
Berrang 2011[19]	Prior to RT	32%
	1 year after RT	16%
	3 years after RT	6%
Vicini 2007[23]	>6 months after RT	32%
	>24 months after RT	22%
	>36 months after RT	0%
Back 2004[26]	Prior to RT	8%
	On completion of RT	20.5%
Olivotto 1996[2]	Prior to RT	26.6%
	3 year after RT	4.3%
	5 years after RT	2.6%
Goyal 2013[34]	Prior to RT	0%
	During RT	0%
	1 month after RT	0%
	3 months after RT	3%
	>2 years after RT	3%

Abbreviations: RT: radiation therapy

The current review has identified the following possible risk factors for breast edema associated with BCS and radiotherapy: increasing irradiated breast volume[13], increasing boost volume[13,18], the use of a photon boost[17], increasing breast separation[17], a higher density of the breast tissue[20], a large

tumor[17], a higher specimen weight[13], postoperative infection[13], acute postoperative toxicity[13] and diabetes mellitus[18]. These factors were only investigated in a limited number of studies, so their prognostic value remains uncertain. Whether the use of chemotherapy and anti-hormone therapy and ALND are risk factors of breast edema is not clear. Because of contradicting results, the association of age and BMI with breast edema also remains unclear.

Women with a large breast size with a large tumor are also suitable for BCS. A larger breast size implicates more adipose tissue. This may have led to an overestimation of breast edema in women with a larger breast size.

Several studies investigated the influence of anti-hormone therapy[5,13,18]. It is difficult to compare these results because one study used tamoxifen[18], another study used adjuvant hormone therapy with either tamoxifen or an aromatase inhibitor[13] and in the study of Adriaenssens et al. it is not described which type of anti-hormone therapy was used[5]. None of the selected articles described the influence of Herceptin® on breast edema.

Although breast edema is common, its treatment is little described in the literature. Mostly its treatment is based upon the knowledge of the treatment of lymphedema of the upper limb. Lymphedema is commonly treated by complex physical therapy (CPT) comprising manual lymphatic drainage, compression therapy, skin care and exercises[9,37]. Another treatment investigated by Jahr et al. is deep oscillation combined with manual lymphatic drainage on breast edema. Deep oscillation is a therapeutic approach that consists in applying an intermittent electrostatic field of low intensity and extremely low frequency to the target area. The study showed that additional deep oscillation supplementary to manual lymphatic drainage can significantly enhance pain relief and swelling of the breast[37]. Further studies are urgently needed to investigate the treatment of lymphedema of the breast.

It is demonstrated that breast edema has a negative impact on the QoL[5]. Since breast cancer has a good survival, long term health problems related to breast cancer treatment and the QoL are becoming increasingly important. This research reveals an important missing link in the lymphedema treatment. Although breast edema is a common complication after BCS and radiotherapy, it is often underdiagnosed and therefor untreated in clinical practice. Since there is an evolution in the use of more BCS, the role of a breast edema treatment will become more important. Further investigation regarding the risk factors, assessment and treatment of breast edema is recommended.

Conclusion

The incidence of breast edema in breast cancer patients following BCS and radiotherapy is very broad, namely 0% to 90.4%. The current systematic review identified a number of possible risk factors: increasing irradiated breast volume, increasing boost volume, the use of a photon boost, increasing breast separation, a higher density of the breast tissue, a large tumor, a higher specimen weight, postoperative infection, acute postoperative toxicity and diabetes mellitus. The onset of breast edema can occur postoperatively, but it is most commonly reported following radiotherapy. Some patients still suffer from this complaint years after their initial treatment and breast edema has a negative impact on the QoL. Therefore, further research is warranted.

Conflict of interest

The authors declare that they have no conflict of interest.

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CHAPTER 4

Development and clinimetric properties of the Dutch Breast Edema Questionnaire (BrEQ-Dutch version) to diagnose the presence of breast edema in breast cancer patients

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Abstract

Purpose: To develop a diagnostic tool, the Breast Edema Questionnaire (BrEQ) and to determine its clinimetric properties.

Methods: The BrEQ was developed based on information from literature, experts and breast edema patients. Content validity, construct validity, test-retest reliability, internal consistency and cut-off point were investigated in a group of breast cancer patients. Construct validity made up two parts; convergent and known-groups validity. Convergent validity was tested by correlating the BrEQ with skin thickness measured with ultrasound (US).

Results: In part 1 of the BrEQ, symptoms of breast edema were scored from 0 to 10: pain, heaviness, swelling, tensed skin, redness, pitting sign, enlarged skin pores and hardness. Taking into account the International Classification of Functioning, Disability and Health (ICF), several activity limitations and participation restrictions were scored from 0 to 10 in part 2. Clinimetric properties of part 1 were examined in 55 patients. US showed that 35 women had breast edema. Content validity was good. Regarding convergent validity, all breast symptoms correlated moderately with skin thickness. The total symptom score had a strong correlation with skin thickness. Concerning known-groups validity, patients with breast edema had a higher total symptom score. Test-retest reliability ranged between moderate and strong. The internal consistency was good for all items and the total symptom score. We identified that a score cut-off point of ≥ 8.5 discriminates between patients with breast edema and those without.

Conclusion: Part 1 of the BrEQ-Dutch version is a valid and reliable tool for assessing clinical indicators of breast edema.

Key words: Breast Neoplasms, breast edema, questionnaire, clinimetric properties, validity, reliability

Introduction

Breast-conserving surgery (BCS) followed by radiation therapy is a safe and effective procedure to treat patients with early stage breast cancer[1]. For many women this type of treatment results in a good survival as well as a good cosmetic result[2]. Despite these advantages, some women however, develop breast edema on the operated and irradiated breast. In contrast to lymphedema of the upper limb as a morbidity of breast cancer treatment, breast edema is little described in the literature. In a systematic review of the literature done by our own research group, an incidence for breast edema between 0 and 90.4% was found in breast cancer patients following BCS and radiation therapy[3]. This broad range in incidence can be explained by the lack of a uniform definition and standardized assessment criteria concerning breast edema. Common criteria for breast edema, as found in scientific literature, are peau d'orange[4–9], redness of the skin[5–7], pain in the breast[4–7,9], a positive pitting sign[5], increased breast volume[5–11], skin thickening[5,11,12], heaviness of the breast[6,8,9] and hyperpigmented skin pores[7]. Up till now, both diagnosis and stage of breast edema are mainly made by physical examination, by observing and palpating the breast[2,13]. Breast ultrasound (US) is considered to be a more reliable and quantitative measure for breast edema[12,14]. By measuring the skin thickness, US can provide a measure of cutaneous edema on a continuous scale[12]. Other assessment tools found in literature were questionnaires like the LENT-SOMA, Common Toxicity Criteria and the EORTC-BR23 questionnaire[3]. However, these questionnaires are often not specific and inclusive enough. Despite the relative high incidence seen in literature, breast edema is largely underdiagnosed, hence untreated, in clinical practice. The development of a standardized assessment tool for the early detection of breast edema is warranted in order to provide an adequate treatment. For clinical practice, a valid and feasible questionnaire for the diagnosis of breast edema is a recommended addition to the current, expensive and time-consuming, investigations provided by US. Therefore, the aim of this study is to develop a patient-reported questionnaire to assess breast edema and to determine its clinimetric properties; being content validity, construct validity (convergent and known-groups validity), test-retest reliability, internal consistency and cut-off point.

Methods

Development of the breast edema questionnaire (BrEQ)

The development of the BrEQ consisted of 3 phases[15]. In the *first phase*, relevant information about breast edema was collected through (1) a systematic review of the literature[3], (2) information from experts in the field, being health care professionals involved in breast cancer treatment and lymphedema treatment, and (3) information from patients suffering from breast edema. The

International Classification of Functioning, Disability and Health (ICF) model was used as a framework to describe the patient's health condition in a bio-psychosocial context (www.who.int/classifications/icf/en). Impairments in body functions and structures, activity limitations and participation restrictions were collected [16]. This information was used to make a pilot version of the BrEQ.

In the *second phase*, the pilot version of the BrEQ was tested and discussed by a response group. Patients (n=4) and health care professionals (breast surgeon (n=1), breast nurses (n=2), physiotherapists specialized in lymphedema treatment (n=6)) , gave feedback on the BrEQ concerning completeness of the questionnaire, relevance of the questions and scoring system. Based on this feedback, the BrEQ was adjusted; the item hardness was added as a complaint related to breast edema. This final questionnaire consists out of 2 parts. In the first part, symptoms of breast edema are scored on a scale from 0 to 10. Taking into account the ICF, besides the aforementioned breast edema symptoms, focusing on impairments of body structures and body functions, a number of activity limitations and participation restrictions are scored on a scale from 0 to 10 as well. This is part 2 of the questionnaire. For both parts, a higher score means more disabilities related to breast edema. The BrEQ (Dutch version) is provided in Appendix 1. An English translation of the BrEQ is provided in Appendix 2. Note that the English translation has not yet been validated.

Clinimetric properties of part 1 of the BrEQ

In the *third phase*, clinimetric properties of the BrEQ were tested in a group of patients. Content validity, construct validity, test-retest reliability, internal consistency and a cut-off point were examined for part 1, i.e. the patient-reported breast edema symptoms. It was not possible to examine criterion validity, because we were unaware of a gold standard for measuring breast edema. For now, only part 1 was examined for clinimetric properties, since both diagnosis and detection were our primary focus. Part 2 concentrates on the impact of breast edema on daily functioning. Clinimetrics were not determined for the second part of the BrEQ.

C*ontent validity* refers to the extent to which a measure represents all facets of a given construct. Content validity was measured by means of an attached questionnaire, consisting of 4 questions about the comprehensiveness of the BrEQ and its scoring system: (1) Was each question understandable? (2) Were all items relevant to your current situation? (3) Do you think the questionnaire is complete? (4) Was the scoring system clear? An explanation was asked if the patient answered "no" on an item. The number of positive and negative answers was counted[17,18].

Construct validity is a process in which validity is evaluated in terms of the extent to which a measure correlates with variables in a manner consistent with theory[19]. The construct validity of the BrEQ was investigated in 2 ways. First, *convergent validity* refers to the degree in which 2 independent measures of the same construct are in fact related[20,21]. This was investigated by correlating skin thickness of the thickest quadrant of the operated breast, with all questions of part 1 of the questionnaire. Second, *known-groups validity* was investigated by comparing the BrEQ-scores between patients with and patients without breast edema in order to verify whether the BrEQ can differentiate between "breast edema" and "no breast edema".

To measure *test-retest reliability*, the patients were asked to fill out the BrEQ again, within 24 to 48 hours after the first consult, because problems with functioning related to lymphedema, can change from one day to another[22]. Scores obtained on these 2 different time points were compared to one another[23,24].

The *internal consistency* was investigated to determine whether the different questions measure the construct in the same consistent matter[24,25].

The receiving operating curve (ROC) was generated to determine a BrEQ-score *cut-off point* which can differentiate between patients with and patients without breast edema[26].

Patient selection and recruitment

In this methodological study with descriptive design, patients were recruited from the multidisciplinary Breast Clinic of the University Hospital of Antwerp during their annual routine US appointment. The electronic agenda was screened from 23 November 2015 till 10 June 2018 for patients who had an appointment at the Radiology Department of the Antwerp University Hospital for an US and mammogram investigation. The electronic medical files of the patients were used to determine if patients met the inclusion criteria. Women older than 18 who underwent unilateral BCS followed by radiation therapy were enrolled. Exclusion criteria were (1) other disorders which can cause breast edema like angiosarcoma, conditions of the skin, heart diseases and lung diseases, (2) plastic surgery such as reconstructive surgery, (3) pregnancy and (4) not capable of understanding the Dutch questionnaire. In total, 57 patients were asked to participate; 55 agreed and were included in the study. Based on a Spearman correlation coefficient >0.50 with a significance of $p<0.05$ and a power of 0.80, sample size of 15 participants in each group was calculated. Taking into account a drop-out of 20%, a minimum of 18 participants in each group needed to be included. At the time of inclusion, patients and researchers were unaware whether patients had breast edema or not. All participants received an information brochure informing them about the study and requesting their voluntary

participation. Patients received information about the nature and purpose of the research, the expected duration of their participation, a statement that participation is voluntary; risks and benefits, information about confidentiality, details of insurance coverage in case of injury; reference contacts for any further answers to pertinent questions about the research and the subject's rights, a statement offering the subject the opportunity to withdraw at any time from the research without consequences. All participants gave written informed consent. Information about participant characteristics is provided in Table 1.

Additionally, a sample of 10 breast cancer patients who underwent BCS and radiation therapy were included in order to assess the test-retest reliability for the item redness. They were asked to fill out the BrEQ twice, within 24 to 48 hours, in order to eliminate the interference of redness induced by the mammogram. None of them received a mammogram before filling out the BrEQ.

Data collection

At the time of their appointment at the Radiology Department (immediately after the US examination), the selected patients were asked to complete the BrEQ. The patients completed it at their own pace and completely independently. Subsequently, a second questionnaire regarding comprehensiveness of the BrEQ was given. Afterwards, participants received a pre-stamped envelope with a copy of the BrEQ and they were asked to fill it out and return it within 24-48 hours.

Ultrasound

In addition, all patients underwent an US of both breasts in order to measure skin thickness (i.e. epidermal and dermal thickness) of the 4 quadrants of each breast, to determine the degree of cutaneous breast edema. The US was performed by 2 experienced radiologists of the Antwerp University Hospital (M.V.G. and L.H.). Skin thickness was measured with a high frequency probe (13 MHz), using Logic E9, GE medical systems (Wauwatosa, WI, USA). The probe was placed perpendicular to the skin 4 cm remote from the nipple for all 4 quadrants. All patients were examined in supine position. Breast edema on US was considered as a deviation of more than 2 standard deviations (SD) from the average skin thickness. Cut-off values were determined by calculating the average thickness and SD's of the non-operated, non-irradiated breast of the entire sample. If the difference of more than 2 SD's was noticeable in at least one quadrant of the operated and irradiated breast, patients were allocated to the breast edema group.

Data analysis

For the statistical analysis, the Statistical Package for the Social Sciences (SPSS, IBM, USA) version 24 was used. The socio-demographic data were descriptively analyzed and displayed as frequencies and rates. Frequencies were used to determine the content validity. The number of positive answers on each of the 4 questions concerning content validity was counted and percentages were calculated. Subsequently, convergent validity was tested by Spearman correlation coefficients, correlating skin thickness of the thickest quadrant of the operated and irradiated breast, with all items of part 1 of the BrEQ. Spearman correlation coefficients were chosen because data were not normally distributed. The known-groups validity was tested by means of a Mann-Whitney U-test in order to verify whether the different items of the BrEQ can significantly differentiate between patients with and without breast edema. Test-retest reliability was investigated by determining the reliability of the total sum of the breast symptoms (part 1) and of the individual items, between the first and second (24 to 48 hours later) measurement, using a two-way mixed intraclass correlation coefficients (ICC) with single measures. The internal consistency of part 1 of the questionnaire was determined by the Cronbach alpha coefficient. To assess whether a cut-off point is available for the BrEQ, a ROC-curve was generated, using the total symptom score of the second measurement as classifier and skin thickness as true status reference (>2 SD's in at least one quadrant of the operated and irradiated breast on US). The area under the curve (AUC) was calculated and the coordinate with the greatest sum of sensitivity and specificity was identified as the BrEQ-score cut-off point [26,27]. AUC is interpreted as follows: 90 - 100 = excellent; 80 - 90 = good; 70 - 80 = fair; 60 - 70 = poor; 50 - 60 = fail [28].

Results

Phase 1: Development of the BrEQ

The BrEQ consists of 2 parts. In part 1, breast symptoms are assessed and part 2 concentrates on the impact on daily functioning. For part 1, the following 8 breast edema symptoms were selected based on information collected through systematic literature search, health care professionals and breast edema patients: pain, heaviness, swelling, tensed skin, redness, pitting sign, enlarged skin pores and hardness of the operated and irradiated breast. Concerning part 2, the following 14 activity limitations and participation restrictions were found: sleeping, lying down, sitting, standing, vocational activities, household chores, driving a car, handicraft, walking, sports, getting (un)dressed, putting on a bra, wearing a bra, computer work.

The constructed BrEQ consisted of 8 questions related to breast edema symptoms (part 1) and 14 questions related to activity limitations and participation restrictions (part 2). Each item was scored on

an 11-point Likert scale (0-10). The anchor points for part 1 were “not at all” and “very severe”. For the total symptom score, the scores of the individual items of part 1 of the BrEQ were added up, resulting in a total symptom score ranging from 0 to 80. The anchor points for part 2 were “no complaints” and “unbearable complaints”. Participants were asked to score their average breast edema symptoms and activity limitations and participations restrictions related to their breast complaints in the preceding week. The BrEQ takes about 5 minutes to complete.

Table 1. Demographic and clinical characteristics of the participants (n=55)

Characteristics	**Breast edema (n=35)**	**No breast edema (n=20)**	**p-value**
Age, mean (y) ±SD	58.20 (± 11.48)	63.05 (± 10.10)	0.122
Height, mean (m) ±SD	164.26 (±6.98)	161.95 (±5.40)	0.208
Weight, mean (kg) ±SD	74.61 (±15.64)	68.65 (±8.54)	0.123
BMI, mean (kg/m^2) ±SD	27.57 (±5.03)	26.15 (±2.77)	0.252
Time since surgery, mean (months) ±SD	52.41 (±45.86)	60.65 (±47.31)	0.676
Treated breast			
Left, n (%)	21 (60.0)	10 (50.0)	0.472
Right, n (%)	14 (40.0)	10 (50.0)	
Handedness			
Right handed, n (%)	28 (80.0)	19 (95.0)	0.129
Left handed, n (%)	7 (20.0)	1 (5.0)	
Menopausal state at time of surgery			
Premenopausal, n (%)	15 (42.9)	10 (50.0)	0.609
Postmenopausal, n (%)	20 (57.1)	10 (50.0)	
Type of surgery			
ALND, n (%)	17 (48.6)	7 (35.0)	0.329
SLNB, n (%)	18 (51.4)	13 (65.0)	
Chemotherapy			
Neoadjuvant, n (%)	6 (17.1)	1 (5.0)	0.225
Adjuvant, n (%)	12 (34.3)	11 (55.0)	
No	17 (48.6)	8 (40.0)	
Hormone therapy			
Yes, n (%)	21 (60.0)	12 (60.0)	1.000
No, n (%)	14 (40.0)	8 (40.0)	
Radiation therapy			
Yes, n (%)	35 (100.0)	20 (100.0)	1.000
No, n (%)	0 (0.0)	0 (0.0)	
Sum of the skin thickness of the 4 quadrants of the treated breast, mean (mm) ±SD	8.45 (± 1.84)	5.61 (± 1.08)	<0.001
Sum of the skin thickness of the 4 quadrants of the untreated breast, mean (mm) ±SD	5.61 (± 1.17)	5.22 (± 0.90)	0.200
Total symptom score BrEQ, mean ±SD	19.46 (± 14.83)	8.20 (± 9.64)	0.003
Total symptom score BrEQ after 48 hours, mean ±SD	15.82 (± 10.99)	5.18 (± 8.43)	0.001

SD = standard deviation, BMI = body mass index, ALND = axillary lymph node dissection, SLNB = sentinel lymph node biopsy

Phase 2: Clinimetric properties of part 1 of the BrEQ

In phase 2, the clinimetric properties of part 1 of the BrEQ were determined. A total of 55 eligible patients participated in phase 2 of the study. Informed consent was obtained from all participants. Breast edema on US was considered as a deviation of more than 2 standard deviations (SD) from the average skin thickness. Following cut-off values were used to determine if the patient had breast edema: 2.192 mm for the superior internal quadrant (SIQ), 2.131 mm for the inferior internal quadrant (IIQ), 2.052 mm for the inferior external quadrant (IEQ) and 1.774 mm for the superior external quadrant (SEQ). US showed that 35 patients had breast edema with a mean age of 58.20 (±11.48). Twenty participants without breast edema (mean age 63.05 ±10.10) were included. The characteristics of the participants are shown in Table 1.

The mean total skin thickness of the treated breast (sum of the 4 quadrants) was 7.42 mm (±2.11) versus 5.47 mm (±1.09) for the untreated breast. This difference was significant ($p<0.001$). Skin thickness of the operated and irradiated breasts is significantly higher for the breast edema group (8.45 mm ±1.84) compared to the non-breast edema group (5.61 mm ±1.08) ($p<0.001$). For the untreated side, there is no significant difference between both groups (5.61 mm ±1.17 and 5.22 mm±0.90 respectively).

The additional questionnaire concerning the comprehensiveness of the BrEQ was completed by all but one patient in order to determine the *content validity*. Of these patients, 53 (98.1%) understood all questions and 49 patients (90.7%) found the questions relevant to their current situation. The other 5 patients answered “no” because their surgery was performed a longer time ago. Forty-seven patients (87.0%) stated that the BrEQ was complete. The other patients felt that questions concerning arm edema and axillary web syndrome should also have been included. The last question about the scoring symptom was answered with “yes” by all participants (see Table 2).

Table 2. Content validity

	Breast edema (n=35)		**No breast edema (n=19)**		**Total sample (n=54)**	
	Frequency	**%**	**Frequency**	**%**	**Frequency**	**%**
All questions are well understood	34	97.1	19	100	53	98.1
All questions are relevant for your current situation	33	94.3	16	84.2	49	90.7
The questionnaire is complete	31	88.6	16	84.2	47	87.0
The scoring system is clear	35	100	19	100	54	100

Concerning the *convergent validity*, the thickness of the thickest quadrant of the operated and irradiated breast is correlated with part 1 of the BrEQ. The correlation coefficients and p-values are shown in Table 3. All separate breast edema symptoms correlate moderately with skin thickness. The total symptom score has a strong correlation with skin thickness. All items reach the level of significance.

Table 3. Correlation of breast edema symptoms and skin thickness for determining convergent validity

Breast edema symptoms	Spearman correlation coefficient ρ	p-value
Total symptom score	0.500	<0.001*
Pain	0.303	0.025*
Heaviness	0.356	0.008*
Swelling	0.392	0.003*
Tensed skin	0.335	0.013*
Redness	0.398	0.003*
Pitting sign	0.422	0.001*
Enlarged skin pores	0.393	0.003*
Hardness	0.305	0.024*

Cut off values correlation coefficient:<0.1 none or very weak; 0.1-0.3 weak; 0.3-0-5 moderate; 0.5-1 strong (Wilson, 2009)

* Significant: p-value <0.05

Table 4 provides an overview of the *known-groups validity*. The questions of part 1 of the questionnaire were compared between the breast edema group and the non-breast edema group. Patients with breast edema have higher symptom scores. This difference is significant for the total symptom score (p=0.03) and for the items heaviness (p=0.026), swelling (p=0.035), redness (p=0.009) and pitting sign (p=0.020). For the other items (pain, tensed skin, enlarged skin pores and hardness) there is a trend towards significance.

Table 4. Known-groups validity

Breast edema symptoms	Mean score breast edema group	Mean score non-breast edema group	p-value
Total symptom score (±SD)	19.46 (±14.82)	8.20 (±9.64)	0.003*
Pain (±SD)	3.49 (±3.25)	1.90 (±2.63)	0.076
Heaviness (±SD)	2.29 (±2.75)	0.90 (±2.00)	0.026*
Swelling (±SD)	2.06 (±2.59)	0.60 (±1.67)	0.035*
Tensed skin (±SD)	2.51 (±3.12)	0.85 (±1.90)	0.051
Redness (±SD)	0.80 (±1.62)	0.00 (±0.00)	0.009*
Pitting sign (±SD)	1.89 (±3.04)	0.35 (±0.93)	0.020*
Enlarged skin pores (±SD)	0.91 (±1.90)	0.10 (±0.45)	0.053
Hardness (±SD)	5.51 (±3.57)	3.50 (±3.76)	0.056

SD = standard deviation

* Significant: p-value < 0.05

Out of 55 patients, 45 patients filled out the BrEQ a second time after 24 to 48 hours (drop-out 18%). Table 5 gives an overview of the ICC's of the breast edema symptoms between first and second measurement. It is shown that the *test-retest reliability* of the total symptom score and the items pain and heaviness is strong. For the other symptoms, reliability is moderate. All items were significant (see Table 5). The item redness had the lowest ICC. For this item, the test-retest reliability was analyzed in an additional sample of 10 breast cancer patients. They filled out the BrEQ twice, with a time difference of 24 to 48 hours and without a prior mammogram. For these 10 extra patients, the test-reliability for the item redness was strong (ICC=0.773, p=0.003).

The *internal consistency* was good for all items of part 1 of the BrEQ and for the total symptom score. The Cronbach alpha coefficients were 0.830 for the total symptom score and 0.839 to 0.869 for scores on the separate items (see Table 5).

A ROC curve was created using the total symptom score 24 to 48 hours after the US as the classifier and skin thickness as true-status reference (>2 SD's in at least one quadrant of the operated and irradiated breast on US) (Fig. 1). The AUC was 0.815. Therefore the accuracy of the test can be considered good [28]. The coordinate with the greatest sum of sensitivity and specificity was 8.5, suggesting that this value can be used to discriminate between individuals who have breast edema and those who have not. A cut-off value of ≥ 8.5 demonstrated a sensitivity of 75.0% and a specificity of 82.4%.

Table 5. Reliability of the total score and breast symptom scores (n=45)

		Test-Retest		Consistency
Breast edema symptoms	**ICC**	**95% CI**	**p-value**	**(α)**
Total symptom score	0.783	0.614-0.879	<0.001*	0.830
Pain	0.807	0.669-0.890	<0.001*	0.858
Heaviness	0.750	0.575-0.857	<0.001*	0.843
Swelling	0.670	0.432-0.813	<0.001*	0.842
Tensed skin	0.709	0.526-0.829	<0.001*	0.839
Redness	0.631	0.417-0.778	<0.001*	0.868
Pitting sign	0.717	0.538-0.834	<0.001*	0.864
Enlarged skin pores	0.730	0.560-0.842	<0.001*	0.868
Hardness	0.672	0.470-0.807	<0.001*	0.869

ICC=intraclass correlation coefficient, CI=confidence interval

Cut off values ICC: <0.4 weak; 0.4-0.75 moderate; 0.75-0.9 strong; >0.9 very strong (McDowell, 1996)

* Significant: p-value < 0.05

Cut off values Cronbach alpha coefficients: <0.5 unacceptable; 0.5-0.6 weak; 0.6-0.7 acceptable; 0.7-0..9 good; >0.9 excellent (Bland &Altman, 1997; McDowell, 1996)

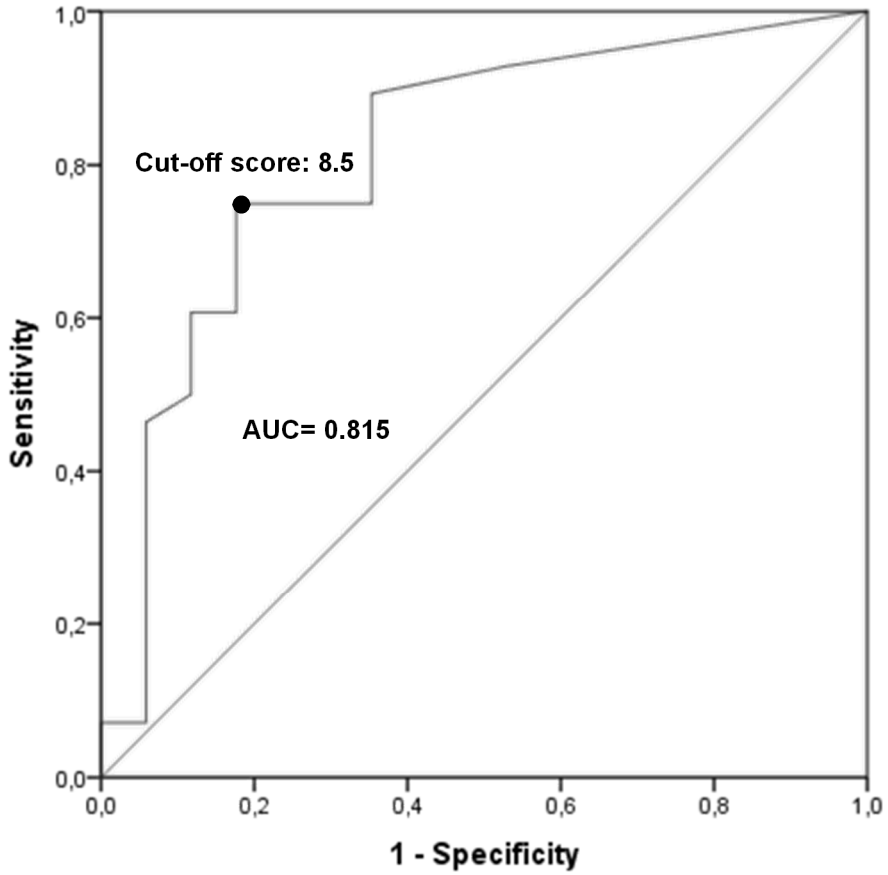

Figure 1. ROC curve to identify the cut-off point of the total symptom score of the BrEQ that discriminates between patients with and patients without breast edema

Discussion

The BrEQ (Dutch version) is the first self-reported questionnaire with evidence of validity and reliability for assessing breast edema in breast cancer patients who underwent BCS and radiation therapy.

Content validity was measured by means of an additional questionnaire and was found very good. Some patients felt that the BrEQ was not relevant for their current situation, because their breast cancer treatment was a longer time ago and they currently did not experience any breast complaints. While analyzing the demographic data, it is noticeable that many of the included patients underwent surgery quite a long time ago (range 8-183 months). Literature shows that the prevalence of breast edema diminishes over time. Although some patients still suffer from breast edema more than 5 years after breast surgery. Clarke et al. demonstrated that breast edema occurs in the first 2 months (early onset breast edema) or in about 20 months (late onset breast edema) after breast cancer treatment[8]. Wratten et al. described the time course of cutaneous breast edema based on the increase in skin thickness. In most cases skin thickness increases to a minor extent during radiation therapy, but more significantly in the post-treatment period. Skin thickness usually peaks at 4 to 6 months post-treatment and in most cases shows signs of returning to baseline levels at 12 months post-treatment[12]. Still, it

was useful to include patients who had surgery a longer time ago. First, because more than 5 years after surgery, there is still a (smaller) risk of developing breast edema and secondly, to compose an extensive control group. Concerning the content validity, other patients would like to add questions about lymphedema of the arm, however this is not the objective of the BrEQ. Perhaps for those patients a specific questionnaire for lymphedema of the arm, like the Lymphedema Functioning, Disability and Health Questionnaire – Upper Limb (Lymph-ICF-UL), is more appropriate[22].

Construct validity was tested by examining convergent validity and known-groups validity. Concerning convergent validity, all breast symptoms have a moderate correlation with skin thickness of the treated breast. For the total symptom score of the BrEQ, correlation is strong. From these results, we conclude that the thicker the skin, the higher the total symptom score. Regarding the known-groups validity, it is seen that for the total symptom score of the BrEQ, patients with breast edema score significantly higher than patients without breast edema. It means that, with regards to the total score of part 1, the BrEQ can differentiate between breast edema and no breast edema.

The test-retest reliability was investigated by filling out the BrEQ a second time 24 to 48 hours later. The lowest ICC was found for the item redness. This can be explained by the fact that the first measurement was preceded by a mammogram of both breasts. It might be possible that patients score lower for this item 24 to 48 hours later. To clarify this, the BrEQ was used in an additional sample of 10 breast cancer patients. None of these patients received a mammogram before filling out the questionnaire, in order to eliminate the interference of the redness induced by the mammogram. These patients filled out the BrEQ for a second time, 24 to 48 hours later. These 10 additional patients were not recruited during their annual mammogram and US appointment, and therefore, could not be included for the entire study. Based on the results of these 10 additional patients, we can conclude that the test- retest reliability of the item redness is strong.

We found that the BrEQ has good strength (AUC 0.815) to discriminate between patients with and without breast edema. The value with the greatest sum of sensitivity and specificity was 8.5 (cut-off point), suggesting that patients with a total symptom score of 9 or more, have breast edema. A score of 8 or less indicates that the patient has no breast edema. This makes the BrEQ a useful instrument for the diagnosis of breast edema in clinical practice.

In total, 55 patients were included in this study, of which 35 patients had breast edema, based on US measurements of skin thickness. No significant differences in the patients' characteristics were found. In the existing literature, we found only 1 study that reported a cut-off value for the presence of breast edema on US[29]. Rönkä et al. considered breast edema on US as a skin thickening over 2 mm. They included additional US measurements as well to determine whether a patient has breast edema,

namely increased echogenicity disturbance or poor visibility of the deeper echogenic line and interstitial fluid accumulation[29]. In our study, we only focused on skin thickening. However, we noticed a difference in the average skin thickness between the 4 quadrants. Therefore, we decided to determine our own cut-off values and considered breast edema as a deviation of more than 2 SD's from the average skin thickness of each quadrant of the non-operated breast. The motivation herein is that breast edema may occur in 1 quadrant only, without affecting the rest of the breast. With this method, we calculated cut-off values between 1.774 (SEQ) and 2.192 (SIQ), which is comparable with the 2 mm boundary[29]. We feel that this method is more accurate. A disadvantage however is that each quadrant is calculated with other complex cut-off values. Another limitation is the potential impact of the mammogram and US on the data gathered with the BrEQ, as mentioned above. Some patients experienced complaints like redness or pain caused by the mammogram. Test-retest reliability was run concurrently with validity of the BrEQ instead of separately from the main sample of the study. This is a limitation of the study. Furthermore, this study was conducted at a single hospital radiology department.

The BrEQ is developed with the intention to cover all domains of disability according to the ICF framework related to breast edema. This study wanted to focus more on the diagnosis of breast edema, than on the impact on daily functioning. Future research in order to validate part 2 of the questionnaire (activity limitations and participation restrictions) needs to be done. The present study did not investigate clinical responsiveness of the BrEQ or cross-cultural validity. Further investigation of those properties is needed. This Dutch questionnaire is the first to specifically assess breast edema. A translation and further investigation of the degree to which the items on a translated or culturally adapted BrEQ adequately reflect the items on the original Dutch version, is mandatory.

The BrEQ may be used in clinical practice to diagnose or assess breast edema in patients who underwent BCS and radiation therapy. It is known that the survival rate of breast cancer is fairly high, certainly compared to other cancers. Therefore, the quality of life (QOL) becomes more important. Since breast edema has a significant impact on body image, it can negatively influence the QOL[2,30]. With an early detection of breast edema in clinical practice, breast edema could be treated in an earlier stage, potentially leading to an improved outcome. Due to its ease of use, the BrEQ could be used by any health care professional involved in breast cancer treatment. In this way, breast edema could be detected more quickly, and the patient could be redirected to a specialist more rapidly to start the appropriate treatment. In addition, the BrEQ could be applied in clinical research.

Conclusion

In conclusion, the first part of the BrEQ is a reliable and valid Dutch questionnaire for assessing clinical indicators of breast edema after breast cancer treatment. We identified that a score cut-off point of 8.5 (AUC = 0.815) discriminates between patients who have breast edema and those who have not. Currently, part 1 of the questionnaire is a useful tool to asses and diagnose breast edema in clinical practice.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethical Committee of the Antwerp University Hospital (registration: B300201317503).

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Appendix 1 Breast edema questionnaire (BrEQ) – Dutch version

Vragenlijst borstoedeem

Instructies

Deze vragenlijst stelt u vragen over uw klachten. Wij willen graag weten hoe u zich op dit moment voelt.

Het invullen van deze vragenlijst neemt slechts enkele minuten van uw tijd in beslag.

- Bij '(Vul in)', vragen wij u een korte en bondige omschrijving van uw antwoord.
- Bij '(Omcirkel)' vragen wij om het antwoord dat voor u van toepassing is te omcirkelen.

Alvast bedankt voor uw bereidwillige medewerking en uw kostbare tijd.

Naam: _____

BORSTKLACHTEN

1. **Duid aan in welke mate u <u>gedurende de voorbije week</u> last had van volgende klachten in de geopereerde borst ?** (Omcirkel het nummertje)

	Helemaal niet										**Zeer ernstig**
<u>Pijn</u> in de geopereerde borst	0	1	2	3	4	5	6	7	8	9	10
Een gevoel van **<u>zwaarte</u>** in de geopereerde borst	0	1	2	3	4	5	6	7	8	9	10
Een **<u>gezwollen</u>** borst aan de geopereerde zijde	0	1	2	3	4	5	6	7	8	9	10
De huid voelt **<u>gespannen</u>** aan aan de geopereerde borst?	0	1	2	3	4	5	6	7	8	9	10
<u>Roodheid</u> ter hoogte van de huid van de geopereerde borst	0	1	2	3	4	5	6	7	8	9	10
Ik zie een **<u>afdruk</u>** van mijn beha staan in de geopereerde borst	0	1	2	3	4	5	6	7	8	9	10
De **<u>poriën</u>** ter hoogte van de huid van de geopereerde borst zijn **<u>vergroot</u>**	0	1	2	3	4	5	6	7	8	9	10
De geopereerd borst **<u>voelt</u>** op sommige plaatsen **<u>hard aan</u>**	0	1	2	3	4	5	6	7	8	9	10

Had u sinds uw operatie nog last van andere klachten ter hoogte van de geopereerde borst de voorbije week? Zo ja, omschrijf zo gedetailleerd mogelijk. (Vul in)

_____

_____

2. **Geef aan** (omcirkel) **op een schaal van 0 tot 10 of u <u>gedurende de voorbije week</u> moeite had met volgende activiteiten als gevolg van de klachten aan de borst. LET OP: we peilen enkel naar activiteitsbeperkingen ten gevolge van klachten aan de borst en niet ten gevolge van klachten aan de arm. Als de activiteit voor u niet van toepassing is, zet u een kruisje in de kolom "NVT".**

	Geen klachten										**Ondraaglijke klachten**	**NVT**
Slapen	0	1	2	3	4	5	6	7	8	9	10	
Neerliggen	0	1	2	3	4	5	6	7	8	9	10	
Zitten	0	1	2	3	4	5	6	7	8	9	10	
Rechtstaan	0	1	2	3	4	5	6	7	8	9	10	
Werk	0	1	2	3	4	5	6	7	8	9	10	
Huishouden	0	1	2	3	4	5	6	7	8	9	10	
Autorijden	0	1	2	3	4	5	6	7	8	9	10	
Handwerk	0	1	2	3	4	5	6	7	8	9	10	
Stappen	0	1	2	3	4	5	6	7	8	9	10	
Lichaamsbeweging/sport	0	1	2	3	4	5	6	7	8	9	10	
Aan- en uitkleden	0	1	2	3	4	5	6	7	8	9	10	
Het aan- en uitdoen van een beha	0	1	2	3	4	5	6	7	8	9	10	
Het dragen van een beha	0	1	2	3	4	5	6	7	8	9	10	
Computerwerk	0	1	2	3	4	5	6	7	8	9	10	
Andere activiteiten (Vul in) _____	0	1	2	3	4	5	6	7	8	9	10	
_____	0	1	2	3	4	5	6	7	8	9	10	

3. **Welke van bovenstaande activiteitsbeperkingen stoort u in het dagelijkse leven het meeste. Geef uw top 3.** (Vul in)

1. _____
2. _____
3. _____

Appendix 2 Breast edema questionnaire (BrEQ) – English version

Breast Edema Questionnaire

Instructions

This questionnaire aims to gain information about your complaints. Please indicate the extent to which you have experienced complaints at this moment.

Completing this questionnaire only takes a few minutes of your time.

- When mentioned '(Circle)' we ask you to circle the answer that applies to you.
- When mentioned '(Fill in)', we ask you for a short and concise description.

Thank you in advance for your cooperation and your valuable time

Name: _____

BREAST COMPLAINTS

1. Indicate to what extent you suffered from following complaints in the operated breast during the past week. (Circle)

	Not at all										**Very severe**
Pain in the operated breast	0	1	2	3	4	5	6	7	8	9	10
A feeling of **heaviness** in the operated breast	0	1	2	3	4	5	6	7	8	9	10
A **swollen** breast at the operated side	0	1	2	3	4	5	6	7	8	9	10
The **skin** feels **tensed** at the operated breast	0	1	2	3	4	5	6	7	8	9	10
Redness of the skin at the operated breast	0	1	2	3	4	5	6	7	8	9	10
A **print** of my bra is visible at the operated breast	0	1	2	3	4	5	6	7	8	9	10
The **pores** of the skin at the operated breast are **enlarged**	0	1	2	3	4	5	6	7	8	9	10
The operated breast feels **hard** at some places	0	1	2	3	4	5	6	7	8	9	10

Since your surgery, have you had any other complaints at the operated breast during the past week? If yes, please describe. (Fill in)

_____

_____

2. **Indicate** (circle) **on a scale from 0 to 10 if you had difficulty with following activities as a result of the breast complaints during the past week. PLEASE NOTE: we only assess activity limitations due to breast complaints and not due to arm complaints. If the activity does not apply to you, please indicate it in the column N/A".**

	No complaints										**Unbearable complaints**	**N/A**
Sleeping	0	1	2	3	4	5	6	7	8	9	10	
Lying down	0	1	2	3	4	5	6	7	8	9	10	
Sitting	0	1	2	3	4	5	6	7	8	9	10	
Standing	0	1	2	3	4	5	6	7	8	9	10	
Vocational activities	0	1	2	3	4	5	6	7	8	9	10	
Household chores	0	1	2	3	4	5	6	7	8	9	10	
Driving a car	0	1	2	3	4	5	6	7	8	9	10	
Handicraft	0	1	2	3	4	5	6	7	8	9	10	
Walking	0	1	2	3	4	5	6	7	8	9	10	
Sports	0	1	2	3	4	5	6	7	8	9	10	
Getting (un)dressed	0	1	2	3	4	5	6	7	8	9	10	
Putting on a bra	0	1	2	3	4	5	6	7	8	9	10	
Wearing a bra	0	1	2	3	4	5	6	7	8	9	10	
Computer work	0	1	2	3	4	5	6	7	8	9	10	
Other activities (Fill in) _____	0	1	2	3	4	5	6	7	8	9	10	
_____	0	1	2	3	4	5	6	7	8	9	10	

3. **Wich of the above mentioned activity limitations disturbs you the most in your daily living? Please give your top 3.** (Fill in)

1. _____
2. _____
3. _____

CHAPTER 5

The natural time course of breast edema after breast-conserving surgery and radiotherapy: a prospective cohort study

Verbelen H, Van Soom T, Dombrecht D, Erven K, De Vrieze T, Fransen E, Tjalma W, Gebruers N. The natural time course of breast edema after breast-conserving surgery and radiotherapy: a prospective cohort study (Submitted in Quality of Life Research)

Abstract

Purpose: To describe the prevalence and the longitudinal course of breast edema in breast cancer patients who underwent breast-conserving surgery (BCS) in combination with radiotherapy. The secondary aim is to investigate possible prognostic factors for the development of breast edema.
Methods: In this prospective cohort study, women older than 18 who received BCS in combination with radiotherapy were included. Breast edema, measured with the Breast Edema Questionnaire (BrEQ), a disease specific questionnaire, was assessed 1) prior to radiotherapy, 2) after termination of radiotherapy, 3) three months and 4) six months post-radiotherapy. Additionally, personal and medical record data were collected in order to investigate their prognostic value.
Results: In total, 88 patients were included in this study. After BCS and prior to radiotherapy (T1), 55.7% of patients had breast edema. After termination of radiotherapy (T2), the prevalence increased up to 63.9%. In the months to follow, the prevalence of breast edema declined to 53.6% after 3 months (T3) and 50.9% after 6 months post-radiotherapy (T4). Few prognostic factors could be identified: younger age, absence of nodal irradiation and shorter time interval between BCS and radiotherapy were associated with the presence of breast edema at some point in time.
Conclusion: BCS followed by radiotherapy results in a high prevalence of breast edema. Further research is necessary in order to gain insight in breast edema, its long-term timeline and its prognostic factors.

Key words: Breast Neoplasms, Breast Edema, Morbidity, Time Course

Introduction

Breast edema is a morbidity which is often seen in breast cancer patients following breast-conserving surgery (BCS) and radiotherapy. In contrast to lymphedema of the arm, breast edema is far less explored in literature. Nevertheless, breast edema following breast cancer treatment is common. In a systematic review, an incidence between 0% and 90.4% has been described[1]. This broad range can be explained by lack of a uniform definition for breast edema and the absence of a standard assessment method[2].

The time course of breast edema is little described in literature. Clarke et al. demonstrated that breast edema occurs within the first 2 months (early onset breast edema) or in about 20 months after breast cancer treatment (late onset breast edema)[3]. In the latter study, however, data were collected from the 70s and 80s. The treatment of breast cancer has undergone a major evolution since then. Wratten et al. described the time course of cutaneous breast edema based on the increase in skin thickness. A peak in skin thickness, 4 to 6 months post-treatment was observed, followed by a decline[4]. Although these findings are very valuable, they do not involve patient-reported outcome measures (PROMs). Since breast cancer morbidity and thereby patients' quality of life[5,6] are becoming more important, it is our purpose to draw attention to PROMs.

Literature shows that some radiotherapy parameters are associated with the development of breast edema, such as increasing irradiated breast volume[7], increasing boost volume[7,8] and the use of photon boost[9]. The prognostic value of these parameters however remains uncertain, since they were only investigated in a limited number of studies. Furthermore, consensus on other treatment-related and personal factors for breast edema, is lacking[1].

The aim of this study is to describe the prevalence and longitudinal course of breast edema in breast cancer patients who underwent BCS and radiotherapy, using modern irradiation techniques. The secondary aim is to investigate possible prognostic factors for the presence of breast edema.

Methods

Patient selection and recruitment

In this prospective cohort study, participants were recruited from the Iridium Cancernetwork hospitals (AZ Klina, AZ Monica, AZ Nikolaas, AZ Sint-Jozef Malle, GZA Hospitals, UZA, ZNA) between May 2017 and August 2018. The electronic agenda was screened for eligible patients who had an appointment for radiotherapy simulation. The patients' electronic medical files were used to determine if they met the inclusion criteria. Women older than 18 years who underwent BCS followed by radiotherapy were

enrolled. Exclusion criteria were (1) only vacuum-assisted core biopsies or mammotome® biopsies, (2) other disorders associated with breast edema like angiosarcoma, conditions of the skin, heart and lung diseases, (3) plastic surgery such as reconstructive surgery, (4) pregnancy, (5) bilateral breast surgery and (6) not able to fill in the Dutch questionnaire. All participants received an information brochure informing them about the study and requesting voluntary participation. All participants provided written informed consent. The study was approved by the Ethical Committees of the GZA Hospitals and the Antwerp University Hospital (registration: B300201317503).

Radiotherapy treatment protocol

Breast radiotherapy was performed with a sliding window intensity modulated radiotherapy technique (IMRT), using a tangential field set-up. If the elective lymph nodes were included in the target volume, additional anterior and tangential quarter beams were added to cover the medial supraclavicular, internal mammary and axillary lymph nodes. Dose prescription was 40 Gy and 36 Gy in 15 fractions to respectively the whole breast and lymph nodes. An additional dose was delivered to the tumor bed by intra-operative electron beam radiation (IEORT): 1 x 9 Gy or post-operative external electron or photon beam radiation (5 x 2 Gy).

Data selection

Participants were asked to fill in the Breast Edema Questionnaire (BrEQ) at several time points during therapy and follow-up. The BrEQ is composed of 2 parts. In part 1, 8 symptoms associated with breast edema are scored on a scale from 0 (no distress) to 10 (maximal distress): swelling, pain, redness, hardness, heaviness, tensed skin, peau d'orange and pitting sign. A total score can be obtained with a minimum of 0 and a maximum of 80. The validity and reliability of part 1 of the BrEQ have been proven in a previous study by correlating the BrEQ with skin thickness, measured with ultrasound (US). A cut-off point of 8.5 has been determined, suggesting that patients with a total score of 9 or more have breast edema[2]. In part 2 of the BrEQ, the impact of breast edema on activities of daily life is scored on a scale from 0 to 10 as well. The impact on daily functioning was not the focus of this study and will therefore not be discussed further.

The BrEQ has been filled in for the first time during the radiotherapy simulation appointment, which is after BCS and prior to radiotherapy (T1). Furthermore, it has been administered immediately after termination of radiotherapy (T2), 3 months (T3) and 6 months post-radiotherapy (T4). At T1, data were collected during a consultation. Depending on the patients' preference, follow-up data were collected

either by email or postal mail. If patients choose to receive the questionnaire by post, it was sent, together with a pre-stamped envelope.

Personal data like age, body mass index (BMI), handedness, cup size and menopausal state were obtained through a self-administered questionnaire during the first consultation. In addition, treatment-related data e.g. type of axillary surgery, surgery date, radiotherapy related data and information about other (neo-)adjuvant therapies were extracted from the patients' electronic medical files.

Data analysis

Socio-demographic and clinical variables were analyzed using descriptive statistics as frequencies, means and standard deviations. Therefore, The Statistical Package for the Social Sciences (SPSS) version 24 was used. For all other statistical analyses, R version 3.5.1 was used (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). To model the longitudinal profile of the total BrEQ-score, a linear mixed model was fitted with the BrEQ-score as dependent variable, time as (categorical) independent variable and participant ID as random intercept. If the fixed effect was significant, the null hypothesis stating that the BrEQ-score is equal across time points, was rejected. In this latter case, a post hoc analysis with Tukey correction for multiple testing was carried out, to test which time points differ from one another. A corrected p-value below 0.05 was considered as a significant difference in total score between two time points. To analyze the association between the presence of breast edema at T1 and follow-up time points, breast edema was recoded as a binary trait, with the patient having breast edema if the BrEQ-score was 9 or higher[2]. Subsequently, the chi-square test was used to test the association between the presence of breast edema at T1, with the presence of breast edema at T2, T3 and T4. A p-value below 0.05 was considered a significant association. A logistic regression model was used to test if personal factors and treatment-related factors of the participants were associated with the presence of breast edema. The presence of breast edema was entered as dependent variable in the logistic regression model. A p-value below 0.05 was considered a significant association between the factor and the presence of breast edema at the given time point.

Results

Respondents and their characteristics

Initially, 92 patients were recruited to take part in this study. Before filling in the BrEQ, 3 patients were excluded after further inspection of the medical files, and one patient had to redraw from the study

Table 1. Demographic and clinical characteristics of the participants (n=88)

Age, mean (y) ±SD	61.92 ±11.14
BMI, mean (kg/m^2) ±SD	26.48 ±5.10
Treated breast	
Left, n (%)	47 (53.4)
Right, n (%)	41 (46.6)
Surgery at the dominant side	
Yes, n (%)	39 (44.3)
No, n (%)	49 (55.7)
Menopausal state at time of surgery	
Premenopausal, n (%)	16 (18.2)
Postmenopausal, n (%)	70 (79.5)
Unknown, n (%)	2 (2.3)
Preoperative bra cup size	
A, n (%)	6 (6.8)
B, n (%)	26 (29.5)
C, n (%)	22 (25.0)
D, n (%)	15 (17.0)
E, n (%)	8 (9.1)
F, n (%)	1 (1.1)
H, n (%)	1 (1.1)
Unknown, n (%)	9 (10.2)
Type of axillary surgery	
ALND, n (%)	13 (14.8)
SLNB, n (%)	75 (85.2)
Chemotherapy	
No, n (%)	61 (69.3)
Neoadjuvant, n (%)	21 (23.9)
Adjuvant, n (%)	6 (6.8)
Hormone therapy	
No, n (%)	36 (40.9)
Aromatase inhibitors, n (%)	22 (25.0)
Tamoxifen, n (%)	29 (33.0)
Unknown, n (%)	1 (1.1)
Trastuzumab (Herceptin®)	
Yes, n (%)	8 (9.1)
No, n (%)	80 (90.9)
Radiotherapy	
WBRT, n (%)	68 (77.3)
WBRT + nodal irradiation, n (%)	20 (22.7)
Nodal irradiation	
No, n (%)	68 (77.3)
Medial supraclavicular nodes + axillary nodes level 3, n (%)	13 (14.8)
Axillary nodes level 1-2, n (%)	4 (4.5)
Medial supraclavicular nodes + axillary nodes level 3 + internal mammary nodes, n (%)	2 (2.3)
Unknown, n (%)	1 (1.1)
Type of boost	
No boost, n (%)	4 (4.5)
Photon, n (%)	47 (53.4)
Electron, n (%)	30 (34.1)
IORT, n (%)	7 (8.0)
Time between surgery and onset of radiotherapy, mean (days) ±SD	82.31±64.10

SD standard deviation, *BMI* body mass index, *ALND* axillary lymph node dissection, *SLNB* sentinel lymph node biopsy, *WBRT* whole breast radiotherapy, *IORT* intraoperative radiotherapy

due to health issues. Therefore, 88 patients were included in this study at T1. At T2, T3 and T4, the BrEQ was filled in completely and was returned by 61, 56 and 53 patients respectively. Reasons for loss to follow-up were due to wrong home addresses, wrong e-mail addresses and emotional distress due to the nature of the questions. Reasons for incomplete questionnaires were due to patients filling them in wrongly and illegible handwriting. Characteristics of the participants are shown in Table 1.

Prevalence and longitudinal course of breast edema

After BCS and prior to radiotherapy (T1), 55.7% of patients had breast edema. After termination of radiotherapy (T2), the prevalence increased up to 63.9%. In the months to follow, it declined to 53.6% 3 months (T3) and 50.9% 6 months post-radiotherapy (T4). The mean BrEQ-scores on each time point are displayed in Table 2. The mean BrEQ-score at T1 is significantly different from the scores at T2 ($p<0.001$) and T3 ($p=0.003$), with the lowest BrEQ score at T1. The scores between T1 and T4 are not significantly different. The BrEQ-score at T4 is significantly lower compared to T2 ($p=0.01$). The presence of breast edema at T1, based upon a score of at least 9 on the BrEQ, is significantly associated with the presence of breast edema at T2 and T3 ($p=0.013$ and $p<0.001$, respectively).

Table 2. Prevalence of breast edema and mean BrEQ-scores at the different time points

	Number of patients	Prevalence (%)	Mean BrEQ-score±SD	Range
After BCS, prior to RT (T1)	88	55.7	10.14±8.53	0-30
After termination of RT (T2)	61	63.9	19.82±17.68	0-66
3 months after RT (T3)	56	53.6	16.71±18.08	0-73
6 months after RT (T4)	53	50.9	13.21±15.48	0-57

BCS breast-conserving surgery, *RT* radiotherapy, *BrEQ* Breast Edema Questionnaire, *SD* standard deviation

Prognostic factors of breast edema

Table 3 gives an overview of the association between personal and treatment-related factors and the presence of breast edema at the 4 time points, as modeled through logistic regression. Only few factors are significantly associated with breast edema. With regards to age at inclusion, it is seen that younger patients are more likely to have breast edema at T1 ($p=0.012$), T2 ($p=0.003$) and T3 ($p=0.002$). However, effect sizes are small (Odds ratio (OR) of 0.95, 0.91 and 0.92 respectively)[10]. After termination of radiotherapy (T2), women who received whole breast radiotherapy (WBRT) with nodal irradiation, are significantly less likely to have breast edema compared to women who received WBRT without nodal irradiation ($p=0.03$, OR=0.25). Furthermore, the presence of breast edema is significantly associated with the time interval between BCS and radiotherapy. Patients with a shorter time interval, are significantly more likely to show breast edema at T2 ($p=0.030$, OR=0.99). Other

Table 3. Logistic regression analysis of factors potentially related to breast edema

	T1			T2			T3			T4		
Variable	**p-value**	**Odds ratio**	**95% Confidence Interval**	**p-value**	**Odds ratio**	**95% Confidence Interval**	**p -value**	**Odds ratio**	**95% Confidence Interval**	**p-value**	**Odds ratio**	**95% Confidence Interval**
Age at inclusion	0.012*	0.95	0.91-0.99	0.003*	0.91	0.85-0.98	0.002*	0.92	0.87-0.97	0.053	0.95	0.90-1.00
BMI	0.426	1.04	0.95-1.13	0.812	0.98	0.85-1.14	0.870	1.01	0.89-1.14	0.974	1.00	0.86-1.17
Menopausal state	0.203	0.48	0.15-1.53	0.509	0.57	0.10-3.15	0.613	0.70	0.17-2.83	0.351	0.43	0.07-2.63
Surgery at dominant side	0.579	1.27	0.54-2.97	0.095	2.55	0.83-7.84	0.086	2.62	0.86-7.97	0.394	1.63	0.53-4.98
Type of axillary surgery	0.455	1.57	0.48-5.12	0.552	1.55	0.37-6.55	0.464	0.52	0.09-3.11	0.967	0.96	0.12-7.38
Trastuzumab (Herceptin®)	0.735	0.78	0.18-3.33	0.672	0.71	0.14-3.50	0.464	1.92	0.32-11.47	0.306	0.32	0.03-3.30
Nodal irradiation	0.109	0.44	0.16-1.22	0.030*	0.25	0.37-6.55	0.589	0.69	0.18-2.62	0.131	0.29	0.05-1.60
Time between surgery and RT	0.055	0.99	0.99-1.00	0.030*	0.99	0.07-0.89	0.327	1.00	0.99-1.00	0.837	1.00	0.99-1.01
BrEQ-score at T1	NA	NA	NA	0.003*	1.13	1.03-1.24	<0.001*	1.23	1.09-1.38	0.007*	1.13	1.03-1.25
Multiple level variable	**p-value**	**Odds ratio**	**95% Confidence Interval**	**p-value**	**Odds ratio**	**95% Confidence Interval**	**p -value**	**Odds ratio**	**95% Confidence Interval**	**p-value**	**Odds ratio**	**95% Confidence Interval**
Pre-operative bra cup size	0.381			0.697			0.870			0.531		
A-B		1			1			1			1	
C		0.93	0.31-2.78		1.77	0.43-7.30		1.55	0.41-5.78		2.25	0.48-10.60
D		0.68	0.20-2.33		2.10	0.45-9.81		1.38	0.26-7.22		2.25	0.48-10.60
E, F, H		3.11	0.57-17.02		2.36	0.21-25.91		2.06	0.28-15.36		3	0.44-20.44
Hormone therapy	0.485			0.541			0.833			0.949		
No		1			1			1			1	
Aromatase inhibitors		0.53	0.18-1.55		1.50	0.41-5.54		1.5	0.40-5.66		1.11	0.26-4.72
Tamoxifen		0.90	0.33-2.44		2.10	0.55-8.00		1.13	0.32-3.99		1.23	0.35-4.41
Chemotherapy	0.171			0.259			0.057			0.718		
No		1			1			1			1	
Adjuvant		0.56	0.20-1.52		0.36	0.11-1.22		0.68	0.18-2.51		1.46	0.34-6.26
Neo-adjuvant		3.71	0.41-33.73		0.83	0.07-10.01		$	$		2.33	0.20-27.91
Type of boost	0.242			0.759			0.914			0.356		
Photon boost		1			1			1			1	
Electron boost		0.52	0.21-1.31		1.53	0.46-5.11		0.86	0.27-2-75		1.31	0.39-4.39
IORT		1.70	0.30-9-67		0.92	0.13-6.38		1.29	0.18-9.02		4.73	0.46-48.78

Abbreviations: *BMI* body mass index, *RT* radiotherapy, *BrEQ* Breast Edema Questionnaire, NA = not applicable

T1= after breast-conserving surgery, prior to radiotherapy, T2= after termination of radiotherapy, T3= 3 months after radiotherapy, T4= 6 months after radiotherapy

*p<0.05

$ Could not be estimated due to lack of observations in the neo-adjuvant chemotherapy category

Cut off values Odds ratio: 0.67<OR<1 small effect size; 0.40<OR<0.67 medium effect size; 0.25<OR<0.4 large effect size; OR<0.25 very large effect size (Rosenthal, 1996)

factors like BMI, menopausal state, whether the surgery was performed at the dominant side, cup size, hormone therapy, chemotherapy, trastuzumab (Herceptin®), type of axillary surgery and type of boost, were not significantly associated with the presence of breast edema. In our logistic regression model, we also tested the association between the BrEQ-score at T1 as a continuous variable, and the presence of breast edema for the subsequent time points. It is seen that a higher BrEQ-score at T1 is significantly associated with the presence of breast edema at later time points (T2 p=0.003, OR=1.13; T3 p<0.001, OR=1.23; T4 p=0.007, OR=1.13).

Discussion

In a cohort of female breast cancer patients who underwent BCS in combination with radiotherapy, a peak in prevalence of 63.9%, was observed after termination of radiotherapy. However, after BCS, but prior to radiotherapy, many patients already showed signs of breast edema (55.7%). Afterwards, the prevalence declined to 53.6% and 50.9% at respectively 3 and 6 months post-radiotherapy. Six months post-radiotherapy, no significant difference could be demonstrated compared to baseline. The observed timing of peak prevalence and the following decline of breast edema, is in line with findings in similar populations in literature[5,6,11–15] (Table 4).

The degree of breast edema has about the same timeline as its prevalence. Few studies investigated its degree longitudinally. Wratten et al. described the time course of cutaneous edema based on the increase in epidermal thickness, measured with US[4]. In most cases, epidermal thickness increases to a minor extent during radiotherapy itself, but more significantly in the post-treatment period. Epidermal thickness usually peaks at 4–6 months post-treatment and in most instances show signs of returning to baseline, 12 months post-treatment. The time course of parenchymal edema is about the same[4]. These findings were similar to our PROMs, although, the peak in the degree of breast edema comes later when compared to our study. It is noticeable that the mean BrEQ-scores are quite low, meaning that although the prevalence is high, most patients experience a mild form of breast edema.

It is seen that breast edema is already present pre-radiotherapy. This has been described in previous studies and can be explained by several factors[5,11–13,16]. Firstly, the fact that BCS itself causes breast edema, due to damage to the lymphatic system. This compromises lymphatic transport and therefore could cause breast edema[1]. Secondly, several breast complaints assessed in the BrEQ such as pain, tensed skin or swelling, can be typical post-operative complaints, without being a sign of breast edema[17]. Therefore, an overestimation of breast edema in the first period after surgery is possible. A peak in prevalence, as well as in the degree of breast edema, is seen after termination of radiotherapy. Also, at this time point, an overestimation could have taken place, because some symptoms of breast

edema are similar to the well-known side effects of radiotherapy. Redness, swelling and pain for example, could be linked with radiation dermatitis, which is typically reported after radiotherapy[18].

Table 4. Time course of breast edema in literature

Reference	Follow-up	Breast edema
Current study	Prior to RT	55.7%
	After termination of RT	63.9%
	3 months after RT	53.6%
	6 months after RT	50.9%
Adriaenssens 2012	0-3 months postoperative	93.3%
	3-6 months postoperative	73.3%
	6-12 months postoperative	82.4%
	12-24 months postoperative	80.6%
	24-60 months postoperative	65.4%
Berrang 2011	Prior to RT	32%
	1 year after RT	16%
	3 years after RT	6%
Vicini 2007	>6 months after RT	32%
	>24 months after RT	22%
	>36 months after RT	0%
Young-Afat 2019	Baseline: prior to RT	12.0%
	3 months after baseline	7.1%
	6 months after baseline	12.4%
	12 months after baseline	8.2%
	18 months after baseline	5.5%
Olivotto 1996	Prior to RT	26.6%
	3 year after RT	4.3%
	5 years after RT	2.6%
Johansson 2015	Prior to RT	29%
	2 weeks after RT	39%
	3 months after RT	63%
	6 months after RT	63%
	12 months after RT	39%
	24 months after RT	28%

Abbreviations: RT: radiation therapy

Few prognostic factors for the presence of breast edema were identified in our study. With regards to personal factors, only age was significantly associated with breast edema. This was not the case for BMI, menopausal state, surgery at the dominant side and bra cup size. When comparing these findings to literature, results are often conflicting. Concerning age, some studies confirm our findings that younger age is associated with more breast edema[6,19]. However, Barnett et al. suggests the exact opposite[8]. For that reason, no firm conclusions can be drawn concerning age. When looking at BMI as a possible risk factor for breast edema, our study confirms 2 other studies which also found no significant association[3,20], opposed to one suggesting otherwise[6]. There was no influence of cup size or breast size according to our study, as in the study of Adriaenssens et al [6]. Nevertheless, other studies found a positive correlation between breast edema and breast size[8,12,19,21]. This can probably be explained by the fact that a larger breast size implicates more adipose tissue. This may have led to an

overestimation of breast edema in women with a larger breast size, since it is misinterpreted as swelling of the breast[1]. For the menopausal state and whether the BCS is performed on the dominant side, no additional literature was found to compare our findings. In our study it is seen that menopausal state is not associated with the presence of breast edema. This is rather unexpected, as menopausal state is a reflection of age (since premenopausal women are younger and age appeared to be significantly associated with the presence of breast edema). Furthermore, it is seen in literature that premenstrual syndrome is seen in up to 91.7% of women of reproductive age[22]. Symptoms associated with premenstrual syndrome are breast tenderness and breast swelling[22,23]. Therefore, we could expect higher BrEQ-scores in premenopausal women. However, this is not the case.

With regards to treatment-related factors, it is seen that, except for the time interval between BCS and radiotherapy and nodal irradiation, none of the investigated factors were associated with the presence of breast edema. Patients in who the time interval between surgery and radiotherapy was shorter, had more breast edema after finishing radiotherapy (p=0.030). A possible explanation could be that patients in who the time interval is shorter, still suffer from morbidities related to the surgery such as pain, scar tissue, seroma etcetera at T2. Another reason could be that in those patients, there is less time for lymphatic regeneration and lymphangiogenesis[24]. The time interval between surgery and radiotherapy depends on the adjuvant treatment(s), and this depends on the type of cancer. It is seen that the range of this time interval is very broad. Patients start with radiotherapy within 4 to 6 weeks after surgery, if no chemotherapy was indicated. If chemotherapy is advised, this will be given before the start of radiotherapy. Adjuvant chemotherapy takes almost 6 months. This means that the time interval between BCS and radiotherapy for those patients is at least 6 months. In this longer time interval, more lymphatic regeneration could be possible. Consequently, it is expectable that patients who underwent chemotherapy, are not likely to have more breast edema, since their time interval between BCS and radiotherapy is longer. Concerning nodal irradiation, results are rather unexpected, as we demonstrated that the absence of nodal irradiation is associated with breast edema. Considering the fact that nodal irradiation targets the lymph nodes, we would therefore assume it damages the lymphatic system and consequently would be associated with breast edema on the long-term. However, the opposite is true. Patients receiving nodal irradiation, often receive chemotherapy as well. This means that their time interval between surgery and radiotherapy is longer. Kelemen et al. demonstrated that nodal irradiation was not significantly associated with breast edema[7]. In our study, we found that breast edema was not associated with the type of boost therapy. This is in contrast with results of Kelemen et al., who found that a photon boost was significantly related to breast edema[7]. The type of axillary surgery was not significantly associated with the presence of breast edema either. When looking at the literature, no consensus was found concerning the type of axillary surgery. Some

studies show similar results as ours[6,20], but Wratten et al. found that axillary lymph node dissection (ALND) is associated with more severe breast edema compared to sentinel lymph node biopsy (SLNB)[4]. Nevertheless, the current study considered breast edema as a binary trait, whereas Wratten et al. used the epidermal skin thickness as a continuous variable. Furthermore, no association was found between breast edema and hormone therapy as such, and its type. Chemotherapy (adjuvant or neo-adjuvant) was not associated with breast edema either. It is seen in literature that neo-adjuvant chemotherapy can downstage the primary tumor and can therefore decrease the rate of more invasive surgery[25]. This could therefore lead to less breast morbidity, however, according to our study results, this is not the case. When looking at the literature regarding hormone therapy and chemotherapy, contradicting results are often found, so its prognostic value remains uncertain[1]. Trastuzumab (Herceptin®) is another factor which is not significantly associated with breast edema. Other research concerning trastuzumab (Herceptin®) and its relation to breast edema is currently lacking.

The current study has several strengths. The BrEQ is a reliable and valid Dutch questionnaire to assess breast edema after breast cancer treatment and is therefore a valuable tool[2]. We feel that other assessment methods described in literature are often not specific or inclusive enough. For example, in the study of Young-Afat et al., only 1 item of the EORTC BR23 questionnaire was used to asses breast edema, namely swelling of the affected breast. Nevertheless, literature shows that breast edema is more than swelling alone. Other breast complaints like pain in the affected breast, hardness, peau d'orange, heaviness, redness, tensed skin and pitting sign are often forgotten, but can be equally bothersome for patients[1]. The most common assessment method found in literature is physical examination. However, different criteria were used to assess the breast, for example the LENT/SOMA criteria, the National Cancer Institute Common Toxicity Criteria, the Modified System of Johanson et al., the RTOG/EORTC criteria (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) and the Harvard Criteria. The use of different criteria can partly explain the conflicting results within the current literature. Wratten et al., used US to measure skin thickness of the breast. This quantitative measure for breast edema is very useful, certainly in clinical research. However, we wanted to focus more on PROMs. Another strength is the prospective design of this study in which patients are followed up to 6 months after radiotherapy.

One limitation of this study is the possibly differential drop-out rate which is partly due to voluntary participation. This makes the study vulnerable for selection bias, which can influence the results. For the longitudinal analysis, this is not likely to be a concern, since linear mixed model analysis is robust to missing at random[26]. Even if the drop-out is not entirely random, but associated with observable characteristics of patients, the resulting analyses are still valid. For the logistic regression, we studied the association between personal and treatment-related factors and breast edema. To determine

possibly differential drop-out, we compared patient characteristics between complete cases (i.e. patients who filled in the BrEQ at the 4 time points) and individuals lacking at least one time point. For none of the characteristics, a significant difference was found (See supplementary file). Therefore, the Odds ratios estimated in Table 3 are not likely to be biased by non-random drop-out. Another limitation is the subjective character of the BrEQ. Although, we wanted to focus on the PROMs, the additional use of an objective assessment method, like US or the MoistureMeter D, could have an added value[15]. Furthermore, it is seen that some of the symptoms of breast edema assessed with the BrEQ, are equal with other side-effects following surgery or radiotherapy. For example, if a patient with a painful erythema post-radiotherapy, scores 5 out of 10 for redness and pain, according to the BrEQ, she will have breast edema, although, the actual problem is erythema. This could lead to an overestimation of breast edema. Finally, it is difficult to compare our results with findings in literature, due to differences in radiotherapy protocols, adjuvant treatments, follow-up times and assessment methods.

This study shows that breast edema is a common phenomenon following BCS and radiotherapy. It is demonstrated that the BrEQ-score at T1 is associated with the presence of breast edema at T2, T3 and T4. Patients who have breast edema prior to radiotherapy are likely to have more breast edema on the long term. This finding can be very valuable in clinical practice when informing breast cancer patients. A self-reporting system, like for example a smartphone application, could be a welcome addition in order to detect breast edema early. To enable further research, it is essential that consensus is reached concerning a clear definition and a standardized assessment for breast edema. A clear definition would allow us to stage breast edema during treatment and follow-up period and open a possibility for intervention trials. Long-term prospective research is vital to gain better insight in breast edema after BCS and radiotherapy. A longitudinal study with longer follow-up could make it possible to detect when an appropriate treatment or information should be provided. Furthermore, we found a discrepancy between breast edema measured with the BrEQ and what is experienced in clinical practice. From a clinical point of view, we presume that the prevalence rates demonstrated in this study are quite high. This is probably due to the low cut-off value that is used to allocate a patient as having breast edema. The cut-off value of only 8.5 on a total score of 80 means that patients with only very limited complaints will already be defined as having breast edema, which can be subclinical. On the one hand, mild edema is often not recognized and acknowledged by health care workers. On the other hand, despite the high prevalence found in this study, we like to stress that the number of patients needing treatment for breast edema is far less, because, in many patients, breast edema resolves spontaneously. Therefore, the take home message should be to closely monitor those patients in who the BrEQ-score doesn’t decline within 6 months after termination of radiotherapy.

Moreover, additional investigations such as interviews of patients to understand the clinical significance of breast edema, could have an added value.

Conclusion

BCS followed by radiotherapy results in a high prevalence of breast edema, assessed with the BrEQ. Prevalence peaks after termination of radiotherapy and drops subsequently during the following months. Few prognostic factors could be identified: younger age, absence of nodal irradiation and shorter time interval between BCS and radiotherapy. Further research is necessary in order to gain insight in breast edema, its long-term timeline, its prognostic factors and intervention trials.

Compliance with Ethical Standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the Ethical Committees of the GZA Hospitals and the Antwerp University Hospital (registration: B300201317503).

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Supplementary file Characteristics in complete cases vs. non-complete cases

Characteristic	**p-value**
Age at inclusion	0.063
BMI	0.104
Treated breast	0.380
Dominant hand	0.330
Surgery at the dominant side	1
Menopausal state at time of surgery	0.779
Preoperative bra cup size	0.142
Type of axillary surgery	0.075
Chemotherapy	0.346
Hormone therapy	0.747
Herceptin®	1
Nodal irradiation	0.302
Type of boost	0.699
Time between surgery and onset of radiotherapy	0.527

The characteristics were compared between the individuals with complete data for BrEQ across all 4 time points, and the individuals lacking at least one time point. For continuous variables, significance was tested using a one-way ANOVA or an independent sample t-test, and using Fisher's exact test for categorical variables.

GENERAL DISCUSSION

The general aim of this thesis is to gain insight in the morbidity after breast cancer treatment. This thesis consists of 2 major parts. In part A, arm and shoulder complaints after SLNB were explored and the incidence, time course and the associated activity limitations and participation restrictions were identified. In part B, firstly, insight into breast edema as a morbidity after BCS and radiotherapy was established, secondly, a questionnaire to assess breast edema was constructed and its clinimetric properties were determined, thirdly, the longitudinal course of breast edema and its prognostic factors were investigated. The 2 major parts and the different research questions are presented in Table 1.

Table 1. Schematic overview if the research questions in the doctoral thesis

Part	Chapter	Research question	Design
Part A: Arm and shoulder complaints after SLNB	1	Which arm and shoulder complaints are present in sentinel negative patients? What is the incidence and time course of these complaints?	Systematic review (published)
	1bis	What is the incidence and time course of lymphedema in sentinel negative patients?	Systematic review (published)
	2	What is the prevalence of arm and shoulder complaints in sentinel negative patients on the short and long term? What are activity limitations and participation restriction?	Cross-sectional study, retrospective (published)
Part B: Breast edema after BCS and radiotherapy	3	What is the incidence of breast edema after BCS and radiotherapy? What are risk factors for breast edema?	Systematic review (published)
	4	What are the clinimetric properties of the BrEQ?	Validity study Reliability study (published)
	5	What is the prevalence and longitudinal course of breast edema after BCS and radiotherapy? What are prognostic factors for breast edema?	Cohort study, prospective (submitted)

In this general discussion, I will provide an overview of the different research questions of this doctoral thesis and discuss the main findings. Furthermore, strengths, limitations and clinical implications will be highlighted. Finally, recommendations for future research will be formulated.

Main findings and discussion of PART A concerning arm and shoulder complaints after sentinel lymph node biopsy

CHAPTER 1 - Which arm and shoulder complaints are present in sentinel negative breast cancer patients? What is the incidence and time course of these complaints?

Arm and shoulder complaints in breast cancer patients who underwent a SLNB were systematically assessed. Literature was explored and following complaints were set forth: loss of mobility[1–20], loss of strength[1,2,5–8,10,11,13,21], pain[2,5,6,8–10,12–15,18], scapula alata[9], AWS[15,19,22] and sensory disturbances[2–10,12–14,17–19,21]. Within the first month after SLNB, the morbidities with the highest incidence were decreased ROM in abduction (range 40.8-100%) and forward flexion of the shoulder (range 37-100%), pain (range 3.4-56.6%) and numbness (range 2-64%). The morbidities with the highest incidence after 2 years were pain (range 5.6-51.1%), numbness (range 5.1-51.1%), loss of strength (range 0-57.7%) and decreased ROM in internal rotation (44.4%) and abduction (range 0-41.4%). Paresthesia was less common after SLNB. At 6 months postoperatively, its incidence was 10.4%, however, it was still present 2 years post-operatively, ranging from 7.5% to 15.8%[3,8,10]. Scapula alata was described in only one study. Not a single SLNB patient developed this impairment[9]. The incidence of AWS ranged between 0.9% and 20%. At 3 months postoperatively, its highest incidence (20%) was measured [15,19,22].

Although this literature search did not focus on breast morbidity after SLNB, none of the selected articles mentioned breast edema, in contrary to lymphedema of the arm. Many morbidities are discussed in the literature, but in this thesis, we would like to draw attention to a neglected complaint after breast cancer treatment, namely breast edema (Chapter 3, 4, 5). Furthermore, an abundance of research on morbidity after SLNB is available, however, the follow-up period is often short (1 to 3 years). Few studies demonstrate the long-term follow after SLNB. Based on this fact, we decided to investigate the long-term follow-up of arm and shoulder morbidity retrospectively (Chapter 2).

CHAPTER 1bis – What is the incidence and time course of lymphedema in sentinel negative breast cancer patients?

The literature was systematically reviewed based on the PRISMA guidelines, addressing the above-mentioned research questions. The overall incidence of lymphedema in patients with sentinel node negative breast cancer ranged between 0% and 63.4%. Two studies are mainly responsible for this high incidence rate and therefore, results should be interpreted with caution. Armer et al. reported only on 9 SLNB patients, of whom 2 (22%) were diagnosed with lymphedema[23]. Francis et al. used a very liberal definition, namely, a 5% volume difference between pre-operative and post-operative arm volumes[24], whilst 10% difference between both arms is the widely accepted definition for lymphedema, along

with others. If both studies were discarded from the results, the incidence range would be 0% to 15.8%, which is in line with the results of a large meta-analysis of Disipio et al[25]. This incidence rate is less compared to the incidence rate after ALND, which has a reported range of 13.5% to 28.2%[25]. We can conclude that the incidence of lymphedema after SLNB is lower in comparison with ALND, as we expected, since the SLNB is the lesser invasive procedure. However, we should be aware of the possibility of lymphedema formation in patients who have had a SLNB. If untreated, this lymphedema can become severe. The studies that have assessed lymphedema at predefined time points, instead of mean follow-up time, demonstrated an incidence rate at <3, 6, 12, or >18 months post-surgery of 3.2% to 5%[26], 2% to 10%[26–28], 3% to 12%[13,26–28] and 6.9% to 8.2%[3], respectively. The long-term incidence was 5%to 5.4%[19,29]. That is why we need to stay perceptive for lymphedema after breast cancer treatment, also on the long term, even in patients with a negative sentinel node.

CHAPTER 2 - What is the prevalence of scapula alata, AWS, loss of mobility, loss of strength, pain, lymphedema and sensory disturbances in sentinel negative breast cancer patients on the short and long term? Which activity limitations and participation restrictions are present in these patients?

To efficiently gather data about the history of a large sample on arm and shoulder morbidity, patients from the Breast Clinic of the Antwerp University Hospital were retrospectively surveyed by means of a questionnaire. The percentages of patients who had ever experienced complaints following SLNB were 43.5% for pain, 22.4% for numbness, 12.3% for paresthesia, 7.1% for lymphedema, 14.6% for AWS, 43.2% for loss of strength and 53.7% for limitations in ROM. For most impairments, the prevalences were well within the range of the prevalences found in the literature (Chapter 1). For paresthesia and loss of strength, the prevalences were slightly higher compared to the literature. This could probably be explained by the differences in assessment method. Since we saw that long-term morbidity was scarcely reported in literature (Chapter 1), we asked patients if the arm and shoulder complaints are currently present. By asking this question, we could report on the prevalence of arm and shoulder complaints, 2 to 7 years post-surgery (average 55.5 months). The long-term prevalences were 25.8% for pain, 12.0% for numbness, 6.4% for paresthesia, 5.6% for lymphedema, 8.0% for AWS, 26.2% for loss of strength and 19.5% for limitations in ROM. This indicates that even on the long-term, these complaints are still present in numerous patients.

In the available literature, there is often focused on a specific domain of dysfunctioning, namely on the level of impairments. To cover all domains of disability, we used the ICF framework. In this study, the secondary aim was to inventory activity limitations and participation restrictions in sentinel negative breast cancer patients. The activity limitations with the highest prevalence were putting on a bra (58.7%), getting dressed (57.9%), wearing a bra (50.8%), sleeping (50%), sports (48.4%) and driving

(35.7%). The prevalence of the participation restrictions was 55.5% for household and 39.7% for work. Based on these results, we can conclude that arm and shoulder complaints in patients who underwent SLNB can persist for many years and that they can influence the activity limitations and participation restrictions.

Although this was not the main focus of the survey, patients who filled in the questionnaire, were also interrogated about a possible treatment of arm and shoulder complaints. More than one third of all participants reported that they were treated by a physical therapist concerning their arm and shoulder complaints (38.1%). This seems little, since the incidences of arm and shoulder complaints were fairly high. It seems that the adequate treatment patients need, is often not provided.

Main findings and discussion of PART B concerning breast edema after breast-conserving surgery and radiotherapy

CHAPTER 3 - What is the incidence of breast edema in female breast cancer patients after BCS and radiotherapy and what are risk factors of breast edema?

Based on a systematic review of the literature, the overall incidence of breast edema following BCS and radiation therapy ranged between 0 and 90.4%. This range included all kinds of assessment methods and definitions of breast edema and therefore results in a very broad range. What follows is a synthesis of the incidences of breast edema per assessment method. Most studies used a physical examination to assess breast edema by observing and palpating the breast. Using this method, the incidence varied between 0% and 43.8%[30–46]. Using a questionnaire, the incidence ranged between 1% and 61.8%[47,48]. Objective assessment tools together with their breast edema incidences found in the literature were MRI (64.1%)[49], mammogram (up to 23.5%)[40,50], US (32-90.4%)[31,40,51] and US elastography (88.9%)[31].

Another purpose of this systematic review was to investigate possible risk factors for breast edema associated with BCS and radiation therapy. Following risk factors were identified: increasing irradiated breast volume[52], increasing boost volume[35,52], the use of a photon boost[34], increasing breast separation[34], a higher density of the breast tissue[50], a larger tumor[34], a higher specimen weight[52], postoperative infection[52], acute postoperative toxicity[52] and diabetes mellitus[35]. These factors were only investigated in a limited number of studies, so their prognostic value remains uncertain. For other parameters, like chemotherapy, hormonal therapy, ALND and BMI, no consensus could be found in the literature.

The selected studies used various methods and standards for assessing breast edema. The development of a standardized assessment tool for the detection of breast edema would be helpful. Hence, to fill this gap, the BrEQ was developed (Chapter 4).

Most studies showed that the incidence of breast edema diminishes over time. However, some patients still suffer from this complaint years after their treatment. The longitudinal course of breast edema is scarcely investigated in the literature. In chapter 5 of this thesis we wanted to elaborate on this.

CHAPTER 4 -What are the clinimetric properties of the Breast Edema Questionnaire?

The BrEQ was developed based on information collected through a systematic review of the literature and interviews with health care workers involved in cancer treatment and/or lymphology and breast edema patients. In the first part of the questionnaire, symptoms of breast edema were scored on a scale from 0 to 10: pain, heaviness, swelling, tensed skin, redness, pitting sign, enlarged skin pores and hardness. Taking into account the ICF, several activity limitations and participation restrictions were scored from 0 to 10 in part 2. Clinimetric properties of part 1 of the BrEQ were tested in a group of 55 breast cancer patients who underwent BCS and radiation therapy. US showed that 35 patients had breast edema and 20 patients did not. Content validity of the BrEQ was good. Regarding convergent validity, all breast symptoms correlated moderately with skin thickness. The total symptom score had a strong correlation with skin thickness. Concerning known-groups validity, patients with breast edema had a higher total symptom score. Furthermore, test-retest reliability ranged between moderate and strong. The internal consistency was good for all items and the total symptom score. Moreover, we identified that a score cut-off point of ≥ 8.5 discriminates between patients with breast edema and those without. Based on these findings, we can conclude that the BrEQ is the first Dutch questionnaire with evidence of validity and reliability for assessing breast edema in breast cancer patients following BCS and radiation therapy.

CHAPTER 5 - What is the prevalence and longitudinal course of breast edema after BCS and radiotherapy? What are prognostic factors for breast edema?

In a cohort of female breast cancer patients who underwent BCS 55.7% of patients had breast edema prior to radiotherapy. A peak in the prevalence of 63.9% was observed after termination of radiotherapy. Afterwards, prevalence declined to 53.6% and 50.9% at respectively 3 and 6 months post-radiotherapy. It is demonstrated that the presence of breast edema after BCS, but prior to

radiotherapy, is significantly associated with the presence of breast edema immediately after radiotherapy and 3 months after radiotherapy.

Few prognostic factors for the presence of breast edema were identified in our study. With regards to personal factors, only age is significantly associated with breast edema. This is not the case for BMI, menopausal state, surgery at the dominant side and pre-operative bra cup size. Regarding treatment-related parameters, it is seen that except for the time interval between BCS and radiotherapy and nodal irradiation, none of the investigated parameters were associated with the presence of breast edema, namely, chemotherapy, hormone therapy, Herceptin®, type of axillary surgery and type of boost. Patients in who the time interval between surgery and radiotherapy is shorter, have more breast edema. Furthermore, the absence of nodal irradiation is significantly associated with breast edema, which is rather unexpected. We would assume more breast edema in patients who underwent nodal irradiation, since it can damage the lymphatic system and therefore can compromise the lymphatic transport. When looking at the literature, results on prognostic factors are often conflicting. This can partly be explained by the lack of a standard definition and assessment tool for breast edema. Therefore, the prognostic value of these parameters must be interpreted with caution.

Strengths and limitations

Definition of a morbidity

After assessing the literature systematically for morbidities after breast cancer treatment, it was noticeable that for many impairments, a clear, uniform definition was lacking. Different standards and criteria were used to describe a morbidity, which makes comparison of data difficult. Let us highlight one example, namely loss of mobility. It is defined in many different ways: as the inability of raising the arm above the shoulder[8], a difference of more than 10° in ROM compared to baseline values[20,53–55] or compared to the unaffected arm[56,57], or a difference of more than 20° in ROM[9]. The same is true for breast edema. Breast edema in literature is often described as a combination of several breast symptoms, however there is no consensus in the literature about which symptoms. The lack of a uniform definition for breast edema is partly responsible for the broad incidence range. When developing the BrEQ, it was partly our purpose to give a thorough description of breast edema. For this reason, alongside of screening the literature, we interviewed patients and clinicians with expertise in breast cancer treatment and lymphology as well. The synthesis of symptoms we found, can possibly be a catalyst to develop a standard definition for breast edema. This could be helpful in clinical research and in clinical practice.

Measurements

When exploring the literature concerning arm and shoulder complaints after SLNB and breast edema after BCS and radiotherapy, it became clear that many different assessment methods are used, which makes comparison of data difficult. Unfortunately, some studies did not describe their assessment method. The differences in assessment methods and standards can partially explain the wide variation in prevalence or incidence data for both arm and shoulder complaints and breast edema (Chapter 1, 1bis and 3). For breast edema, we saw that a physical examination is often used to diagnose breast edema. According to Delay et al., stage 1 breast edema presents as thickening of the skin, without volume changes of the breast[58]. Therefore, stage 1 breast edema could easily be missed during a physical examination which leads to an underestimation. Often questionnaires were used to measure breast edema. The disadvantage of this method is that the questionnaires which are used in literature, often assess limited aspects of breast edema and are therefore not inclusive enough. For example, in the study of Young-Afat et al., breast edema was evaluated by means of the EORTC-QLQ BR23 question 51 (ie, "During the past week; was the area of your affected breast swollen?")[59]. However, literature shows that breast edema is more than swelling alone. We feel that important aspects of breast edema like pain, hardness, redness, pitting sign, tensed skin, heaviness and peau d'orange are often forgotten, but can be equally bothersome for patients. Therefore, it was our focus to develop an instrument which assesses numerous patient-reported outcome measures (PROMs) related to breast edema. The BrEQ is a reliable and valid Dutch questionnaire which is specific and inclusive enough to measure breast edema after breast cancer treatment.

In Chapter 2, data were collected via a self-administrated survey. Arm and shoulder complaints are self-reported and moreover data were collected retrospectively, making it vulnerable for recall bias. We are aware of the limitations of this design for data gathering, however, we strongly believe that this is an efficient way to collect information about the history of a large sample. The response rate is often a difficult aspect when using a survey. We have anticipated this difficulty by contacting the participants by phone before sending the survey. Using this methodology, we managed to achieve an excellent response rate of 83%.

To determine the clinimetric properties of the BrEQ, we used the skin thickness of the breast to correlate with the breast symptoms. Several parameters to measure breast edema with US are described in the literature. The reason why we chose skin thickness is versatile. First, skin thickness is a measure for cutaneous breast edema. According to Delay et al., stage 1 of breast edema is characterized by thickening of the skin. There are no volume changes –a measure associated with parenchymal breast edema- present yet in this stage[58]. Wratten et al. reported that cutaneous breast

edema can occur by itself, however breast edema is often a combination of both cutaneous and parenchymal breast edema[60]. This implicates that cutaneous breast edema is a more sensitive measure for breast edema compared to parenchymal breast edema. If we would have chosen parenchymal breast edema to correlate with the BrEQ, we would have missed numerous patients with breast edema. Second, skin thickness measured with US, is a quantitative measure for cutaneous breast edema on a continuous scale. It is measured as the distance between 2 thin echogenic lines with the hypoechoic dermis within[31,54,60,61]. There are other US parameters for cutaneous breast edema available, however they don't report on a continuous scale. Poor visibility of the deeper echogenic line is such a parameter. It is measured by scoring the visibility of the subcutaneous fat interface between 0 (not visible) and 4 (clearly visible)[54]. This involves the use of an ordinal scale and is subject to inter- and intraobserver variation. Presence of interstitial fluid accumulation on US is also a measure for breast edema which is scored as present or absent. The dichotomous character of this measure makes it less suitable to correlate with the BrEQ. Third, for another US measure, namely echogenicity of the subcutis, there is no consensus in the literature. In the study of Delay et al., 85% of patients who underwent BCS and radiation therapy had an increase in breast tissue density[58]. Rönkä et al. and Adriaenssens et al. also observed an increased echogenicity[31,54]. In contrary, Wratten described a decrease in echogenicity of the breast following BCS and radiation therapy. Echogenicity depends strongly on the probe that is used, tissue characteristics, location on the breast and follow-up time. Due to the lack of consensus in literature, we decided not to use this parameter to compare with the findings of the BrEQ. In conclusion, we used the skin thickness in order to determine whether a patient has breast edema.

Concerning the skin thickness, Rönkä et al. considered breast edema on US as a skin thickening over 2 mm. They included the additional US measurements as well to determine whether a patient has breast edema, namely increased echogenicity disturbance or poor visibility of the deeper echogenic line and interstitial fluid accumulation[54]. In our study, we only focused on the skin thickening. However, we noticed a difference in the average skin thickness between the 4 quadrants. Therefore, we decided to determine our own cut-off values and considered breast edema as a deviation of more than 2 standard deviations from the average skin thickness of each quadrant of the non-operated breast. This is because breast edema may occur in 1 quadrant, without affecting the rest of the breast. With this method we calculated cut-off values between 1.774 (SEQ) and 2.192 (SIQ), which is comparable with the 2 mm boundary. We feel that this method is more accurate. A disadvantage however is that each quadrant is calculated with other complex cut-off values. The differences in skin thickness among quadrants in healthy women's breasts, is seen among several studies. The skin is the thinnest in lateral

quadrants and superior quadrants[62–64]. This is in line with the skin thickness we found in our study in the unaffected breasts of breast cancer patients.

In the validity and reliability study (Chapter 4), patients completed the BrEQ after the US. In their clinical path, the US was preceded by a mammogram for all patients. This could possibly induce redness of the breast and therefore could interfere with the results of the BrEQ. This could possibly explain why the test-retest reliability of the item redness had the lowest ICC. To clarify this, the BrEQ was used in an additional sample of 10 patients, who were not involved in the clinical path and did therefore not receive a mammogram prior to the US and prior to completing the BrEQ. This was done in order to eliminate the interference of redness induced by the mammogram. Based on the results of these 10 additional patients, we can conclude that the test-retest reliability for the item redness is strong.

When using the BrEQ longitudinally, in the clinical path of breast cancer patients, it was noticeable that some of the symptoms, assessed with the BrEQ, are comparable with complaints following surgery and/or radiotherapy, which are in fact not related to breast edema. For example, if a patient with a painful erythema post-radiotherapy, scores 5 out of 10 for the items redness and pain, according to the BrEQ, she will have breast edema, although the actual problems is erythema. This could lead to an overestimation of breast edema. We are aware of the overlap between common complaints after BCS and radiotherapy and breast edema. However, we saw breast edema patients in who redness was still part of their complaints related to breast edema on the long term. From that point of view, we found it important to keep the item redness included in the BrEQ.

Patient enrolment

When looking for arm and shoulder morbidity after SLNB or for breast edema after BCS in the literature (Chapter 1, 1bis and 3), patients who are enrolled in the selected studies, underwent a more extensive breast cancer treatment than only SLNB or BCS. Breast cancer surgery is almost always a combination of breast surgery and axillary surgery and moreover, most patients receive adjuvant treatment as well. Thus, when determining the arm and shoulder complaints after SLNB, it is possible that the reported outcomes are related to other potential factors besides SLNB. In case of breast edema, it is possible that not only BCS and radiation therapy determine the development of breast edema. It is possible that other parameters such as hormone therapy, targeted therapy, type of boost etcetera could also affect the breast. It is probable that these differences contribute to the differences in incidence and prevalence data found in the literature.

Clinical implications

Chapter 1

However arm and shoulder morbidity is less common after SLNB compared to ALND, it is a substantial problem that can be associated with less QOL[53]. Since the survival rate in breast cancer patients is high, health problems related to breast cancer treatment and therewith the QOL are becoming more important. Therefore, information on arm and shoulder complaints in sentinel negative patients should be used to raise awareness. This could improve the prevention and/or rehabilitation strategies of these patients.

Chapter 1bis

Clinicians and therapists need to be aware that lymphedema remains a complication to consider when assessing patients who have had SLNB. As demonstrated by different studies, 6 to 12 months after SLNB is a critical follow-up period for assessing the presence of lymphedema in these patients. However, lymphedema can also occur more than 24 months post-surgery. For that reason, close follow-up short-term and long-term, is recommended. Not only therapists, but also patients themselves should be attentive to all possible complications that could arise after breast cancer treatment, including lymphedema. This could enhance the early detection of these complications. Therefore, patients should be carefully informed and instructed. Providing sufficient information, not only about lymphedema, but all possible complications after breast cancer treatment, is essential. This could be provided by handing out an information brochure or by using an online tool or application with complaints that warrant action by the patients. Additionally, health care workers should be more aware of the time course and take time to question these complaints during patient interviews.

Chapter 2

Despite the fact that impairments in body functions and activity limitations are very common after SLNB, few patients received adequate therapy. From this point of view, it is important to include early detection of morbidities and referral for appropriate treatment. Currently, many patients do not receive the adequate treatment they need. Moreover, they sometimes receive unnecessary treatment like for example preventive manual lymphatic drainage. It has been demonstrated in literature that in order to prevent arm and shoulder complaints, early physical rehabilitation is recommended. The reason why many patients do not receive adequate treatment could be due to the mismatch between the knowledge by the physical therapists and physicians. More carry-over of knowledge between disciplines is recommended.

Chapter 3

Based on the systematic review concerning breast edema after BCS and radiation therapy, it has become clear that breast edema, with an incidence up to 90.4% is not negligible. We recommend that all patients who receive this type of breast cancer treatment get informed about this possible complication. To aid in the detection of breast edema, the BrEQ was developed.

Chapter 4

The BrEQ is a reliable and valid Dutch questionnaire for assessing impairments in body functions and structures related to breast edema. The BrEQ may be used in clinical practice to diagnose breast edema in patients who underwent BCS and radiation therapy. With an early detection of breast edema in clinical practice, breast edema could be treated in an earlier stage, potentially leading to a better outcome. Due to its ease of use, the BrEQ could be used by any health care professional involved in breast cancer treatment. In this way, breast edema could be suspected more quickly, and the patient could be redirected to a specialist more rapidly to start the appropriate treatment. In addition, the BrEQ could be applied in clinical research.

Chapter 5

It is seen that breast edema is often already present after BCS, and prior to radiotherapy. Moreover, the BrEQ-score pre-radiotherapy is associated with the presence of breast edema at following time-points up to 6 months after finishing radiotherapy. This finding can be very valuable when informing breast cancer patients, certainly the ones who are at risk of developing breast edema. In order to detect breast edema earlier, a self-reporting system, like for instance a smartphone application, could be a welcome addition.

Breast edema follows a natural course in which we see a spontaneous decline in the months after radiotherapy. Moreover, breast edema is often subclinical and therefore not recognized and acknowledged by health care workers, because breast complaints are mild. For those reasons, not all patients need treatment for breast edema. The take home message should be to closely monitor those patients in who the BrEQ-score doesn't decline within 6 months after termination of radiotherapy and provide them with the appropriate therapy.

Recommendations for future research

Although this doctoral thesis offered valuable insights with respect to morbidity after breasts cancer treatment, several questions remain unanswered and warrant future research.

Long term prospective research is vital to gain better insight in the morbidity after breast cancer treatment. Especially, since we see that some patients still suffer from arm, shoulder or breast complaints more than 2 years after surgery. A longitudinal study could make it possible to detect when problems arise and therefore could be valuable to determine when appropriate treatment or sufficient information should be provided. Concerning the longitudinal course of breast edema, it has to be noted that the aforementioned results are preliminary. In our prospective cohort study, patients will be followed until 5 years post-radiotherapy, in order to understand the longitudinal course of breast edema over a longer period.

Predictors for morbidity after SLNB have not been explored elaborately. Further research among this matter is recommended so risk factors can be taken into account in clinical practice. For breast edema after BCS and radiotherapy, results on prognostic factors in literature are conflicting. Researchers should pay more attention to more homogeneous protocols. This will increase the comparability throughout different studies that claim to investigate the same morbidity.

An international consensus should be reached among clinicians and researchers concerning the definition of such morbidities. Furthermore, we need to consider similar methods of assessment and outcome parameters to allow pooling of data. It is however important to note that a single perfect gold standard for the assessment of some morbidities, does not exist and why it is a difficult topic to study. Therefore, in future research, efforts should be made in order to develop a valid and reliable assessment method or combine existing instrument that cover all aspects of a certain morbidity. In view of that, this could potentially serve as a gold standard. With the development of the BrEQ we aimed at doing this for breast edema.

The BrEQ is developed with the intention to cover all domains of disability according to the ICF framework. Future research in order to validate part 2 of the questionnaire (activity limitations and participation restrictions) needs to be done (data are available). The present study did not investigate clinical responsiveness of the BrEQ or cross-cultural validity. Further investigation of those properties is needed. This Dutch questionnaire is the first to specifically assess breast edema. A translation and further investigation of the degree to which the items on a translated or culturally adapted BrEQ adequately reflect the items on the original Dutch version is mandatory. Moreover, it is important to encourage researchers to consistently report whenever a modified version of the BrEQ is used. The initiative is already taken to translate and validate the BrEQ in English.

We recommend a morbidity screening after breast cancer treatment on regular basis. Self-assessment, using a checklist or smartphone application, or regular evaluation during follow-up are both feasible approaches. Based on the screening, an individual program could be added to a patient's cancer

treatment. Concerning the treatment of breast cancer morbidity, high quality studies are necessary to prove the effectiveness of passive mobilization, stretching, myofascial therapy and other therapy modalities as part of a multifactorial treatment[65]. In addition, the appropriate timing and content of the exercise programs need to be further investigated.

Conclusion

Compared with ALND, SLNB is a minimally invasive procedure. Arm and shoulder morbidities including loss of mobility, loss of strength, pain, scapula alata, AWS, lymphedema and sensory disorders are less common or absent after SLNB alone when compared to ALND. However, arm and shoulder morbidities in sentinel negative patients are not negligible and have an impact on the QOL. The same applies for breast edema after BCS and radiotherapy. We expect that BCS has better cosmetic results compared to the more invasive mastectomy. However, a significant number of patients get troubled by breast edema. Although we encourage the evolution in surgical techniques that took place over the years, it is important to draw the attention to the treatment-related morbidity. Understanding morbidity and its timeline is essential to organize adequate health care.

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SUMMARY / SAMENVATTING

Summary

Breast cancer is the most common cancer among women in the Western World. The last decades, breast cancer treatment has changed dramatically, and surgery has evolved to less invasive techniques. Currently, more patients are treated using the sentinel lymph node biopsy (SLNB) and/or breast-conserving surgery (BCS). These techniques are now widely used and have become standard procedures in breast cancer treatment. We can expect that the less invasive SLNB and BCS, compared to the axillary lymph node dissection (ALND) and mastectomy, result in considerable less arm, shoulder and breast morbidity. However, their negative aspects may be underestimated. There is still risk for treatment-related morbidity. Because of the evolution in the treatment of breast cancer, the survival rate has increased. Fortunately, it is fairly high when compared to other cancers. As a result, the treatment-related health problems and the quality of life (QOL) are becoming more important. The general aim of this PhD project is to gain insight in the morbidity after breast cancer treatment. This thesis is divided in 2 parts. In part A, arm and shoulder complaints after SLNB are identified and explored. Part B elaborates on breast edema after BCS and radiotherapy.

The incidence and time course of arm and shoulder complaints after SLNB was not yet clear. Therefore, in **chapter 1 and 1bis**, literature was explored addressing that topic. Shoulder and arm impairments among sentinel negative patients found in the literature were loss of mobility, loss of strength, pain, axillary web syndrome, scapula alata, sensory disorders and lymphedema. Within the first month after SLNB, the morbidities with the highest incidence were decreased abduction (range:40.8%-100%) and forward flexion of the shoulder (range:37%-100%), pain (range: 3.4%-56.6%) and numbness (range: 2%-64%). Morbidities with the highest incidence after 2 years were pain (range: 5.6%-51.1%), numbness (range: 5.1%-51.1%), loss of strength (range: 0%-57.7 %), decreased internal rotation (44.4%) and decreased abduction (range:0%-41.4%). The overall incidence of lymphedema of the arm in sentinel node negative breast cancer patients ranged from 0% to 63.4%. These wide ranges in incidence can be explained by the lack of a uniform definition of some of these complaints, and the lack of a standardized assessment method. This makes comparison of data very difficult. Based on these systematic reviews, it was seen that literature on long-term morbidity is scarce. Therefore, in **chapter 2** of this dissertation, long-term morbidity in sentinel negative patients was investigated. Furthermore, it was our aim to cover all health related QOL aspects. Therefore, we used the ICF-framework in order to describe the health condition of a patient in a bio-psychosocial context. The self-reported measures in chapter 2 focus on all the domains of the ICF. After a mean follow-up of 55.5 months (range 25-86 months) the prevalence of the self-reported arm and shoulder complaints was 25.8% for pain, 12.0% for numbness, 6.4% for paresthesias, 7.1% for lymphedema, 8.0% for axillary web syndrome, 26.2% for loss of strength and 19.5% for limitations in range of motion. The activity limitations with the highest prevalence are putting on a bra (58.7%), getting dressed (57.9%), wearing

a bra (50.8%), sleeping (50.0%), sports (48.4%) and driving (35.7%). This study demonstrates that a considerable number of patients still suffer from arm or shoulder complaints, months and even years after their cancer treatment, which has an impact on the activities of daily living.

Although many morbidities of breast cancer treatment are discussed in literature, it was our aim to draw attention to a neglected complaint, which is often underdiagnosed in clinical practice, namely breast edema. **Chapter 3** focused on the incidence and risk factors of breast edema after BCS and radiotherapy by means of a systematic review of the literature. A great variation in the incidence of breast edema (0%-90.4%) was observed. Furthermore, several possible risk factors for breast edema were identified, namely increasing irradiated breast volume, increasing boost volume, the use of a photon boost, increasing breast separation, a higher density of the breast tissue, a large tumor, a higher specimen weight, postoperative infection, acute postoperative toxicity and diabetes mellitus. However, results on these risk factors were often conflicting in literature and therefore, their prognostic value remains uncertain. Currently, there is no consensus on the definition of breast edema and on standardized assessment criteria. The development of a standardized assessment tool for the early detection of breast edema is warranted in order to provide an adequate treatment. For clinical practice, a valid and feasible questionnaire for the diagnosis of breast edema is a recommended addition to the current, expensive and time-consuming, investigations provided by for example ultrasound (US). Therefore, it was our aim in **chapter 4**, to develop a patient-reported questionnaire to assess breast edema and to determine its clinimetric properties. The Breast Edema Questionnaire (BrEQ) was developed based on information from literature, experts and breast edema patients. Content validity, construct validity, test-retest reliability, internal consistency and cut-off point were investigated in a group of breast cancer patients. Construct validity made up two parts; convergent and known-groups validity. Convergent validity was tested by correlating the BrEQ with skin thickness measured with US. In part 1 of the BrEQ, symptoms of breast edema were scored from 0 to 10: pain, heaviness, swelling, tensed skin, redness, pitting sign, enlarged skin pores and hardness. Taking into account the ICF, several activity limitations and participation restrictions were scored from 0 to 10 in part 2. Based on this study, we can conclude that part 1 of the BrEQ-Dutch version is a valid and reliable tool for assessing clinical indicators of breast edema. Based on the findings of chapter 3 and 4, some questions arose. Literature on the longitudinal course of breast edema in breast cancer patients is scarce. Moreover, the prognostic value of personal factors like BMI, cup size, menopausal state etcetera and medical factors such as type of axillary surgery, after-treatment and radiation parameters remained uncertain. Therefore, **chapter 5** investigated the longitudinal course of breast edema after BCS and radiotherapy and identified its prognostic factors. It is demonstrated that after BCS and prior to radiotherapy, 55.7% of patients had breast edema. After termination of radiotherapy, the

prevalence increased up to 63.9%. In the months to follow, the prevalence of breast edema declined to 53.6% after 3 months and 50.9% after 6 months post-radiotherapy. Few prognostic factors could be identified: younger age, the absence of nodal irradiation and shorter time interval between BCS and radiotherapy were associated with the presence of breast edema at some point in time.

In conclusion, this project contributed to the knowledge on the incidence, time course, assessment and prognostic factors of arm, shoulder and breast complaints after breast cancer treatment. Although SLNB and BCS are less invasive procedures compared to ALND and mastectomy, arm, shoulder and breast complaints cannot be neglected. A considerable number of patients get troubled by these morbidities, even on the long term. Although we encourage the evolution in surgical techniques that took place over the years, it is important to draw the attention to the treatment-related morbidity. A uniform definition and assessment method of some of these complaints remains an issue. Efforts have been made, for example with the development of the BrEQ to assess breast edema. However, the standardization of assessment methods for some of these morbidities should be further explored. Furthermore, long-term prospective research in order to gain better insight in the morbidity after breast cancer treatment has to be encouraged. Understanding morbidity and its timeline is essential to organize adequate health care.

Borstkanker is de meest voorkomende vorm van kanker bij vrouwen in de westerse wereld. De laatste decennia is de behandeling van borstkanker drastisch veranderd en is chirurgie geëvolueerd naar minder invasieve technieken. Momenteel worden meer patiënten behandeld met de sentinelprocedure (SLNB) en/of borstsparende chirurgie (BCS). Deze technieken worden nu op grote schaal gebruikt en zijn standaardprocedures geworden bij de behandeling van borstkanker. We kunnen verwachten dat de minder invasieve SLNB en BCS, vergeleken met de okseluitruiming (ALND) en mastectomie, resulteren in aanzienlijk minder arm-, schouder- en borstmorbiditeit. Hun negatieve aspecten kunnen echter worden onderschat. Er is nog steeds een risico op behandelingsgerelateerde morbiditeit. Vanwege de evolutie in de behandeling van borstkanker is de overlevingskans toegenomen. Gelukkig is deze vrij hoog, zeker in vergelijking met andere vormen van kanker. Als gevolg hiervan worden de behandelingsgerelateerde gezondheidsproblemen en de kwaliteit van leven steeds belangrijker. Het algemene doel van dit doctoraatsproject is om inzicht te krijgen in de morbiditeit na de behandeling van borstkanker. Dit proefschrift bestaat uit 2 delen. In deel A worden arm- en schouderklachten na SLNB geïdentificeerd en onderzocht. Deel B gaat dieper in op borstoedeem na BCS en radiotherapie.

De incidentie en het tijdsverloop van arm- en schouderklachten na SLNB was nog onduidelijk. Daarom werd in **hoofdstuk 1 en 1bis** de literatuur hieromtrent nagekeken. Arm- en schouderklachten bij sentinelnegatieve patiënten waren bewegingsbeperking van de schouder, krachtsverlies, pijn, axillair websyndroom, scapula alata, sensorische stoornissen en lymfoedeem. Binnen de eerste maand na SLNB waren de morbiditeiten met de hoogste incidentie verminderde abductie (range: 40,8% -100%) en anteflexie van de schouder (range: 37% -100%), pijn (range: 3,4% -56,6%) en hypo-esthesieën in de okselregio (range: 2% -64%). Morbiditeiten met de hoogste incidentie na 2 jaar waren pijn (range: 5,6%-51,1%), hypo-esthesieën (range: 5,1% -51,1%), krachtsverlies (range: 0% -57,7%), verminderde endorotatie (44,4%) en verminderde abductie (range: 0% -41,4%). De totale incidentie van lymfoedeem van de arm bij sentinelnegatieve patiënten met borstkanker varieerde van 0% tot 63,4%. Deze brede incidentiecijfers kunnen worden verklaard door het ontbreken van een uniforme definitie voor sommige van deze klachten en een gestandaardiseerde meetmethode. Dit maakt het vergelijken van gegevens erg moeilijk. Op basis van deze systematische reviews is gebleken dat literatuur over morbiditeit op lange termijn schaars is. Daarom werd in **hoofdstuk 2** van dit proefschrift de morbiditeit op lange termijn onderzocht bij sentinelnegatieve patiënten. Bovendien was het ons doel om alle gezondheidsgerelateerde aspecten van levenskwaliteit na te gaan. Daarom hebben we het ICF-kader gebruikt om de gezondheidstoestand van een patiënt in een bio-psychosociale context te beschrijven. De uitkomstmaten in hoofdstuk 2 zijn gericht op alle domeinen van het ICF. Na een gemiddelde follow-up van 55,5 maanden (range 25-86 maanden) was de prevalentie van arm- en schouderklachten 25,8%

voor pijn, 12,0% voor hypo-esthesieën, 6,4% voor paresthesieën, 7,1% voor lymfoedeem, 8,0% voor axillair websyndroom, 26,2% voor krachtverlies en 19,5% voor bewegingsbeperking. De activiteitsbeperkingen met de hoogste prevalentie zijn het aandoen van een beha (58,7%), aankleden (57,9%), het dragen van een beha (50,8%), slapen (50,0%), sporten (48,4%) en autorijden (35,7%). Deze studie toont aan dat een aanzienlijk aandeel patiënten nog steeds last heeft van arm- of schouderklachten, maanden en zelfs jaren na hun behandeling van kanker, wat een impact heeft op de activiteiten van het dagelijks leven.

Hoewel veel morbiditeiten na de behandeling van borstkanker in de literatuur worden besproken, was het ons doel om de aandacht te vestigen op een vergeten morbiditeit, die in de klinische praktijk vaak ondergediagnosticeerd is, namelijk borstoedeem. **Hoofdstuk 3** richtte zich op de incidentie en risicofactoren van borstoedeem na BCS en radiotherapie door middel van een systematisch literatuuronderzoek. Een grote variatie in de incidentie van borstoedeem (0% -90,4%) werd waargenomen. Verder werden verschillende mogelijke risicofactoren voor borstoedeem geïdentificeerd, namelijk toenemend bestraald borstvolume, toenemend boostvolume, het gebruik van een fotonboost, een grotere afstand tussen de punten waarbinnen de stralen het lichaam binnentreden, een hogere densiteit van het borstweefsel, een grote tumor, een hoger specimengewicht, postoperatieve infectie, acute postoperatieve toxiciteit en diabetes mellitus. Deze resultaten waren echter in de literatuur vaak tegenstrijdig en daarom blijft hun prognostische waarde onzeker. Momenteel bestaat er geen consensus over de definitie van borstoedeem en over een gestandaardiseerde meetmethode. De ontwikkeling van een gestandaardiseerd meetinstrument voor de vroege opsporing van borstoedeem is nodig om een adequate behandeling te kunnen instellen. Voor de klinische praktijk is een gebruiksvriendelijke vragenlijst voor de diagnose van borstoedeem een waardevolle aanvulling op de huidige, dure en tijdrovende onderzoeken zoals bijvoorbeeld echografie. Daarom was het ons doel in **hoofdstuk 4** om een vragenlijst te ontwikkelen om borstoedeem te beoordelen en de klinimetrische eigenschappen ervan te bepalen. De borstoedeemvragenlijs (BrEQ) is ontwikkeld op basis van informatie uit literatuur en van experten en patiënten met borstoedeem. Inhoudsvaliditeit, constructvaliditeit, test-hertestbetrouwbaarheid, interne consistentie en cut-off point werden onderzocht in een groep borstkankerpatiënten. Constructvaliditeit bestond uit twee delen; convergente en known-groups validiteit. De convergente validiteit werd getest door de BrEQ te correleren met de huiddikte gemeten met echografie. In deel 1 van de BrEQ werden de symptomen van borstoedeem gescoord van 0 tot 10: pijn, zwaartegevoel, zwelling, gespannen huid, roodheid, pitting, vergrote huidporiën en hardheid van de borst. Rekening houdend met het ICF, werden verschillende activiteitsbeperkingen en participatieproblemen gescoord van 0 tot 10 in deel 2. Op basis van deze studie kunnen we concluderen dat deel 1 van de

Nederlandstalige BrEQ een valide en betrouwbaar meetinstrument is voor het meten van borstoedeem. Op basis van de bevindingen in hoofdstuk 3 en 4 kwamen enkele vragen naar boven. Literatuur over het longitudinale verloop van borstoedeem bij patiënten met borstkanker is schaars. Bovendien blijft de prognostische waarde van persoonlijke factoren zoals BMI, cupmaat en menopauzale status en medische factoren zoals het type axillaire chirurgie, nabehandeling en bestralingsparameters onzeker. Daarom werd in **hoofdstuk 5** het longitudinale verloop van borstoedeem na BCS en radiotherapie onderzocht en de prognostische factoren geïdentificeerd. Er is aangetoond dat na de BCS en voor de radiotherapie, 55,7% van de patiënten borstoedeem had. Na het beëindigen van de radiotherapie, steeg de prevalentie naar 63,9%. In de daaropvolgende maanden, daalde de prevalentie naar 53,6% drie maanden post-radiotherapie en naar 50,9% zes maanden post-radiotherapie. Slechts enkele prognostische factoren konden worden geïdentificeerd: jongere leeftijd, de afwezigheid van bestraling van de lymfeknopen en een korter tijdsinterval tussen BCS en radiotherapie werden geassocieerd met de aanwezigheid van borstoedeem.

Dit doctoraatsproject heeft bijgedragen tot de kennis over de incidentie, het tijdsverloop, de evaluatie en de prognostische factoren van arm-, schouder- en borstklachten na de behandeling van borstkanker. Hoewel SLNB en BCS minder invasieve procedures zijn in vergelijking met ALND en mastectomie, kunnen arm-, schouder- en borstklachten niet worden verwaarloosd. Een aanzienlijk aandeel patiënten heeft last van deze morbiditeiten, zelfs op lange termijn. Hoewel we de evolutie in chirurgische technieken, die in de loop van de jaren heeft plaatsgevonden toejuichen, is het belangrijk om de aandacht te vestigen op de behandelingsgerelateerde morbiditeit. Een uniforme definitie en meetmethode voor sommige van deze klachten blijft een probleem. Er zijn inspanningen gedaan, bijvoorbeeld met de ontwikkeling van de BrEQ om borstoedeem te beoordelen. De standaardisatie van meetmethoden voor sommige van deze morbiditeiten moet echter verder worden onderzocht. Verder moet toekomstig prospectief onderzoek worden gestimuleerd om beter inzicht te krijgen in de morbiditeit na behandeling van borstkanker. Inzicht in morbiditeit en de tijdlijn is essentieel om adequate gezondheidszorg te organiseren.

LIST OF ABBREVIATIONS

A

Abd: abduction

Add: adduction

ALND: axillary lymph node dissection

ARM: axillary reverse mapping

AUC: area under the curve

AWS: axillary web syndrome

B

BCS: breast-conserving surgery

BMI: body mass index

BrEQ: breast edema questionnaire

C

CBO: Centraal BegeleidingsOrgaan

CI: confidence interval

CPT: complex physical therapy

CT: chemotherapy

E

EBRT: external beam radiation therapy

EORTC: European Organization for Research and Treatment of Cancer

F

FU: follow-up

G

GZA: GasthuisZusters Antwerpen

H

HFUS: high frequency ultrasound

HH: handheld

Hor: horizontal

HT: hormone therapy

I

ICC: intraclass correlation

ICF: International Classification of Functioning, Disability and Health

IEQ: inferior external quadrant

IIQ: inferior internal quadrant

IMRT: intensity-modulated radiotherapy

IORT: intraoperative radiation therapy

L

LENT/SOMA: Late effects in Normal Tissues-Subjective, Objective, Management and Analytic Score

Lymph-ICF-UL: Lymphedema Functioning, Disability and Health Questionnaire – Upper Limb

M

Mesh: Medical Subject Headings

MOCA: Medical Oncology Center Antwerp

Morb: morbidity

MRI: magnetic resonance imaging

MTC: mastectomy

N

NA: not applicable

P

Phys exam: physical examination

PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis

PROMs: patient-reported outcome measures

Q

QOL: quality of life

R

RCT: randomized controlled trial

ROC: receiving operating curve

ROM: range of motion

RT: radiotherapy

RTOG: Radiation Therapy Oncology Group

S

SD: standard deviation

SEQ: superior external quadrant

SIQ: superior internal quadrant

SLN: sentinel lymph node

SLNB: sentinel lymph node biopsy

SPSS: Statistical Package for the Social Sciences

U

US: ultrasound

UZA: Universitair Ziekenhuis Antwerpen

V

VAS: visual analogue scale

W

WBRT: whole-breast radiation therapy

CURRICULUM VITAE

General information

Name	Hanne Verbelen
Date of Birth	11 January 1988
Place of Birth	Dendermonde, Belgium

Education and diplomas

2013-present	PhD Eductation, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium.
2011-2012	Specific teacher education program CVO De Oranjerie, Leuven, Belgium
2009-2011	Master Rehabilitation Sciences and Physiotherapy, Internal Diseases *Magna Cum Laude* Vrije Universiteit Brussel, Belgium
2006-2009	Bachelor Rehabilitation Sciences and Physiotherapy Vrije Universiteit Brussel, Belgium
2000-2006	Secondary School – Maths Sciences Vrij Katholiek Onderwijs, Opwijk, Belgium

Clinical experience

2011-2012	Physiotherapist (self-employed) in a private practice specialized in lymphology, Merchtem
2012	Physiotherapist in Rehabilitation Center Buggenhout
2011	Physiotherapist in the University Hospital of Brussels

Teaching experience

2014-present	Interuniversity course for edema therapy Oedema
2012-present	Bachelor and Master in Rehabilitation Sciences and Physiotherapy Department of Rehabilitation Sciences and Physiotherapy, University of Antwerp

List of publications

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The Breast Edema Questionnaire (BrEQ): a new tool for the diagnostic assessment and follow-up of patients suffering from breast edema
Conference: 27th ISL World Congress of Lymphology, 23-29 September, Buenos Aires, Argentina: *Oral presentation*

Verbelen H, van Breda E, Van Soom T, Tjalma W, Gebruers N
The longitudinal course of breast edema in breast cancer patients following breast-conserving surgery and radiotherapy
Conference: 27th ISL World Congress of Lymphology, 23-29 September, Buenos Aires, Argentina: *Oral presentation*

Verbelen H, van Breda E, Van Soom T, Tjalma W, Gebruers N.
Validity and reliability of the breast-edema-questionnaire (BrEQ) for the assessment and follow-up of breast edema
Conference: 8th International Lymphedema Framework Conference, 6-9 June 2018, Rotterdam, The Netherlands: *Oral presentation*

Verbelen H, Moeyersoms E, Van Dooren N, van Breda E, Tjalma W, Gebruers N.
Development of a questionnaire for breast edema: BreQ questionnaire
Conference: 26th World congress of Lymphology, 25-29 September 2017, Barcelona, Spain: *Oral presentation*

Verbelen H, Moeyersoms E, Van Dooren N, van Breda E, Tjalma W, Gebruers N.
Validity and reliability of a breast edema questionnaire: BreQ questionnaire
Conference: 26th World congress of Lymphology, 25-29 September 2017, Barcelona, Spain: *Poster presentation*

Verbelen H, Tjalma W, Gebruers N.
Lymphedema in sentinel node negative breast cancer patients: a long term view
Conference: 42nd Congress of the European Society of Lymphology, 13-14 May, 2016, Mulhouse, France: *Poster presentation*

Verbelen H, Tjalma W, Gebruers N.
Arm and shoulder complaints in sentinel node negative breast cancer patients: a long term view
Conference: 9th World Congress of the International Society of Physical and Rehabilitation Medicine, 19-23 June 2015, Berlin, Germany: *Oral presentation*

Abstracts in abstract books of national meetings

Verbelen H, Gebruers N, Tjalma W.
The influence of arm and shoulder complaints on activities of daily life in sentinel node negative breast cancer patients
Conference: 5th International Congress of Breast Disease Centers. 6th of February 2015, Antwerp, Belgium: *Poster Presentation*

Invited oral presentations national

Verbelen H. "Borstoedeem, behandeling noodzakelijk?" Oedemasymposium: Lymfoedeem out of the box, 17th of March, 2018, Ghent, Belgium

Verbelen H. "Borstkanker en armmorbiditeit" Oedemasymposium: Lymfologie en Oncologie, 1st of March, 2014, Leuven, Belgium

Other Scientific Contributions

Peer review contribution to Dove Medical Press

Peer review contribution to JSCC

Professional memberships

Belymph (Belgian association of the International Lymphedema Framework), member and secretary of the scientific committee

Oedema, board member

Vakgroep REVAKI-MOVANT, member

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