Breast cancer related lymphedema

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Breast Cancer Related Lymphedema

Studies on prevalence, effect on quality of life, and
microsurgical treatment options

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For Brigitte

“Don’t be dismayed at good-byes.

A farewell is necessary before you can meet again.

And meeting again, after moments or lifetimes,

Is certain for those who are friends.”

- Richard Bach

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List of abbreviations

ADL	activity of daily living
ALND	axillary lymph node dissection
ARM	axillary reverse mapping
BCRL	breast cancer related lymphedema
BIS	bioimpedance spectroscopy
BMI	body mass index
BR	breast reconstruction
CDT	complex decongestive therapy
CG	compression garment
ChTx	chemotherapy
DIEP-flap	deep inferior epigastric perforator flap
EORTC	European organization of research and treatment for cancer
HRQOL	health related quality of life
Htx	hormone therapy
IFP	inguinal fat pad
IPC	intermittent pneumatic compression
LDM-flap	latissimus dorsi myocutaneous flap
LN	lymph nodes
LYMPHA	lymphatic microsurgical preventative healing approach
LVA	lymphaticovenous anastomoses
MLD	manual lymphatic drainage
MLVI	microsurgical lymphaticovenous implantation
msTRAM-flap	muscle sparing tranverse rectus abdominus myocutaneous flap
QOL	quality of life
Rtx	radiation therapy
SLNB	sentinel lymph node biopsy
SOAC	sum of arm circumference
TDC	tissue dielectric constant
Ue	skin extensibility
Uv	delayed distension
Uf	final deformation
Ur	immediate retraction
Ua	final retraction
WLSE	wide local scar excision

Chapter 1

General introduction

General introduction

Approximately one in eight women in the Netherlands will develop breast cancer during her lifetime.¹ Fortunately, due to the increased awareness among women about the early signs of breast cancer, implementation of population based screening programs and advancements in treatment options, a large proportion of these women will survive the initial treatment phase. The fact that more women are successfully being treated for breast cancer has caused a shift of attention towards the period after active cancer treatment, also known as the period of survivorship.² Survivorship refers to the period following active cancer therapy, the period in which the late effects of treatment occur.³ In saying this, the management of the late effects of breast cancer treatment is imperative for maintaining an acceptable long-term quality of life. Of the late effects of breast cancer treatment, lymphedema is one of the most underestimated and debilitating morbidities.⁴⁻⁶ Between 6% and 43% of breast cancer survivors develop breast cancer related lymphedema (BCRL).^{7,8} The large variability in the reported figures of BCRL is explained by differences in the definitions used and by differences in treatment and risk factors between populations. Adjuvant treatment for breast cancer, such as axillary surgery, radiation and chemotherapy can cause damage to the lymphatic system of the upper-limb resulting in lymph fluid stasis and an increased limb volume.^{9,10} This limb swelling may present with symptoms of heaviness, tightness and pain sensations. Furthermore, loss of normal upper-limb function and range of motion can be experienced. The negative psychological effects brought on by the impairments of activities of daily life and reduced limb aesthetics constitute an additional burden.^{5,11,12} An overview of the important aspects of BCRL such as the etiology, pathophysiology, diagnostic techniques and treatment options will be given in this chapter, as well as the aims of this thesis, following from this overview. The onset of BCRL can occur any time after primary cancer treatment, but in most cases develops in the first four years after treatment.¹³ The following risk factors are associated with the development of BCRL: the extent of breast/axillary surgery, adjuvant radiation, adjuvant chemotherapy, the

number of positive lymph nodes, treatment on the side of the dominant limb, older age and obesity.¹⁴⁻¹⁶

Pathophysiology

Basic knowledge on the working mechanism of the lymphatic system is necessary in order to understand the pathophysiology of BCRL. The lymphatics of the upper extremity are divided into superficial and deep vessels, which form two communicating systems. The superficial (epifascial) vessels transport lymph fluid from the skin, subcutis and structures therein. Whereas the deep system (subfascial) transports lymph fluid from muscles, fascia, nerves, joints, ligaments and bones.¹⁷ Moreover, the axillary lymph nodes receive lymph fluid from the upper extremity, supra-umbilical anterolateral body wall and part of the breast.¹⁷ Lymph fluid transport is determined by interstitial pressure in extra cellular spaces, which in turn is influenced by three important factors: by the contraction of subjacent skeletal muscles, arterial pulsation near lymphatic vessels and by contraction of smooth muscle cells in the lymphatic wall stimulated by the sympathetic nervous system.¹⁸ Lymph vessels, like other vascular structures, are trilaminar and consist of¹⁹:

- An internal membrane, containing endothelial cells;
- A medial membrane, containing varying proportions of smooth muscle cells;
- An outer membrane, extra cellular matrix containing fine bundles of collagen and elastin fibers.

The limb swelling that is seen in BCRL is the result of a combination of an accumulation of protein rich fluid in the interstitial tissues, tissue fibrosis, fat deposition and thickening of the skin.¹⁷ Its chronic and progressive nature makes BCRL an intricate disease. The International Society of Lymphology (ISL) has developed a widely used and accepted staging system based on clinical assessment. The ISL staging system consists of three stages each representing a phase in disease progression (Table 1).²⁰

Table 1: International Society of Lymphology staging system

0	Subclinical stage; swelling not evident despite impaired lymph transport
I	Early accumulation of fluid which subsides with limb elevation, pitting may occur
II a	Limb elevation rarely reduces tissue swelling, pitting is manifest
II b	Excess fat and fibrosis supervene, the limb may or may not pit
III	Lymphostatic elephantiasis

Damage to the local (breast/axilla) lymphatic system causes obstruction of normal lymph flow, which leads to lymph stasis and an increase of pressure in the collecting lymphatics.²¹ The exact histopathological changes that occur as a result of the lymphatic outflow impairment are yet to be fully elucidated. However, the few studies available focusing on the ultra-structural aspects of edema, have given us some insight.^{18, 21-26} As a reaction to tissue injury an inflammatory process is triggered, activating lymphocytes and leukocytes that release cytokines. Degeneration of media smooth muscle cells and the proliferation of collagen fibers further impair lymph fluid drainage.^{21, 24-26} The excessive deposition of extracellular matrix, especially collagens, is the complex tissue response that is called fibrosis.²² In case of inadequate disease management, lymphedema progresses: arm-swelling transforming from a predominantly fluid encompassing entity to fibrosis and fat.²⁴ BCRL in its late chronic phase is irreversible and accompanied by more symptoms and physical impairments. The time-line in which disease progression takes place, remains unknown.

Measurement techniques

Part of the wide range in the reported incidence and prevalence rates of lymphedema is due to the lack of a uniform measurement protocol and criteria for diagnosis.²⁷⁻⁴⁴ Moreover, the different measurement techniques have considerable intra- and inter-rater variability. The affected limb is usually

compared to the non-affected side, irrespective of the type of measurement technique. Measurement techniques most commonly used are the following:

Water displacement technique³¹: this is considered the current “golden standard”, in which limb volume is assessed using an inverse water displacement volumeter. The criteria for the diagnosis of BCRL using this technique is a difference in limb volume of 200ml or more between the affected and non-affected contralateral limb.

Circumferential limb measurement^{27, 28}: here a tape measure is used to assess limb girth at predetermined intervals along the limb. A difference between the affected and non-affected contralateral arm of 2cm or more at any measured point is considered clinically significant limb swelling.

Optoelectronic perometry³⁵⁻³⁷: here infrared laser technology is used to assess limb volume. The contralateral unaffected limb as a comparison is also used for lymphedema diagnosis, a volume difference of 10% or 200ml or more.

However, the above-mentioned techniques used for assessing limb volume represent an indirect measurement of BCRL. These techniques do not take tissue composition into account, and thus make no distinction between extra- and intracellular fluid when measuring limb volume. Furthermore, volume assessment does not give an indication of the severity of the BCRL.

Bioimpedance spectroscopy (BIS) is an alternative method for assessing BCRL that uses skin electrodes to pass a small alternating current through a limb and measures the impedance to the flow of this current.^{36, 38, 39} The fluids in the body conduct electrical current and as fluid volume increases, impedance to current flow decreases. BIS therefore gives a measure that correlates with the amount of extracellular fluid.

Disease specific questionnaires can be used to diagnose BCRL and also measure the consequences of the symptoms on the quality of life.^{27, 43, 44} Patient reported signs and symptoms are often the first indication of clinically relevant lymphedema.²⁷ The symptoms women with BCRL may present with include: tingling, pain heaviness, reports of poor clothing fit, or even as minimal as the limb “feels different”.^{27,43} Examples of disease specific questionnaires are the Wesley Clinic Lymphedema Scale (WCLS)⁴⁵, the Freiburg Life Quality Assessment (FLQA-1)⁴⁶, the Upper Limb Lymphedema 27 (ULL-27)⁴⁷ and the Lymphedema, Functioning, Disability and Health (Lymph-ICF)⁴⁸.

Treatment

The current standard of treatment for BCRL is a combination of different methods of conservative therapy, also known as *complex decongestive therapy* (CDT)⁴⁹ CDT incorporates two stages of treatment. The first treatment phase entails: skincare, exercises aimed at improvement of mobility/range of motion in the shoulder, elbow or wrist joints, compression therapy through multi-layered bandaging and *manual lymphatic drainage* (MLD). Moreover, MLD is the manual stretching and pressure application to the skin in slow, rhythmic and circular motions to stimulate the activity in the lymphatic vessels to increase lymphatic fluid drainage. In the second treatment phase, CDT is aimed at maintenance of the achieved limb volume/ circumference reduction through compression therapy in the form of *therapeutic elastic stockings* for the arm. Skincare, mobility exercises and MLD is continued in this phase if needed. In addition to CDT, other methods can be applied, including *intermittent pneumatic compression* (IPC) and *kinesio taping*.

IPC is a device with pneumatic cuffs connected to a pump that mimic the naturally occurring muscle pump effect of muscles contracting around peripheral lymphatics.⁴⁹

Kinesio taping is a method used mostly by athletes, is used in some instances for BCRL with the hypothesis that it can help improve lymphatics and reroute lymph in superficial lymphatic vessels.^{50, 51}

These two additional therapeutic methods are applied dependent on the preference of the lymph therapist, as the literature contains no evidence on the most effective combination of treatments.

Conservative therapy is initially aimed at alleviating symptoms without curative intent, which for most patients means lifelong treatment. Dutch breast cancer treatment guidelines suggest a three-month treatment period with compression stockings in case of a 5-10% limb volume increase.⁴⁵ Adding compression therapy to complete decongestive therapy could induce significant limb volume reduction. When maximum limb volume reduction is achieved compression stockings should be worn for the rest of the patient's life. A systematic review evaluating the effects of conservative and dietary interventions for BCRL demonstrated compression garments or compression bandaging to reduce limb lymphedema volume, with a reported percentage reduction ranging from 17%

to 60 %.⁴⁸ Furthermore, a statistically significant beneficial effect was found for the addition of MLD to compression therapy for reducing upper extremity lymphedema volume.

Surgical intervention to treat BCRL in the form of lymphatic microsurgery is mentioned in Dutch lymphedema guidelines, although the exact role of such interventions is not made clear as the current evidence base for the effectiveness of Lymphatic microsurgery as treatment for BCRL is ambiguous.⁵³⁻⁶¹ More importantly, no prospective randomized trials have been published as of yet.

Aim and outline of this thesis

The main purpose of the studies described in this thesis is to gain more insight on BCRL in order to substantiate the need for improvement of its management amongst breast cancer survivors.

Firstly, in **Chapter 2** we investigated the prevalence of BCRL in a group of breast cancer survivors 5 years after initial treatment, using three different measuring methods. Knowledge on how lack of uniform criteria for the measurement of BCRL may affect its prevalence is essential for interpreting current literature on BCRL.

Next, in **Chapter 3** the quality of life of women with BCRL was assessed in the same cohort of breast cancer survivors. All these women were treated in the sentinel lymph node biopsy era.

In **Chapter 4** the biomechanical properties of the skin of the arm of women with BCRL were compared with the properties of the skin of their healthy arm. This was done to determine how BCRL affects the elasticity, visco-elasticity and level of hydration of the skin.

The role of breast reconstruction as a possible risk factor or protective factor for the development of BCRL in women after mastectomy is explored in **Chapter 5**.

In **Chapter 6** we assessed if the improvement in quality of life, which is usually seen in breast cancer survivors after reconstructive breast surgery, was influenced by the presence of BCRL.

Chapter 7 gives an overview of studies on the effectiveness of different microsurgical treatment options for BCRL.

In **Chapter 8** an overview of the current changes taking place in axillary staging and treatment of breast cancer patients is given with the aim to identify patients with a high risk of developing morbidity in the arm and/or shoulder.

Chapter 9 describes a strategy to improve early detection and the treatment of BCRL.

Chapter 10 concludes this thesis with a general discussion, including conclusions and approvals for clinical practice and future research.

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Chapter 2

The prevalence of lymphedema minimally five years after breast cancer treatment

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Adapted from: Eur J Surg Oncol. 2011 Dec; 37(12): 1059-6

Abstract

Aim: The lack of consistency in the definition of breast cancer related lymphedema (BCRL) and of uniform measurement criteria contributes to the wide prevalence range found in current literature. This report aims to describe the long-term prevalence of BCRL and secondly, to compare the long-term prevalence of BCRL when assessed by two objective measures and one subjective measure.

Methods: The upper limbs of 145 post-surgical breast cancer patients were evaluated for the presence of lymphedema using the water displacement method. Two circumference methods and patient perceived swelling were applied secondarily for comparison. Limb measurements were performed once, more than five years after surgery.

Results: The long-term prevalence of BCRL using water displacement was 8%. Prevalence varied when the sum of arm circumference (SOAC), the arm circumference and the self-report methods were used: 16, 31 and 17% [$P < 0.001$], respectively. Of the women identified with BCRL using the water displacement technique, 82% were detected with the SOAC method, 82% with the arm circumference method and 91% by self-report. Using water displacement as the gold standard the methods with the highest specificities were the SOAC (90%) and self-report method (89%), arm circumference resulted in a low specificity of 73%.

Conclusion: The prevalence of BCRL more than five years after surgical treatment differs depending on the measuring method used. Our data underlines the necessity for consensus on the diagnostic criteria for BCRL.

Introduction

Early breast cancer detection and concomitant advancements in treatment options have not only resulted in an increase in breast cancer survival rates, but also in that of disease related morbidities with upper limb lymphedema being one of the most debilitating. Swelling of the oedematous limb is brought on by obstruction of normal lymph flow, with known treatment risk factors which cause damage to the lymph vessels being axillary dissection, mastectomy and adjuvant radiation therapy.^{1–7}

Breast cancer related lymphedema (BCRL) could present with pain, loss of sensibility, strength and mobility of the affected limb, reducing activity and causing physical and psychological impairments.^{8–12} Lack of consistency in the definition of BCRL and a lack of uniform measurement criteria have contributed to the wide prevalence range found in current literature.^{1–4} This is illustrated in a review on the late morbidity after treatment of breast cancer, in which the prevalence was reported to range between 6 and 43%⁵ Moreover, few studies have described the long-term prevalence of BCRL^{13–16} and none, to our knowledge, have done so with the use of different measuring methods within the same patient group.

Therefore, the current study was conducted primarily with the aim of assessing the long-term prevalence of BCRL in women more than five years after breast cancer treatment. We also sought to assess the source of variation in BCRL prevalence by comparing prevalence outcomes of four different measuring methods (water displacement method, two arm circumference methods and self-reported limb swelling).

Methods

Patients

A database of patients treated at the Maastricht University Medical Centre (MUMC+) between January 2001 and December 2003 was queried to identify women operated for breast cancer five or more years prior to search (n=386). Exclusion criteria were death (n=96), migration (n=8) and loco-regional recurrence (n=34). 248 eligible women were asked to take part in our study. 93 patients withheld written consent and ten patients ultimately did not take part

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due to personal circumstances or illness, resulting in a study population of 145 women. The hospital's medical ethics committee approved the study and the consent form.

Lymphedema Measurements

Four methods were used to assess the long-term prevalence of BCRL: the water displacement method, two arm circumference methods and the self-report method. The water displacement method was regarded as the gold standard. In order to evaluate the type of measurement as a probable source of variance, we compared the prevalence of the two circumference methods and the self-report method with the gold standard. All limb measurements were performed at one moment in time, five or more years after breast cancer surgery. For each method the breast cancer treated side was compared to the untreated side. One researcher (JS) performed all limb measurements.

1. Water displacement method

For the assessment of upper-limb volume a home built volumeter was used according to J. Lette.¹⁷ This method carries a high reproducibility.¹⁸ A line was drawn at 80% of the arm length, measured from the tip of the third digit to the tip of the acromion. Subjects were instructed to lower the arm straight and slowly into the volumeter and to stop and keep it still when the 80%-line reached the water surface. Both upper-limbs were measured twice. The overflowing water was collected in a bucket and weighed on a calibrated scale. (PR balance, Mettler-Toledo, Switzerland). The conversion value of 1 kg = 1000 mL was applied. Lymphedema was defined as a limb volume difference greater than 200 mL between the treated and untreated side.

2. Circumference method

The arm circumference was measured at ten sites on both limbs using a tape measure. The locations measured were: mid-metacarpal, the wrist and at 20, 15, 10 and 5 cm below and above the elbow fold. The sum of these circumferences was calculated per limb. Lymphedema was defined as a difference of the sum of arm circumferences (SOAC) of more than 5 cm between the treated and untreated side or as a difference of arm circumference of more than 2 cm between the treated and untreated side at any of the 10 measured locations on the limb.¹⁹

3. Self-reported lymphedema

Patients were asked to indicate the presence of (refractory) swelling during a standardized interview by answering the following question with a “yes” or “no”: Have you experienced swelling of the upper-limb on the breast cancer treated side in the past year? Self-assessment was described as negative or positive for BCRL.

Statistical Analysis

Patient and clinical characteristics were described using descriptive statistics. Continuous variables were evaluated for normal distribution and expressed by providing the median and range. χ^2 was used to test the relationship between categorical variables. A P-value <0.05 was considered statistically significant. The sensitivity and specificity were measured for the SOAC, the circumference and the self-report methods, using the water displacement method as a reference. All data-analysis was conducted using SPSS for Windows 17.0 (SPSS Inc. Chicago, Illinois).

Results

Patient Characteristics

The 145 women included in this study were evaluated for BCRL after a median period [range] of 6.2 years since time of surgery [5.0 – 7.8]. At time of surgery, subjects' age ranged from 33-86 years with a median of 55.0 years. The median [range] body mass index (BMI), calculated using the patients weight and height at time of surgery, was 25.1 [17.1- 48.9]; a total of 28 patients were considered obese (BMI $\geq$ 30) at that time. The majority (n=123) of the women underwent breast-conserving surgery; 22 women underwent ablative breast surgery. Of all patients, 69 had an axillary lymph node dissection (ALND) and 76 had a sentinel lymph node biopsy (SLNB). Radiation treatment either to the breast or chest wall and supraclavicular was given to 125 women.

Prevalence of lymphedema

Lymphedema measurements

Using the gold standard, 11/145 women met the criteria of the water displacement method for the diagnosis of lymphedema. When patients were evaluated for lymphedema using the SOAC, the circumference and patient self-report methods, prevalence differed: 23/145, 45/145 and 25/145, respectively. The difference between the four prevalence rates was significant [$P < 0.001$]. Of the 28 obese women at baseline, 18 developed lymphedema according to at least one of the four measuring methods [$P = 0.008$]. As for the 69 women who underwent ALND, almost half ($n = 37$) had either self-reported lymphedema and/or objectified limb swelling. In contrast, SLNB ($n = 24$) resulted in fewer patients with lymphedema [$P = 0.007$].

Sensitivity and specificity of lymphedema measurements

Table 1 presents the sensitivity and specificity of the SOAC, the circumference and self-report methods using the water displacement method as reference measure. The self-report method displayed the highest sensitivity of the three. Comparatively, the circumference and the SOAC methods each identified fewer women presenting with lymphedema according to the water displacement method. The highest specificity was however measured by the SOAC method. Moreover, there were several cases in which patients had measured lymphedema according to criteria of the SOAC ($n = 14$) or the circumference method ($n = 36$) without having a difference in limb volume greater than 200 mL and vice versa ($n = 3$).

Table 1. The sensitivity and specificity

Measurement methods	Sensitivity, % (95% CI)	Specificity, % (95% CI)
<i>Circumference</i>	82 (0.48-0.97)	73 (0.65-0.80)
SOAC	82 (0.48-0.97)	90 (0.83-0.94)
<i>Self-report</i>	91 (0.57-0.99)	89 (0.82-0.93)

95% CI; 95% confidence interval, SOAC; sum of arm circumference

Patient perception and measured lymphedema

We were also interested in the prevalence of women with subjective lymphedema. In order to get a wider scope on the problem at hand, we combined self-reported complaints of swelling with objective (measured) swelling. Table 2 presents patients categorized as follows: no BCRL (no subjective complaints and no measured swelling), asymptomatic BCRL (no subjective complaints but measured swelling), symptomatic non-BCRL (subjective complaints but no measured swelling) and symptomatic BCRL (subjective complaints and measured swelling). Once again, the prevalence rates varied depending on the diagnostic method used. Interestingly, there were women with the perception of arm swelling but without clinical signs of lymphedema according to all three methods. However, there were also women with clinical signs of lymphedema who did not have self-perceived arm swelling.

Table 2. Patient's perception and measured lymphedema

BCRL category	Water displacement	SOAC	Circumference
No BCRL, %	82	76	63
<i>Asymptomatic BCRL, %</i>	1	6	20
<i>Symptomatic non-BCRL, %</i>	10	8	6
<i>Symptomatic BCRL, %</i>	7	10	11

BCRL; breast cancer related lymphedema, SOAC; sum of arm circumference

Discussion

In the current study we assessed the prevalence of BCRL at a median time of 6.2 years after breast cancer surgery. To our knowledge this is the first study that used more than one measuring method for describing the long-term prevalence of BCRL. A wide point prevalence range of 8-31% was found in our data, with the circumference method at prevalence rate of 31% being the biggest outlier. In contrast, the water displacement, the SOAC and self-report methods yielded point prevalence estimates closer in range, 8-17%. Of the scant long-term data that is available, Sagen et al reported a BCRL prevalence of 13% measured with the water displacement method five years after breast cancer treatment.²⁰

Lymphedema: more than just limb swelling?

Lymphedema constitutes more than just limb volume increase; symptoms that patients experience as result of that volume change should therefore also be identified. Creating BCRL sub-categories, depicting subjective complaints against the different objective measurements, resulted in a better insight on this topic.^{21, 22} Symptomatic BCRL was identified in 7% of the patients using the water displacement method; this was 10% for the arm circumference method and also 10% for the SOAC method. At a follow-up time of five years after breast cancer treatment McLaughlin et al reported a prevalence of 5% for symptomatic BCRL measured with the circumference method.¹⁴ We assessed a point prevalence double that after a median time of 6.2 years, which is likely explained by the fact that our cohort included more women who underwent axillary lymph node dissection (47 vs. 36%). Not all patients with self-reported complaints of BCRL had clinical measurable signs of limb swelling (symptomatic non-BCRL). The discordance seen between patient perceptions and measured swelling is consistent with the results reported in other studies.^{14, 23} A reason why not all of the subjective BCRL complaints might have shown a measured increase of limb volume or circumference could be due to the timing of the study. Many patients reported to have an increase in complaints after more than average exercise and with warm weather. The measurements in this study gave an impression of a patient's lymphedema status at one specific moment in time, and thus, cannot exclude the existence of refractory limb swelling. Furthermore, symptomatic non-BCRL could also be explained by sensory changes in the treated limb due to neurological damage caused by axillary surgery or radiation treatment. Vice versa, some women with measurable volume and or circumference difference had no subjective complaints of pain or swelling (asymptomatic BCRL). An important question is whether this BCRL category is clinically relevant; in other words if these patients will eventually go on to develop symptomatic BCRL.

Method selection: a matter for consideration

Volumetry is the most reliable method for the assessment of lymphedema, with the classic water and the novel optoelectronic (perometer) volumeter forming the two methods of choice. Both methods have comparable reliability²⁴⁻²⁷; therefore, our selection of the water displacement method was based on cost-efficiency, the most applied method and readily available device. Even though we have used the water displacement method as our gold standard, we believe

it to have its shortcomings in cases where minor swelling is accompanied by muscle atrophy. This can develop over time when normal use of the affected limb is avoided due to lymphedema related symptoms, such as pain and heaviness. Minor volume increase in the form of extracellular lymph accumulation can be compensated by a volume decrease in muscle mass, in which case lymphedema will go undetected. Bioelectrical impedance spectroscopy (BIS) on the other hand can accurately differentiate extracellular fluid from other tissues and thus solely assess lymph volume by measuring the impedance of a spectrum of low frequency electric current passed through a body region.²⁸⁻³⁰ It could therefore be argued as to why BIS was not used in the current study as the gold standard for BCRL assessment instead of the water displacement method. Hayes et al described the short-term prevalence at six months after breast cancer treatment using the BIS method as the gold standard and the sum of arm circumference and the patient self-report method for comparison.³¹ Importantly, in the early stages of lymphedema swelling is refractory and predominately constitutes of extracellular lymph fluid, thereby making BIS a suitable tool for diagnosis.³²⁻³⁵ However, as disease progression ensues, limb swelling becomes a more permanent entity with the occurrence of fibrosis and fat deposition.³⁶ As the aim of our study was to assess the long-term prevalence of BCRL five or more years after breast cancer treatment, some lymphedema cases might have already progressed into the chronic phase during this period. Thus, the use of BIS instead of the water displacement method as the gold standard for the identification of BCRL in this study's setting is not justified. For lack of a more reliable assessment method we have accepted the possible limitations of the water displacement method.

Study limitation

A weakness of this study is the fact that it was performed without preoperative or direct postoperative baseline measurements; these could have produced a more accurate identification of changes in limb volume and circumference. Instead, the contra-lateral upper-extremity was used as comparison to determine the presence of lymphedema. Differences in circumference or arm volume may exist between a woman's dominant and non-dominant arm. In most women these differences are less than 2 cm and therefore not significant.^{6, 7} However, slight pre-operative limb volume or circumference differences might mask the presence of minor lymphedema in the smaller extremity.

Conclusion

The prevalence of BCRL more than five years after surgical treatment differs depending on the measuring method used. The range of prevalence rates observed in this one group of women measured at a single point in time by four different methods, underlines the necessity for consensus on the diagnostic criteria for BCRL. Currently, there is no single measuring method that can identify lymphedema error-free, this is in part due to the changing nature of lymphedema. We advise screening breast cancer patients by using a combination of subjective complaints and preoperative and sequential postoperative limb volume measurements (water displacement method), eliminating the chance of missing minor cases of limb swelling. This approach will result in more knowledge on the true prevalence of BCRL. Furthermore, the efficacy of therapeutic regimens and the design of optimal therapeutic approaches can be assessed creating the beginning of an accepted evidence based systemic approach of the problem of BCRL. Finally, the implementation of a lymphedema screening program will clarify the clinical relevance of the asymptomatic BCRL and symptomatic non-BCRL categories.

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Chapter 3

The quality of life in long-term breast cancer survivors with breast cancer related lymphedema

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Abstract

Aim: To compare the health related quality of life (HRQOL) of long-term breast cancer survivors with and without breast cancer related lymphedema (BCRL) treated in the sentinel lymph node biopsy (SLNB) era.

Methods: HRQOL was assessed as subject of a secondary analysis of data gathered for a study evaluating the prevalence of BCRL in long-term breast cancer survivors. The 145 women in this study cohort had undergone SLNB and or axillary lymph node dissection (ALND) according to Dutch breast cancer treatment guidelines. HRQOL was assessed using two quality of life questionnaires: the European Organization for Research and Treatment of Cancer Quality (QLQ-C30) and the Breast Cancer-specific Quality of Life (QLQ-BR23).

Results: Twenty-six women, of whom 5 only underwent SLNB, were identified with objectively measured lymphedema and/or self-perceived arm swelling. Patients with BCRL scored significantly lower on the social ($p=0.000$) functioning scale after adjustments for BMI and age compared to women without BCRL. Compared to normative data, women with BCRL scored significantly lower on social- ($p<0.001$) and role ($p=0.001$) functioning scales.

Conclusion: HRQOL in long-term breast cancer survivors with BCRL is structurally lower than of those without BCRL, even in this small cohort of cancer survivors treated in the SLNB-era.

Introduction

As a concomitant effect of the increase of the survival rate after breast cancer treatment¹, attention is being shifted towards treatment-related complications and their effect on the quality of cancer survivorship.²⁻⁵ One of the most frequent and burdensome complications of breast cancer treatment is lymphedema. Breast cancer related lymphedema (BCRL) can develop as a result of damage to the lymphatic system brought on by (axillary) surgery and adjuvant therapy. BCRL is characterized by an accumulation of fluid in the interstitial tissue that causes limb swelling, functional disability, recurrent pain and infections and increased psychological distress.⁶⁻⁹

Both patients undergoing sentinel lymph node biopsy (SLNB) alone and SLNB followed by an axillary lymph node dissection (ALND) are at risk for developing upper-limb lymphedema. Despite the efforts of reducing upper-body morbidities by the introduction of the SLNB, BCRL rates are still significant. One of the largest RCT's comparing morbidity rates between SLNB and ALND reported a fairly high BCRL incidence rate of 7% and a subclinical BCRL rate of 13% after three years in patients having undergone SLNB.¹⁰

The studies published up till now on the health-related quality of life (HRQOL) in long-term breast cancer survivors (≥5 years) with BCRL are derived from patient cohorts in the pre-SLNB era.^{7,11-13} A HRQOL assessment of contemporary patients, in which less invasive axillary surgery is being performed more often, is of added value to the available body of evidence. Therefore, the aim of this study is to compare the HRQOL of long-term breast cancer survivors with and without BCRL in a cohort of women treated in the SLNB-era. Furthermore, we will compare the HRQOL of this cohort with normative data computed from individuals drawn from the general Dutch population.

Patients and Methods

Patients

The HRQOL was assessed as subject of a secondary analysis of data gathered for a study evaluating the prevalence of BCRL more than five years after breast cancer treatment.¹⁴ We evaluated the HRQOL of 145 women treated for primary unilateral breast cancer at the Maastricht University Medical Centre

(MUMC+) between January 2001 and December 2008. Patients were excluded in case of disease recurrence, metastases, death and withheld written informed consent. Study participants visited the MUMC+ five or more years after breast cancer treatment for a one-time clinical assessment. The quality of life questionnaires were filled in by the patients themselves. Oncologic and treatment-related characteristics of each patient were abstracted from hospital records. The hospital's medical ethics committee approved this study and the consent form.

Lymphedema measurements

Arm swelling was assessed using the water displacement method, the current gold standard. A home built volumeter was applied according to J. Lette¹⁵ for volume measurements. Both limbs were measured twice, comparing the treated side to the untreated side. An arm volume difference greater than 200 ml was defined as objective lymphedema. A detailed description of the arm volume measurement has been previously published.¹⁴

Furthermore, participants were asked to indicate the presence of (refractory) swelling during a standardized interview by answering the following question with a "yes" or "no": Have you experienced swelling of the upper-limb on the breast cancer treated side in the past year? Self-reported lymphedema was described as positive if the question was answered with a yes.

Study participants were divided into two groups: 1) patients with self-reported and/or objectively measured arm swelling, 2) patients without arm swelling.

Quality of life measurements

The HRQOL was assessed using the Dutch version of two validated questionnaires developed by the European Organization of Research and Treatment for Cancer (EORTC): QLQ-C30 version 3.0 and QLQ-BR23 breast cancer supplementary module.¹⁶ Authors received permission from the EORTC to use the questionnaires for research purposes.

From the QLQ-C30 questionnaire, the Global Health (self-perceived quality of life and health) scale and function scales including physical- (activity in everyday life), role- (leisure time & work life), social- (family & social life), emotional- (feelings of worry, depression & irritability) and cognitive (concentration & memory) function were used. As for the QLQ-BR23 questionnaire, we only analyzed the seven questions pertaining to arm and

breast symptoms (questions about the presence of symptoms of pain and/or swelling in the treated arm and/or breast and the presence of reduced shoulder mobility). All of the raw scores were standardized by linear transformation so that scores ranged from 0-100, as indicated by the EORTC. A higher score on the functioning scale and Global Health scale corresponds with a more healthy level of functioning and health.

The QLQ-C30 scores acquired from this study were compared to normative values computed from individuals drawn from the general Dutch population.¹⁷ This population was designed to be representative of the Dutch-speaking population in the Netherlands. While the cohort consisted of men and women, we only used the data acquired from the 796 women (mean age of 50.8 years) for this study.

Statistical analyses

Statistical analysis was conducted using SPSS for MAC 17.0 (SPSS Inc. Chicago, Illinois). Continuous variables were presented as mean and standard deviation with mean difference and 95% confidence interval (95% CI). Categorical variables were presented in numbers and percentages. The differences between groups (BCRL versus no BCRL) were tested using the independent-samples t-test for continuous variable and Chi-square test for categorical variables. A multivariate analysis was conducted using a model containing BCRL and two variables, BMI and age. The analysis was restricted to three variables because of the small number of patients in the BCRL group. A two-sided p-value ≤ 0.05 was considered statistically significant.

Results

BCRL prevalence

Of the 145 women, 11 (7.6%) were identified to have an arm volume difference greater than 200 ml. As for the rate of women with self-perceived arm swelling, 25 (17.2%) reported to have had swelling in the past year. Almost all (n=10) of the participants with objective BCRL also reported self-perceived arm swelling, bringing the total of women in the lymphedema group to 26 (17.9%).

Baseline characteristics of the women with BCRL (n=26) and those without BCRL (n=119) are presented in Table 1. Women with BCRL were more likely to

have a higher BMI at surgery and at follow-up (both $p < 0.001$), have undergone adjuvant chemotherapy ($p = 0.003$) and hormonal treatment ($p = 0.009$) compared to women without BCRL. Furthermore, they were also more likely to have undergone total axillary lymph node dissection ($p < 0.001$), have more positive lymph nodes ($p = 0.024$) and more total lymph nodes excised ($p = 0.001$). Of the 76 women who only underwent a SLNB, 5 (6.6%) met the criteria for BCRL versus 21/69 (30.4%) women after ALND.

EORTC QLQ-C30 and QLQ-Br23 scores

Compared to women without BCRL, those with BCRL scored significantly lower on the physical functioning ($p = 0.003$), role functioning ($p = 0.008$), social functioning ($p < 0.001$), breast symptoms ($p = 0.034$) and arm symptoms ($p = 0.001$) scales (Table 2). We also compared normative QLQ-C30 scores of women in the general Dutch population with the scores of the two groups in our study. Both the BCRL and no BCRL group scored significantly lower on QLQ-C30 function scales when compared to the normative scores, but only the BCRL group scored statistically lower on the role ($p = 0.001$) and social functioning ($p = 0.000$) scales (Table 2). Furthermore, women without BCRL had a significantly higher Global Health score ($p = 0.003$) compared to data from the normative Dutch population (Table 2).

Multivariate analysis

The statistically significant lower scores for the physical-, role- and social functioning scales seen in the BCRL group were further assessed by multivariate analysis in order to control for confounding factors. BCRL and BMI were independently associated with a decrease in the social functioning scale. Standardized coefficients showed a small impact of both BCRL and BMI, $\beta = -.20$, $p < 0.05$ and $\beta = -.23$, $p = 0.01$ respectively. As for the other two functioning scales, after multivariate correction for BMI and age, BCRL was not significantly associated with the physical functioning ($p = 0.070$) nor with the role functioning scales ($p = 0.17$).

Table 1. Patient characteristics of those with and without BCRL

Clinical-factors	BCRL N= 26	No BCRL N= 119	Difference between means (95% CI)	P-value
<i>Age at surgery, mean (SD), in years</i>	55.4 (11.1)	56.5 (11.3)	-1.1 (-3.7 – 6.0)	0.644
<i>Age at FU, mean (SD), in years</i>	61.6 (11.2)	62.7 (11.2)	-1.1 (-3.7 – 5.9)	0.655
<i>Time from surgery to FU, mean (SD), in months</i>	77.0 (10.0)	75.6 (9.6)	1.4 (-5.5 – 2.8)	0.523
<i>BMI (kg/m²) at surgery, mean (SD)</i>	30.3 (6.2)	25.1 (4.0)	5.2 (-7.2 – -4.7)	< 0.001
<i>BMI (kg/m²) at FU, mean (SD)</i>	31.6 (6.8)	25.4 (4.1)	6.2 (-8.1 – -4.1)	< 0.001
<i>Tumor status, no (%)</i>				
Tis – T1	18 (69.2)	99 (83.2)		0.109
TII – TIV	8 (30.8)	20 (16.8)		
<i>Breast surgery, no (%)</i>				
Mastectomy	9 (34.6)	25 (21.0)		0.199
Lumpectomy	17 (65.4)	94 (79.0)		
<i>Axillary surgery, no (%)</i>				
SLNB	5 (19.2)	71 (59.7)		< 0.001
ALND	21 (80.8)	48 (40.3)		
<i>Total nodes excised, mean (SD)</i>	12.3 (7.6)	7.0 (7.2)	5.3 (-8.4 – -2.2)	0.001
<i>Total positive nodes excised, mean (SD)</i>	2.1(2.7)	0.8 (2.5)	1.3 (-2.3 – -0.2)	0.024
<i>Dominant arm is affected, no (%)</i>	12 (46.2)	59 (49.6)		0.752
<i>Post-menopausal, no (%)</i>	18 (69.2)	77 (64.7)		0.660
<i>Adjuvant Therapy, no (%)</i>				
Rtx (Breast / loco regional)	19 (73.1)	90 (75.5)		0.785
CHtx	18 (69.2)	44 (37.0)		0.003
Htx	20 (76.9)	58 (48.7)		0.009

SD; standard deviation, no; number, FU; follow-up, BMI; body mass index, SLNB; sentinel lymph node biopsy, ALND; axillary lymph node dissection, RT; radiotherapy, CHtx; chemotherapy, Htx; hormone therapy

Table 2. QLQ-C30 & QLQ-BR23 scores of patients with BCRL, without BCRL and in the general Dutch population

EORTC	BCRL (n=26)	No BCRL (n=119)	Normative data (n=796)	BCRL VS no BCRL	BCRL VS normative data	no BCRL VS normative data
QLQ-C30, mean (SD)				Difference between means (95% CI)	Difference between means (95% CI)	Difference between means (95% CI)
Global Health status	78 (18)	83 (16)	78 (17)	-5 (-12 – 2)	0 (-7 – 7)	5 (2 – 8)**
Physical function	73 (17)	84 (18)	90 (15)	-11 (-19 – -4)**	-17 (-23 – -11)***	-6 (-9 – -3)***
Role function	75 (28)	88 (21)	89 (21)	-13 (-22 – -3)**	-14 (-22 – -6)***	-1 (-5 – 3)
Emotional function	79 (20)	80 (19)	89 (16)	-1 (-9 – 7)	-10 (-16 – -4)***	-9 (-13 – -6)***
Cognitive function	78 (24)	82 (19)	92 (15)	-4 (-13 – 5)	-14 (-20 – -8)***	10 (-13 – -7)***
Social function	81 (23)	94 (14)	94 (16)	-13 (-20 – -16)***	-13 (-19 – -7)***	0 (-3 – 3)
QLQ-BR23, mean (SD)						
Breast symptoms	18 (17)	11 (15)		7 (-13 – -1)*		
Arm symptoms	36 (28)	14 (18)		22 (-31 – -13)***		

* p < 0.05, **p < 0.01, ***p ≤ 0.001, 95% CI; 95% confidence interval, BCRL; breast cancer related lymphedema

Discussion

The aim of this study was to assess the HRQOL of long-term breast cancer survivors with BCRL using the EORTC QLQ-C30 and BR23 questionnaires. After adjustment for BMI and age, the women with BCRL scored lower on the social functioning scale when compared to the women without BCRL. Moreover, the presented cohort as a whole scored lower on a majority of the functioning scales compared to that of the general Dutch population, but it was only the BCRL group that scored significantly lower on role- and social functioning.

Our findings are in line with other studies reporting on the impact of BCRL on the HRQOL in long-term breast cancer survivors (≥ 5 years). The available studies are few, but all to some degree show functional impairment (Table 3). An important point to address is the fact that the patients in these long-term studies were largely included prior to the implementation of the SLNB. Almost all of the women in these studies underwent ALND. To our knowledge, this is the first study reporting on the HRQOL of long-term breast cancer survivors with BCRL depicted in the SLNB-era. It is known that ALND is associated with a higher risk of objective and subjective upper-limb morbidities compared to SLNB, resulting in a higher risk of impaired HRQOL.¹⁸⁻²² In the current study we simply assessed the influence of BCRL on the HRQOL, not regarding the possible effect of other upper-limb morbidities such as pain, decreased range of motion etc. Half of the women in this cohort underwent a SLNB (76/145). Of these 76 women, five were in the BCRL group, which equals to a 6.6% rate in the SLNB patients. This incident rate fits well into the 3%-23% BCRL incident range reported after SLNB in a review of procedure specific incidence rates of BCRL by Shah et al.²³

The cohort of breast cancer survivors presented with a statistically significant higher Global Health score as compared to the normative population, meaning that breast cancer survivors were more satisfied with their general health and quality of life than healthy women. This observation, also known as the “response-shift phenomenon”, has been described in previous publications reporting on the quality of life in long-term breast cancer survivors.³ The history of illness could have caused the patient to redefine her concept of quality of life and therefore being more satisfied.²⁴ That said, women with BCRL in this study nevertheless suffered from an impaired functioning, with respect to social and role functioning.

In light of the recent publication of the ACOSOG-Z0011 trial, the role of ALND performed currently with the aim of maintaining regional nodal control is being questioned. Results of this trial demonstrated no survival benefit in sentinel node positive (1-2 nodes) patients undergoing breast-conserving surgery in combination with radiation therapy randomized to undergo additional ALND as compared to those randomized not to.²⁵ It is expected that the next generation of trials will provide more insight on the matter, which as a consequence might eventually lead to fewer indications for ALND in the future. The authors of the present study are of the opinion that regardless of this, BCRL will remain a clinically relevant morbidity of the upper-limb as demonstrated by the BCRL incident rates after SLNB.^{6,23}

Several limitations should be considered in this study. Firstly, not all potential sociodemographic and psychological confounders were recorded. We were not able to control for the potential confounding effects of anxiety/ depression²¹, lack of social support²⁶ and coping mechanisms²⁷ to name a few, as they have shown to play an important role in predicting the HRQOL. Secondly, the power was low due to a small number of subjects in the lymphedema group, this causing us the limit the use of variables to three for the multivariate analysis.

Conclusion

In conclusion, our findings indicate that the HRQOL in breast cancer survivors with BCRL is structurally lower than of those patients without BCRL, even in this small cohort of cancer survivors treated in the SLNB-era.

Table 3. Overview of HRQOL assessment studies in long-term breast cancer survivors with and without BCRL

Ref.	Population	Time since surgery	BCRL definition	HRQOL assessment
7	N=245, cross-sectional study. Inclusion: 1985-1991. Axillary surgery: 100% underwent ALND	Ranging 9.4-16.5 years	Self-report of swelling	BCRL (n=75) VS no BCRL SF-36: Severe swelling & activity limiting swelling each significantly associated with worse physical function.
11	N=1287, population based study. Inclusion: 1986-2003. Axillary surgery: not provided	Mean 8.1 SD 0.2 years	Self-report of BCRL diagnosis	BCRL (n=104) VS no BCRL or arm symptoms SF-36: significantly ↓scores for all scales except mental health & role limitations emotional subscale.
12	N=990, prospective study. Inclusion: 1996 -1998. Axillary surgery: 93% underwent ALND	5 years	Self-report of swelling and/ or limitations in arm movement (arm problems)	Arm problems (n= not provided) VS none EORTC QLQ-C30: arm problems scored significantly lower on Global Health & all functioning domains.
13 ¹	N=151, retrospective cohort study. Inclusion: 1986-2000. Axillary surgery: 100% underwent ALND	Mean 4.8 SD 0.2 years	Volume difference $\geq 200\text{cm}^3$ between operated and non-operated limb	BCRL (n=42) VS no BCRL FACT-B: BCRL significantly associated with decreased emotional-, functional-, physical-, and breast well-being.
Current study	N=145, cross-sectional study. Inclusion: 2001-2008 Axillary surgery: 48% underwent ALND	Mean 6.2 SD 0.81 years	Self-report of swelling and/or volume difference $\geq 200\text{cm}^3$ between operated and non-operated limb	BCRL (n=26) VS no BCRL EORTC QLQ-C30: BCRL significantly associated with decreased social functioning.

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Chapter 4

Biomechanical properties of the skin in patients
with breast cancer related lymphedema
compared to healthy individuals

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Abstract

Background: Biomechanical skin changes in breast cancer related lymphedema (BRCL) have barely been described and objectively tested. This study aims to compare the skin of upper-limb lymphedema with skin of the healthy contralateral arm, in order to demonstrate changes of elasticity, visco-elasticity and level of hydration of the skin in BCRL. The secondary aim is to investigate the correlation between biomechanical skin changes and measurements that are currently used in clinical practice, such as volume measurement and Lymph-ICF score.

Methods and Results: Eighteen patients with BCRL and 18 healthy individuals were included in the study. A Cutometer® was used for measurements for skin-elasticity and visco-elasticity, a Corneometer® was used for measurements of skin-hydration. Measurements of both test groups were compared. In BCRL patients, there was a significant difference ($p < 0,028$) between the elasticity of the skin of the lymphedema arm compared to the healthy contralateral arm. There were no significant differences for level of skin-hydration or visco-elasticity in lymphedema patients between the measurements on the skin of the lymphedematous and healthy arm. In healthy individuals, there were no significant differences for all measurements between skin of both arms. Spearman's correlation was significant ($p = < 0,01$) for difference in volume and difference in elasticity in BCRL patients.

Conclusion: This study shows an impaired elasticity for the skin of the lower arm in patients with lymphedema compared to the contralateral healthy arm. Promising evidence is suggested for the use of the Cutometer device in the diagnostic evaluation of BCRL.

Introduction

One of the most underestimated and debilitating morbidities breast cancer survivors may experience is breast cancer related lymphedema (BCRL). BCRL may present with symptoms of heaviness, tightness and pain. It is a result of the accumulation of lymphatic fluid in the interstitial tissues and is characterized by swelling of the arm, hand, breast and/or trunk. In the initial stage of lymphedema, the edema may be soft and pitting. If left untreated, the reaction to tissue injury induces the accumulation of inflammatory cells, which is a hallmark of pathophysiological events in the skin. Activation of lymphocytes, leukocytes and release of cytokines induce connective tissue synthesis in fibroblasts. The excessive deposition of extracellular matrix, especially collagens, is the complex tissue response which is called fibrosis.³

Ultrastructural research has shown that this process is accompanied by the degeneration of smooth muscle cells in the lymphedematous tissue.⁴ The contraction of these smooth muscle cells, together with the compression of skeletal muscles, determine the interstitial pressure that stimulates lymphatic drainage. The above-described pathological changes of the lymphedematous tissue can be regarded as a key step for the progressing pathological status of lymphedema.^{5, 6}

Tissue resistance in post-surgical lymphedema has previously been measured and evaluated with the use of tonometry.⁷ Indentation measurement on lymphedema patients has shown increased tissue resistance in lymphedematous skin.^{8, 9} Both the pathogenesis of BCRL and the previous findings of increased tissue indentation in lymphedematous tissue, implicate a role of biomechanical skin changes within development of BCRL.

The Cutometer device is seen as an attractive and suitable option for testing and monitoring changes in biomechanical properties of the skin^{10, 11}. This device has been used in previous research for the evaluation of skin properties in facial wrinkles, wounds and scar healing.¹²⁻¹⁴ Furthermore, it has been used for measuring elasticity of the skin after radiotherapy.¹⁵ Besides the biomechanical skin properties in the evaluation of BCRL, fluid accumulation is an initial component in edematous and lymphedematous conditions. Tissue fluid water and proteins accumulate in the interstitial space,^{16, 17} this makes it both of fundamental and clinical interest to know what relationship exists between tissue water and tissue resistance.

Local tissue water in lymphedema has already been quantified using the tissue's dielectric constant (TDC), showing significantly greater values in lymphedematous legs compared to healthy legs.⁹ These outcomes gained our interest for determining skin hydration in lymphedematous conditions. In the past, measurements of skin hydration have particularly been used in dermatologic testing of products and for the evaluation of skin development.¹⁸⁻²⁰ Measurements are mostly performed by use of a Corneometer, which is a validated tool for measuring hydration of the stratum corneum of the skin.²⁰

The primary aim of this study is to compare the lymphedematous skin to that of the healthy contralateral arm in breast cancer survivors, in order to demonstrate the biomechanical changes (elasticity, visco-elasticity) and level of hydration of the skin. The secondary aim is to correlate biomechanical skin changes with current clinical assessment measurements of lymphedema, such as objective volume measurement as well as subjective functional impairments measured with the Lymph-ICF score.

Materials and Methods

Subjects

A total of 34 women with BCRL were asked to participate in the study, of which 24 were willing to participate. All subjects were over 18 years and were treated for unilateral early stage breast cancer in Maastricht University Medical Centre+ (MUMC+) between May, 14th 2004 and December 21st, 2010. During routine follow-up visit after primary breast cancer surgery, upper-limb volume of the affected side was measured with the water-displacement method and compared to that of the healthy contralateral arm. Patients were enrolled in the study if they had more than 200 milliliters (ml) volume difference and had subjective complaints or if they were currently being treated by a lymphedema therapist. Patients were excluded from participation if they had, recurrent breast cancer, bilateral breast cancer, distant breast cancer metastases, or if they had a medical history of cancer other than breast cancer. A total of 22 patients met the inclusion criteria. Subjects were instructed not to wear elastic arm garments on the test day so that volume measurements were not influenced. Written consent was obtained from each subject prior to inclusion of this study.

Eighteen healthy participants, all women, without BCRL or open lesions on their upper extremity were asked to participate. Three subjects with unilateral BCRL wore an elastic arm garment on the test day (against the given instructions). One patient exceeded the maximum arm volume measurable by the water displacement method. These four BCRL patients were excluded from the study before calculations were made.

Ultimately 36 subjects completed the study, 18 subjects with unilateral BCRL and 18 healthy individuals. Baseline characteristics of all subjects were collected before testing.

Study design

All subjects were invited for a single consultation in the outpatient clinic of MUMC+. Measurements were done in the same room with specified conditions; a temperature of 20-22°C and 40-60% humidity as instructed in the measuring principles of the Cutometer® MPA 580 (Courage and Khazaka, Köln, Germany). Patients were seated with their arm on the surface of the table with their hand and fingers relaxed during Cutometer measurements. The angle of the elbow was approximately 120°, the angle between the upper arm and the supporting surface was approximately 40°, and the angle between the upper arm and the shoulder was approximately 90°. Measurements for elasticity, visco-elasticity and hydration were performed on each subject on both arms.

Elasticity measurements were taken of the skin of both lower arms, at the volar midpoint between the tip of the ulnar styloid process and medial epicondyle of the humerus (F-MP). This is one of the predetermined sites of the lower arm where extra lymphatic fluid of the upper-limb can accumulate.²¹ The volar site of the arm was taken so that measurements were not influenced by body hair on the dorsal site of the arm. Cutometer measurements were repeated after ten minutes, as advised by the device manufacturer. The suction and release time of the Cutometer could cause the skin to be strained and might distort the results of the next measurement. The average of both measurements was taken and used for analysis.

All study procedures were in accordance with the ethical standards of the Medical Ethical Committee Maastricht and with the Helsinki Declaration of 1975, as revised in 2008.

Elasticity and visco-elasticity of the skin

Vertical extensibility of the skin was measured using a Cutometer MPA 580 system with a Cutometer Q probe; a non-invasive suction device that measures the vertical deformation of the skin surface. A constant negative pressure of 450 mbar during 6 seconds was applied, to draw the skin up into the circular aperture (6mm diameter) of the probe, followed by normalization of the pressure and returning of the skin in original shape.²² The Cutometer device generates a graph showing skin extensibility (U_e), delayed distension (U_v), final deformation (U_f), immediate retraction (U_r) and final retraction (U_a). (Figure 2) The Cutometer software MPA 580 was used to automatically generate R parameters (R0 to R9). These parameters are relative parameters which are thought to be independent on skin thickness, which varies in age, sex and anatomical region.¹¹ Skin elasticity is reflected by R2, R5 and R7.²³ These values were generated as follows (figure 2): R2 (U_a/U_f) (gross elasticity), R5 (U_r/U_e) (net elasticity) and R7 (U_r/U_f) (biological elasticity). Value R6 (U_v/U_e) represents the viscoelasticity ratio.

Hydration of the skin

An additional Corneometer CM 825 probe was used to assess the level of hydration of the stratum corneum in the lymphedema and healthy contralateral arm. The probe contains a grid of electrodes, which are used for measuring the capacitance of the electrodes and epidermal skin to calculate total skin capacitance. The values of capacitance of the skin are converted in the instrument in arbitrary units of skin hydration ranging from 0 to 120.¹⁸ Calibration was performed using a cellulose filter paper saturated with a 15% NaCl aqueous solution, giving a maximal hydration value of 120. To increase reliability, measurements at F-MP on both arms were taken three times from which the average was taken.

Determining severity of lymphedema

The degree of lymphedema is determined by different measurements and values, including volume difference of the upper-limb and experienced disabilities as a result of the lymphedematous limb.^{24, 25} All lymphedema patients in the study underwent an objective measurement of volume of both arms, and had to fill-out the Lymphedema Functioning, Disability and Health” (“Lymph-ICF”) questionnaire for evaluation of the current functional impairments they were experiencing from the lymphedema.

The Lymph-ICF is a validated questionnaire that assesses the impairments in function, activity limitations and participation restrictions in patients with upper limb lymphedema, based on 29 questions corresponding with a score between 0-100. A higher score indicates more problems with functioning related to upper-limb lymphedema.²⁶

Inter-limb volume difference measured using the water displacement method, the golden standard for measuring arm volume.²⁵ A Volumeter (Varitex, Haarlem, The Netherlands) was filled with tap water with a temperature of 25 °C and 32 °C. Water temperatures across the range of 20 to 32 degrees Celsius were not found to affect the volume measured.^{27, 28} A circumference line was drawn at 80% of the arm length, measured from the tip of the third digit to the tip of the acromion. Subjects were instructed to lower the arm into the Volumeter until the water reached the circumference line. The Volumeter weighed the overflowing water with an integrated calibrated scale with an accuracy of 1cc. All water displacement measurements were done after hydration measurements with the Corneometer CM 825 probe, so that the hydration state of the stratum corneum of the skin could not be influenced by the water exposure of the arm in the Volumeter.

Data analysis

Patients and clinical characteristics were described using descriptive statistics. Reliability analysis was used to calculate intraclass correlation coefficient (ICC) to determine the intra-rater reliability of the Cutometer measurements in the lymphedematous arm. The Intraclass Correlation Coefficient (ICC) was used to determine the intra-rater reliability of all elasticity measurements in healthy and lymphedema skin. Intra-rater reliability was determined from two repeated measurements with the Cutometer done by the same investigator. To assess differences between biomechanical skin properties in both arms, a Paired Samples t-test was used. A p-value of <0,05 was considered statistically significant.

The measurement parameters (elasticity or hydration) that were significantly different in the BCRL arm and the healthy contralateral arm, were correlated to clinical assessment points (difference in limb volume and lymph-ICF score). These correlations were calculated with Spearman's correlation coefficient. Data were analyzed using statistical software (SPSS 20.0 Inc Chicago, Ill).

Results

Participants

All 36 subjects were able to complete the study. BCRL patients had a median age of 63 years [SD 9,2]. Ten patients had left-sided lymphedema, 8 patients had right-sided lymphedema. Healthy individuals had a mean age 23 [SD 12,4] of and a mean BMI of 22 [2,7]. All 18 individuals were female. Patient characteristics of both groups are described in Table 1.

Table 1. Patient characteristics

Patient Characteristics	Healthy individuals (N=18)		BCRL Patients (N=18)	
	Mean [SD]	n=18 (100%)	Mean [SD]	n=18 (100%)
Age (years)	23 [12,4]		63 [9,2]	
BMI (kg/m ²)	22 [2,7]		27 [5,1]	
Right-handed N (%)		17 (94,4%)		16 (88%)
Smoking N (%)		2 (11,1%)		2 (11,1%)
Lymphedema		0 (0%)		21 (100%)
Arm volume difference (cc)	-		385 [369,1]	
Lymph-ICF score	-		36 [19,5]	
Right- sided lymph edema N (%)		-		10 (55,5%)
Dominant-hand lymph edema N (%)		-		8 (44,4%)

Reliability of measurements

Intraclass correlation coefficients (ICC) for all elasticity parameters were high, namely: 0,707 for biological elasticity (R7), 0,715 for net elasticity (R5) and 0,882 for gross elasticity (R2). ICC for viscoelasticity (R6) was 0,753.

Interlimb difference – elasticity and viscoelasticity

Patients with BCRL had an impaired elasticity of the skin in the lower lymphedematous arm, compared to their healthy contralateral arm. All values for elasticity showed a significant difference. (R2: p= 0,028; R5: p=0,019; R7: p=0,013). The mean elasticity difference between both arms ranged from 0,127 (R5) to 0,08 (R7). There was no significant difference between viscoelasticity of the lymphedematous arm and contralateral healthy arm (R6:-p=0,409). Healthy individuals showed no difference for values of elasticity and visco-elasticity

between the skin of both lower arms (R2: $p=0,782$; R5: $p=0,339$; R7: $p=0,147$ and R6: $p=0,632$). (Table 2)

Interlimb difference – hydration

The hydration of the skin between both arms was not significantly different in BCRL patients ($p=0,218$). In healthy individuals, the difference was also not significant ($p=0,488$) (Table 2).

Table 2. Difference in skin properties in healthy individuals and BCRL patients

Arm difference	Healthy individuals (N=18)					BCRL patients (N=18)				
	Mean	95% confidence interval		T	Sign (2-tailed)	Mean	95% confidence interval		T	Sign (2-tailed)
		Lower	Upper				Lower	Upper		
Hydration	0.611	-1.207	2.429	0.709	0.488	2.596	-1.685	6.877	1.28	0.218
Elasticity										
R2 - gross elasticity	0.002	-0.015	0.020	0.281	0.782	0.085	0.010	0.159	2.404	0,028*
R5 - net elasticity	0.023	0.023	0.026	-0.983	0.339	0.128	0.024	0.238	2.591	0,019*
R7 - biological elasticity	0.006	-0.031	0.019	-0.488	0.632	0.082	0.020	0.144	2.779	0,013*
Viscoelasticity										
R6 - visco-elasticity	0.030	-0.071	0.012	-0.519	0.147	-0.026	-0.091	0.039	-0.846	0.409

Paired sample t-Test, * significance level <0.05

Interlimb difference – volume

Mean difference for volume between both arms in BCRL patients was 385cc [SD 369].

Lymph – ICF score

Mean Lymph-ICF score for BCRL patients were 36 [SD 19,5].

Correlations (between biomechanical skin changes and volume difference or Lymph ICF score)

Spearman correlations for inter-limb differences in elasticity (R2, R5 and R7) and inter-limb volume difference were significant for R2: $r = 0,591$ ($p = 0,010$); R5: $r = 0,618$ ($p = 0,006$) and R7: $r = 0,649$ ($p = 0,004$) (Figures 1,2,3). Correlation coefficients for elasticity and Lymph-ICF score were low and not significant, ranging from $r = 0,031$ (R7) to $r = 0,088$ (R2).

Figure 1. Correlation between elasticity difference (R2) and volume difference (cc) between both arms.

Figure 2. Correlation between elasticity difference (R5) and volume difference (cc) between both arms.

Discussion

The results of this study show a significantly lower elasticity of the skin in upper-limb lymphedema. This finding is supported by the theory that there is an increase in volume of the subcutaneous tissue which affects the skin by increasing its tension at rest.²⁴ The proportional changes within the tissue result in modification of the intermolecular bridging and thickening of the collagen bundle.³⁰

The Cutometer device revealed to be a reliable method for the evaluation of skin elasticity in lymphedematous skin using the suction method. Values for extensibility and elasticity were reliable with a reproducibility ranging from 0,707 to 0,882. Other studies using a Cutometer for measuring skin properties found small coefficients of variation between measurements ranging from 0,7%-6,2%.^{10, 31} Inter-relation parameters for elasticity measurements show high correlations. (R: 0.7 - >0,9).³² The advantage of measurements with the Cutometer is that the outcome for elasticity is corrected for the depth of deformation applied with the instrument. The small size of the measuring probe

makes it very applicable in clinical practice. In addition, the minimal measuring diameter decreases the chance of bias due to topographical irregularities.

Figure 3. Correlation between elasticity difference (R7) and volume difference (cc) between both arms.

Tools that have previously been used for the measurement of biomechanical properties of the skin are a Tonometer or a caliper. A tonometer can be applied to the skin and measures the depth of the mass that is descended. Results of measuring with the tonometer highly relied on the correct positioning and amount of pressure applied when placing the tool on the skin.^{7,33} A caliper, which is used to measure skin creases of the arm, appeared to be a reliable measuring method, but edema of the deeper tissues is not taken into account.³⁴ Tissue indentation measurements for the assessment of lymphedema have previously been developed to evaluate tissue resistance. Tissue resistance is not only dependent on the biomechanical properties of the skin, but also influenced by the underlying accumulated interstitial water.⁹ The amount of

interstitial water can be easily influenced by therapy such as manual lymphatic drainage. Indentation measuring is therefore not suitable for quantifying the biomechanical properties of the skin alone. Measurements with the Cutometer are less dependent on the amount of interstitial water, as it measures only the skin extensibility with use of the suction method. This can make the measurement very suitable for diagnostic of follow-up measurement in clinical practice to investigate the pathological changes of the skin in BCRL.

There are a few other studies that use a Cutometer for measuring skin extensibility and elasticity in lymphedematous skin. Auriol et al. showed a 20% reduction of skin extensibility (Ue) and elasticity (R5) in the lymphedema lower-limb in comparison to its healthy contralateral limb.³⁴ These results are consistent with our findings of an impaired elasticity in the skin of upper-limb lymphedema. In addition, the current study shows a significant correlation between elasticity- and volume difference of both arms. This suggests a clinical relevance for the elasticity parameter. In other words: a continued decrement in the elasticity parameters may be an indication for further progression of lymphedema.

Lymphedema evaluation in clinical practice tends to focus on volume change. Although volume is important and is the most objective current clinical measure, using only volume may overlook important tissue texture changes, as well as latent stage lymphedema disease.²⁹ Hacard et al. set up a study with patients undergoing therapy for lymphedema, and used values of elasticity measured with a Cutometer to evaluate the changes in skin properties before and after therapy.²³ Correlations were calculated for elasticity parameters and decrease of volume after therapy. A correlation was not found. This could be explained by the fact that in severe stages of lymphedema, where skin fibrosis and accumulation of extracellular matrix occurs³, elastic fibers might be destroyed. The elasticity parameter is therefore probably not applicable for a solitary follow-up measurement after treatment. However, elasticity parameters might be very useful in the late stages of lymphedema where fibrosis of the skin occurs despite a constant volume of the limb.

Considering that a relatively small population group is used in this study, individual patients might have had a big influence on results and significance. If elasticity parameters are to be used as a follow-up or diagnostic tool in clinical practice, research should be further carried out in a prospective setting with

more patients in different stages of lymphedema and measurements taken before and after lymphedema treatment. Subgroup analyses can then be performed to investigate for which purposes in clinical practice the Cutometer measurements are most relevant.

Our Corneometer measurements showed no significant differences for levels of hydration in the lymphedematous arm compared to the contralateral healthy arm. This is explained by the fact that the Corneometer mainly measures the hydration state of the stratum corneum of the skin.³⁵

Fluid in lymphedema usually accumulates in the subcutaneous tissue of the arm, which cannot be measured on the skin surface. Measurements with use of tissue's dielectric constant (TDC) have shown a significantly higher amount of local tissue water in lymphedematous arms when compared to healthy arms or arms of breast cancer patients prior to surgery.^{36, 37} TDC measurement might therefore be more suitable for assessing local tissue water in BCRL than the Corneometer measurement.

Conclusion

In this article a new method for measuring skin-elasticity of upper-limb lymphedema is proposed. This study showed an impaired elasticity of the skin of the lower arm in lymphedema compared to the contralateral healthy arm. There is no significant difference in elasticity in skin of both arms in healthy individuals. This study reports promising evidence for the use of Cutometer device in the evaluation of BRCL. Further research is planned which includes a larger population in a prospective setting in subgroups for different stages of lymphedema, so subgroup analyses can be performed. The use of the Cutometer as a diagnostic or follow-up tool in clinical practice can then be more extensively evaluated.

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Chapter 5

Reduced prevalence of lymphedema in patients
with reconstructive breast surgery

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Abstract

Aim: To determine if breast reconstruction has an influence, either protective or risk increasing, on the prevalence of breast cancer related lymphedema (BCRL).

Methods: Women who underwent unilateral mastectomy and axillary lymph node dissection (ALND) with or without immediate or delayed breast reconstruction between January 2006 and December 2010 were included. BCRL was defined as subjective complaints of arm swelling accompanied by an inter-limb volume difference of >200ml or receiving treatment for arm lymphedema.

Results: A total of 130 women were included. Breast reconstruction (n= 59) was performed with a tissue expander or implant in 26 cases, with an autologous free flap in 29 cases and with a combination of an implant and latissimus dorsi myocutaneous flap in 4 cases. The prevalence of BCRL was 45% (32/71) in the mastectomy only group and 19% (11/59) in the reconstruction group ($p=0.001$). After multivariable adjustment breast reconstruction was associated with a significantly lower BCRL risk (OR=0.30; 95% CI 0.13 – 0.72).

Conclusion: BCRL was less frequently observed in patients undergoing breast reconstruction after mastectomy and ALND. Further studies are needed to confirm this association of breast reconstruction with BCRL. This information is of interest for the surgical decision making process.

Introduction

Breast reconstruction, either with an implant or tissue flap, has become an indispensable addition to breast cancer management. Not only do modern reconstructive techniques provide good aesthetic results, they also have been demonstrated beneficial with regards to quality of life and body image^{1,2} without interfering with cancer management.^{3,4} The wide application of reconstructive breast surgery has raised the question whether it should be considered as a risk factor or protective factor for the development of breast cancer related lymphedema (BCRL). The current literature provides some evidence for a protective effect of breast reconstruction, autologous and implant based, on the development of BCRL.⁵⁻⁷

Breast reconstruction is an important component of rehabilitation after ablative breast surgery. In cases where breast-conserving surgery is impossible due to tumour size, mastectomy followed by an immediate or delayed reconstruction is optional. These procedures do not only provide good aesthetic results, but have also been demonstrated beneficial with regards to quality of life and body image¹⁻⁴ without interfering with cancer management.^{5,6} Hence, it is evident why breast reconstructions have become an indispensable addition to breast cancer management.

Arm lymphedema is one of the most burdensome breast cancer treatment related complications.^{7,8} Breast cancer related lymphedema (BCRL) can occur when local lymphatic vessels are damaged, causing fluid stasis that manifests as arm swelling and structural tissue changes.^{9,10} Some treatment modalities are notorious lymphedema risk factors, namely chemotherapy, radiation therapy and axillary surgery.¹¹⁻¹³ The question whether reconstructive breast surgery should be added to the list of risk factors has lead to an increased interest in the role of this commonly performed surgery within the context of breast cancer treatment. The current literature bears some data on the role of breast reconstruction, autologous and implant based, on the development of BCRL.¹⁴⁻¹⁸

The aim of this study was to determine the impact of reconstructive breast surgery on the development of BCRL by comparing the prevalence rate of BCRL in breast cancer survivors who only underwent mastectomy and of those with an additional breast reconstruction.

Methods

Patients

We retrospectively identified all women who underwent a unilateral mastectomy with or without breast reconstruction for primary breast cancer between January 1st 2006 and December 31st 2010 in one university hospital, Maastricht University Medical Centre+, and two neighbouring community hospitals, Orbis Medical Centre in Sittard and VieCuri Medical Centre in Venlo. Approval for the study was obtained from the Medical Ethics committee of the Maastricht University Medical Centre+. Information on the surgical procedures (oncological and reconstructive), tumour characteristics and adjuvant medical treatment was extracted from hospital medical records. Patients who had died or who were alive with recurrent/metastatic disease or contralateral breast involvement were excluded. The remaining 692 women were contacted via mail and were asked to take part in a one-time medical examination and standardized interview. Two hundred ninety two (42%) agreed to participate. However, 9 were excluded secondarily, 5 because recurrent disease had developed and 4 because bilateral disease had been treated, resulting in a study population of 283 women. For this study, only those 130 patients were selected who had undergone a full axillary lymph node dissection, as this is known to be the most important risk factor for developing BCRL. The 153 women who either had no axillary surgery (n=7) or only underwent sentinel lymph node biopsy (SLNB) (n=146) were excluded from analyses.

Study procedures

The participants were interviewed and examined by the chief investigator (TLP) with assistance of two dedicated researchers (NH, CI).

1. Standardized interview

A standardized interview was conducted using a lymphedema risk assessment questionnaire, which was specifically developed for the purpose of the study. This questionnaire includes questions on post-operative seroma formation, history of an episode(s) of erysipelas in the affected arm since surgery and history of injury (bone fracture and/or distortions) of the affected arm since mastectomy. Furthermore, each patient was asked to indicate the presence of subjective swelling by answering the following question with a “yes” or “no”:

Have you experienced swelling of the upper-limb on the breast cancer treated side in the past year?

2. Clinical examination

The patients' bodyweight and height were measured in order to determine the body mass index (BMI kg/m²). This was followed by a clinical examination of the chest wall and upper limbs, in which information on limb symmetry, skin texture/ thickness/tension and the aspect of surgical scar(s) was documented. Lastly, bilateral limb volume was assessed using the water displacement technique.¹⁹ BCRL was defined as subjective complaints of arm swelling accompanied by an inter-limb volume difference of >200ml or if the patient was undergoing treatment for arm lymphedema (compression garment/bandages, manual lymphatic drainage, or kinesiotape applications).

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (Chicago, Illinois). Data are presented as numbers with percentages for categorical variables and means with standard deviation or medians with range for continuous variables. Summary statistics were obtained using Chi square tests and Fisher's exact tests for categorical data and student's t-test and Mann-Whitney U test (non normal distribution) for continuous variables. Univariable and multivariable logistic regression analyses were performed to determine the association between BCRL and clinical characteristics, specifically the association of BCRL with breast reconstruction. The odds ratio (OR) and 95% confidence interval (95% CI) are provided. A p-value of <0.05 was considered statistically significant.

Results

Patient characteristics

130 patients underwent mastectomy with (55%) and without (45%) breast reconstruction. These women were examined and interviewed after a mean follow-up of 42.86 (SD 19.92) months after mastectomy. The patients in the breast reconstruction group were significantly younger ($p<0.001$) and had fewer lymph nodes removed ($p=0.04$) than their counterparts in the mastectomy only group. The majority of the reconstructive surgeries were done immediately

Table 1. Characteristics of the women with and without BCRL

Variables	No BCRL (n=87)	BCRL (n= 43)	p-value
Age at mastectomy, mean (SD), years	53.92 (10.36)	54.61 (11.37)	0.73
Age at FU, mean (SD), years	57.65 (10.11)	57.82 (11.12)	0.93
BMI (kg/m ²) at FU, mean (SD)	26.17 (5.36)	27.22 (4.94)	0.07
Time since mastectomy, mean (SD), months	44.78 (19.21)	37.75 (18.27)	0.08
Time since reconstruction, mean (SD), months	35.68 (17.03)	31.45 (16.67)	0.44
Lymph nodes removed, mean (SD)	15.80 (4.62)	17.60 (5.88)	0.06
Positive lymph nodes removed, median [range]	2 [0 – 18]	2 [0 – 20]	0.93
Side of surgery is dominant, no (%)	45 (51)	22 (51)	0.95
Neo-adjuvant chemotherapy, no (%)	19 (22)	11 (26)	0.63
Adjuvant Therapy, no (%)			
Chemotherapy	50 (57)	27 (64)	0.42
Trastuzumab	21 (24)	7 (17)	0.35
Radiation therapy	41 (46)	24 (56)	0.35
Hormone therapy	63 (72)	33 (77)	0.60
Seroma, no (%)	23 (26)	16 (38)	0.21
History of erysipelas in arm, no (%)	4 (5)	9 (21)	0.01
History of injury in arm, no (%)	1 (1)	6 (14)	0.005
Difference in arm volume, mean (SD), ml	40.58 (115.25)	221.18 (220.30)	<0.001
Breast reconstruction, no (%)			0.001
Autologous	23 (26)	6 (14)	
TE /implant	22 (25)	4 (10)	
LDM flap & implant	3 (3)	1 (2)	

Abbreviations: SD; standard deviation, no; number, FU; follow-up, BMI; body mass index, SLNB; sentinel lymph node biopsy, ALND; axillary lymph node dissection, TE; tissue expander, LDM; latissimus dorsi myocutaneous.

following mastectomy in the same surgical session (54%). Of the total number of breast reconstructions performed, 29 were autologous-based, 26 were with a tissue expander- or an implant and 4 were with a combination of a latissimus

dorsi myocutaneous flap and an implant. The deep inferior epigastric perforator (DIEP) flap was the most performed autologous-based breast reconstruction (83%).

Prevalence of BCRL

A total of 56 (43%) women had complaints of subjective arm swelling. The prevalence was 49% (n=35) in the mastectomy only group and 36% (n=21) in the reconstruction group ($p=0.12$). As for an inter-limb volume difference of >200ml, this concerned 28 (21%) women, of which 30% (n=21) were in the mastectomy only group and 12% (n=7) in the reconstruction group ($p=0.01$). Furthermore, 36 (28%) women were undergoing treatment for arm lymphedema, 38% (n=27) in the mastectomy only group and 15% (n=9) in the reconstruction group ($p=0.004$). Ultimately, 43 (33%) patients met the criteria for BCRL at the time of follow up (Table 1). When looking at the BCRL prevalence of each group individually, a rate of 45% (n=32) was observed in the mastectomy only group and 19% (n=11) in the reconstruction group ($p=0.001$).

Predictors of BCRL

Table 2 presents univariable & multivariable logistic regression analyses of factors associated with the development of BCRL. On univariable logistic regression analyses, patients with a history of injury of the affected arm since mastectomy (OR= 14.50) or a history of an episode of erysipelas (OR= 5.73) in the affected arm since mastectomy were associated with BCRL. A multivariable logistic regression analysis was performed using the following three variables: history of erysipelas, history of injury, and breast reconstruction (Table 3). In this model, breast reconstruction was associated with a significantly lower risk of having BCRL (OR= 0.30; 95% CI 0.13 – 0.72). Furthermore, history of injury and history of erysipelas in the affected arm were significantly associated with an increased likelihood of having BCRL, with an OR of 12.55 (95% CI 1.32 – 112.09), 5.07 (95% CI 1.36 – 18.83), respectively. A distinction could not be made between the different types of reconstructive breast surgeries due to the small number of patients in these subgroups.

Table 2. Univariable & multivariable logistic regression analyses of factors associated with the development of BCRL

Prognostic factor	OR	95% CI	p-value	OR	95% CI	p-value
Age	1.01	0.97 – 1.04	0.61	---	---	---
LN's removed	1.07	0.99 – 1.15	0.07	---	---	--
Erysipelas (yes/no)	5.73	1.65 – 19.88	0.006	5.07	1.36 – 18.83	0.015
Injury (yes/no)	14.50	1.68 – 124.77	0.015	12.55	1.32 – 112.09	0.028
BR (yes/no)	0.25	0.11 – 0.57	<0.001	0.30	0.13 – 0.72	0.007

Abbreviations: OR; odds ratio, 95% CI; 95% confidence interval, LN's; lymph nodes, BR; breast reconstruction

Discussion

In this study, breast cancer survivors who underwent mastectomy with ALND followed by breast reconstruction had a significantly lower risk of developing BCRL compared to their counterparts who only underwent mastectomy with ALND. This finding is in line with the current body of evidence; reports from comparative studies show a possible protective effect of breast reconstruction on the risk of developing BCRL.^{14–16} Moreover, when looking at the incidence of BCRL in a cohort of women after delayed autologous reconstruction¹⁷ and after a combination of immediate autologous or implant-based reconstructions¹⁸, rates were found to be low. We were not able to determine if the difference amongst the reconstructive methods influenced the prevalence of BCRL in our population, due to the small number of patients in each group and the low prevalence of BCRL in the study cohort. Although the method of reconstruction is not likely to have an influence on the development of BCRL, choosing the internal mammary vessels as recipient instead of the axillary vessels in free autologous reconstructions seems to be associated with a lower BCRL risk.¹⁸ All free flap reconstructions in our study were anastomosed to internal mammary vessels or their perforator vessels.

Besides the patients undergoing compression therapy for BCRL, we diagnosed BCRL using subjective and objective measurements. Volumetric limb analysis by means of water displacement is currently considered to be “the gold standard” for diagnosing BCRL.¹⁹ However, we included patient perception of arm swelling as a criterion for defining BCRL with the intention to reduce false positive diagnoses and ensure that the measured inter-limb volume difference was due to lymphedema and not pre-existing non pathologic volume

differences (muscle, fat).^{20, 21} We also identified women reporting subjective arm swelling without a limb volume increase, which could be the result of sensory changes interpreted by the patient as a feeling of swelling. In saying this, the method of limb measurement strongly influences outcome (BCRL).²⁰ In a previous publication we demonstrated the need for uniformity of the diagnostic criteria for BCRL, as using different measuring methods resulted in variable prevalence rates in a single cohort.²⁰ Many authors do not elaborate on their criteria used to define BCRL. Of the five studies published on the association of BCRL with breast reconstruction, only Avraham et al¹⁶ provided a clear definition for their criteria for BCRL, while the other four authors^{14, 15, 17, 18} disregarded this important factor.

In the literature several physiological mechanisms have been mentioned through which breast reconstruction might protect against the development of BCRL. Firstly, it is suggested that an autologous flap reconstruction serves as a lymphatic bridge²² or even constitutes regenerative properties due to the newly transposed lymphatic tissue accompanied in the flap.²³ Moreover, in the case of an implant-based reconstruction, Blanchard et al propose a hypothesis of a “vacuum pump” effect for the lymphatic system.²⁴ We assume that the increased circulation in the highly vascularized capsule, which forms around the implant, induces a concomitant increase in lymphatic flow. Future investigations with flow imaging lymphoscintigraphy are needed to confirm this hypothesis. Some authors have established the positive impact of autologous breast reconstruction on patients with already existing BCRL, reporting a decrease in limb volume post-operatively.^{24–26} In addition, simultaneous breast and lymphatic reconstruction as a treatment for upper-limb BCRL showed promising short-term results.²⁷ If confirmed in further studies these findings would significantly influence the current management of post-mastectomy patients.

The strength of our study is the use of a combination of clearly defined subjective and objective measurements to define BCRL and the fact that assessment was done by the same dedicated investigators for all patients in this study cohort, thus reducing the risk of inter-observer variability of the measured outcomes. In addition, by describing the prevalence instead of the incidence of BCRL at 3.5 years after mastectomy we believe to have filtered out the cases with acute lymphedema that develop in the direct post-operative stage but disappear, thus only identifying the chronic BCRL cases during follow-up. Even though BCRL can develop any time after breast surgery, with a follow-up of almost 4 years after mastectomy we expect to have included a

representative group.²⁸ On the other hand, the lack of a preoperative assessment of the limb volume might be considered as a limitation of our study. Another potential weakness is its non-randomized design and thus the risk of confounding by indication. A statistically significant difference in the mean age and the number of lymph nodes removed was found between the mastectomy and reconstruction group. As for age, the literature shows inconsistent results about the relationship between this variable and the risk of BCRL. Most studies report no association between age and BCRL, while some found a decreased risk among older patients.³¹ These reports make younger age in the reconstruction group an unlikely explanation for our observation of a lower prevalence of BCRL in this group. When looking in the literature reporting on the association of the number of lymph nodes removed and BCRL, a decreasing trend in the odds for BCRL is seen as the difference in removed lymph nodes between the compared groups becomes smaller. Ahmed et al. report a 3.52 higher odds of having BCRL in women with >20 lymph nodes removed versus those with no lymph nodes removed.²⁹ Meeske et al. describe a 2.16 higher odds of having BCRL in women with ≥ 10 lymph nodes removed versus those with no lymph nodes removed.³⁰ The most recent study, by Dominick et al., reports a 1.65 higher odds of BCRL in women with ≥ 16 lymph nodes removed as compared to those with ≤ 10 lymph nodes removed.³¹ The mean number of lymph nodes removed in our study was only 1.8 nodes higher in the mastectomy only group than in the reconstruction group. Taking the above evidence into account, it is unlikely that such a small difference would lead to a clinically relevant increase of the BCRL risk in the mastectomy group. Unfortunately, it is most unlikely that a randomized study will ever be performed with the aim to determine the effect of reconstructive breast surgery on the BCRL risk. Being aware of that, the best evidence we can acquire is evidence from studies like ours in which sufficient measures have been taken to rule out the impact of potential confounders.

Conclusion

In summary, BCRL was less frequently observed in patients undergoing breast reconstruction after mastectomy. Further studies are needed to confirm the association of breast reconstruction with BCRL. This information is of interest for the surgical decision making process.

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Chapter 6

Quality of life in patients with breast cancer
related lymphedema and reconstructive breast
surgery

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Abstract

Aim: To evaluate the quality of life (QOL) of breast cancer survivors who have undergone breast reconstruction and have breast cancer related lymphedema (BCRL).

Methods: Patients with a unilateral mastectomy with or without breast reconstruction were evaluated for BCRL and their QOL. Patients were divided into a non-BCRL and a BCRL group. Patients with subjective complaints of arm swelling and/or an inter-limb volume difference of >200ml, or undergoing treatment for arm lymphedema were defined as having BCRL. QOL was assessed using cancer-specific (EORTC QLQ-C30 and EORTC QLQ-B23) and disease specific (Lymph-ICF) questionnaires.

Results: 253 patients with a mean follow-up time of 51.7 ($\pm$ 18.5) months since mastectomy completed the QOL questionnaires. Of these patients, 116 (46%) underwent mastectomy alone and 137 (54%) had additional breast reconstruction. A comparison of the QOL scores of 180 patients in the non-BCRL group showed a significantly better physical function ($p=0.004$) for patients with reconstructive surgery compared to mastectomy patients. In the 73 patients with BCRL, a comparison of the QOL scores showed no significant differences between patients with mastectomy and reconstructive surgery. After adjusting for potential confounders, multivariate analysis showed a significant impact of BCRL on physical function ($\beta = -7.46$; $p=0.009$), role function ($\beta = -15.75$; $p=0.003$), cognitive function ($\beta = -11.56$; $p=0.005$), body vision ($\beta = -11.62$; $p=0.007$), arm symptoms ($\beta = 20.78$; $p=0.000$) and all domains of the Lymf-ICF questionnaire.

Conclusions: This study implies that BCRL has a negative effect on the QOL of breast cancer survivors, negating the positive effects on QOL reconstructive breast surgery has.

Introduction

Survival rates of breast cancer have increased over the past years.¹ With a long-term survival rate of >80%, a growing number of women are living with the side effects of breast cancer treatment.² It is therefore logical that the quality of life (QOL) has become an important outcome measure in many breast cancer studies.

One of the most debilitating side effects of breast cancer treatment is upper-limb lymphedema, also known as breast cancer related lymphedema (BCRL). The lymphatic system of the upper-limb can be damaged due to axillary surgery, radiation and/or chemotherapy, resulting in stasis of lymph fluid and an increased limb volume. BCRL can develop directly after surgery or, in most cases, in the first four years after breast cancer treatment.⁵ Patients may develop symptoms of heaviness, tightness, pain sensations, loss of normal upper-limb function and range of motion.⁶ Breast cancer survivors with BCRL have a significantly lower QOL than patients without arm morbidity.⁵⁻¹¹

There is evidence that breast reconstruction has a positive effect on the QOL of breast cancer patients.¹² However, is this positive effect also present in patients with BCRL? As of yet, no attention has been given to the assessment of the QOL in patients with BCRL who have also undergone breast reconstruction. With this study we hope to obtain a better understanding of the impact of BCRL on the QOL of breast cancer survivors with reconstructive breast surgery. Therefore, our aim is to explore the QOL in patients with or without BCRL who have undergone mastectomy alone or mastectomy followed by reconstructive breast surgery.

Methods

Patients

This study is part of a secondary analysis of a multicenter study analyzing the influence of breast reconstruction on the development of BCRL.¹³ A total of 283 patients, who underwent a unilateral mastectomy with or without a breast reconstruction between January 2006 and December 2010, were analyzed for the development of BCRL. Information on the surgical procedures (oncological and reconstructive), tumor characteristics and adjuvant medical treatment were obtained from hospital medical records. The Medical Research Ethics

Committee of the Maastricht University Hospital approved this secondary analysis.

A total of 274 (97%) patients gave written approval to be contacted for a secondary study. All patients were asked to participate in a standardized QOL interview. 21 patients were excluded because they could not be reached, had deceased, or refused to participate, resulting in a study population of 253 patients. In order to investigate the QOL in patients with BCRL, patients were divided into two groups: a non-BCRL group and a BCRL group.

The BCRL group consisted of patients with subjective complaints of arm swelling and/or an inter-limb volume difference of >200ml, or undergoing treatment for arm lymphedema. Subjective complaints of arm swelling were positive when patients said to have experienced swelling in the upper-limb on the breast cancer treated side in the past year. The inter-limb volume difference was measured using the water displacement method, which currently is considered as the gold standard.¹⁴

Quality of life questionnaires

Standardized interviews were conducted by telephone by one researcher (BB). Patients were surveyed using three validated QOL questionnaires: the Dutch version of the European Organization of Research and Treatment for Cancer (EORTC) QLQ-C30 version 3.0 with the EORTC QLQ-BR23 breast cancer supplementary module^{15–17} and The Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF).¹⁸ Permission to use the questionnaires for research purposes was granted.

EORTC QLQ-C30

The EORTC QLQ-C30 measures the QOL of cancer patients. As indicated by the EORTC answers were converted in to a 0-100 score on five functional scales: physical, role, emotional, cognitive and social functioning, a global health status scale and several symptom scales including: fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties. Due to the mean follow-up time of this study (51.7±18.5 months since mastectomy), the symptoms scales were not included in the analyses as they mostly relate to systemic therapy and their side effects. A lower score on the functional scales and the global health status scale correlates with a lower QOL.

EORTC QLQ-BR23

The breast cancer specific EORTC QLQ-BR23 consists of 23-items, divided into four functional scales – body image, sexual functioning, sexual pleasure and future perspective – and four symptom scales – arm symptoms, breast symptoms, systemic therapy side effects and upset by hair loss. Scoring is identical to the EORTC QLQ C-30 questionnaire. Systemic therapy side effects and upset by hair loss were not included in the analyses due to the mean follow-up time. The sexual functioning and the sexual pleasure domain were also excluded from analyses, as almost half of the population (44%) chose not to fill in the question or indicated not to be sexually active.

Lymph-ICF

The Lymphedema Functioning, Disability and Health questionnaire (Lymph-ICF) is a condition specific instrument, consisting of seven questions related to arm symptoms and twenty-two questions pertaining to impairments in function of activity of daily living (ADL). Per subscale patients were asked to score their level of complaints, on a scale of 0 to 10 centimeters, where 0 was comparable to no complaints and 10 to a lot of complaints to that specific question. Answers were converted in to a 0-100 score, where 1 cm corresponds with 10 points on the 0-100 score.

QOL measurements

The QOL was assessed in all patients using the three questionnaires. We compared the QOL scores at four different levels. The first comparison was made to assess the impact of BCRL on QOL in this cohort; the QOL scores in the non-BCRL group were compared to the QOL scores in the BCRL group. Furthermore, in order to obtain an understanding of the impact of BCRL on the QOL in breast cancer survivors who have undergone breast reconstruction, the following three comparisons were made: the QOL scores of reconstructive patients with mastectomy patients in the non-BCRL group, the QOL scores of reconstructive patients with mastectomy patients in the BCRL group and lastly, the QOL scores of reconstructive patients in the non-BCRL group with reconstructive patients in the BCRL group.

Statistics

SPSS for Windows 20.0 (SPSS Inc. Chicago, Illinois) was used for statistical analysis. For describing patient and clinical characteristics, descriptive statistics were used. Mean and standard deviation were reported in case of continuous variables, using the independent-samples t-test. Non-normal distributions were reported as median and ranges, the Mann-Whitney-Wilcoxon test was used for testing significance. Categorical variables were reported as number and percentages, for testing significance the chi-square test was used. Multiple linear regression analysis was used to adjust for potential confounders in the group of patients with reconstructive surgery, using a model containing each QOL domain as a separate outcome. The following confounders were used in the model: total number of lymph nodes removed during sentinel node biopsy and/ or full axillary clearance, BCRL, radiation treatment and chemotherapy. A P-value of <0.05 was considered statistically significant for all tests.

Results

Patient characteristics

Of the 253 patients, 116 (46%) underwent mastectomy alone and 137 (54%) had additional breast reconstruction. Patients with breast reconstruction were significantly younger ($p<0.001$), had a lower BMI at follow-up ($p=0.02$) and less frequently underwent axillary lymph node dissection ($p=0.00$). Mastectomy patients had a significantly higher level of history of seroma ($p=0.01$) and trauma to the arm ($p=0.03$). Interviews were performed after a mean follow-up of 51.7 (± 18.5) months post-mastectomy (table 1). Reconstructive surgery was performed in the same surgical session in 66% and secondarily in 34% of the total breast reconstructions. Tissue expander/implant reconstruction was done in 56%, autologous reconstruction in 39% and 5% of the patients had a combination of an implant and a latissimus dorsi flap.

Table 1. Patient characteristics

Variables	Total (n=253)	Mastectomy (n=116)	Reconstruction (n=137)	p-value
Age at mastectomy, mean (SD)	54.6 (10.1)	59.6 (10)	50.4 (8.1)	0.00
Age at FU, mean (SD)	58.1 (10.2)	63.2 (10.1)	53.8 (8.0)	0.00
BMI (kg/m ²) at FU, mean (SD)	27.0 (5.4)	27.8 (5.8)	26.2 (4.9)	0.02
Time since mastectomy, mean (SD), mo	51.7 (18.5)	52.8 (19.7)	50.9 (17.4)	0.28
Tumor stage, no (%)				0.16
pT0 – pT1	119 (48)	47 (40)	72 (54)	
pT2 – pT3	100 (39)	54 (47)	46 (33)	
ypT0 – ypT4	34 (13)	15 (13)	19 (13)	
Axillary surgery, no (%)				0.00
SNLB	131 (52)	55 (47)	75 (55)	
SNLB/ALND	117 (46)	61 (53)	56 (41)	
LN's removed, median [range]	5 [0 – 29]	10 [1 – 29]	3 [0 – 29]	0.02
Positive LN's removed, median [range]	0 [0 – 20]	0 [0 – 20]	0 [0 – 13]	0.03
BCRL (%)	75 (30)	38 (33)	35 (25)	
Dominant arm, no (%)	126 (50)	57 (49)	69 (50)	0.89
Seroma, no (%)	68 (27)	40 (34)	28 (20)	0.01
History of erysipelas, no (%)	17 (7)	10 (9)	7 (3)	0.26
History of injury, no (%)	10 (4)	8 (7)	2 (1)	0.03
Neo-adjuvant chemotherapy, no (%)	31 (12)	15 (13)	16 (12)	0.75
Adjuvant therapy, no (%)				
Chemotherapy	115 (45)	52 (45)	63 (46)	0.90
Trastuzumab	38 (15)	16 (14)	22 (16)	0.63
Radiation therapy	62 (24)	35 (30)	27 (20)	0.05
Hormone therapy	139 (55)	69 (59)	70 (51)	0.16

Abbreviations: SD; standard deviation, no; number, mo; months, FU; follow-up, BMI; body mass index, SLNB; sentinel lymph node biopsy, ALND; axillary lymph node dissection, LN's; lymph nodes

Characteristics of patients with BCRL

A total of 73 (29%) patients had subjective complaints of arm swelling and/or an inter-limb volume difference of >200ml or undergoing treatment for arm lymphedema, of which 38 (33%) were in the mastectomy group and 35 (25%) in the reconstruction group. The patients in the breast reconstruction group were significantly younger ($p<0.001$) and had significantly less lymph nodes removed ($p=0.05$) compared to the patients in the mastectomy group. Reconstructive surgery was performed in the same surgical session in 49% and secondarily in 51% of the patients. Autologous reconstruction was done in 58% of the patients, 31% had a tissue expander/implant and 11% received a combination of an implant and a latissimus dorsi flap.

Overall QOL scores: non-BCRL vs BCRL group

Significantly lower scores were found in the BCRL group on all domains of the three QOL questionnaires, as compared to the non-BCRL group. Figures 1 – 4 provide an overview of the mean scores arranged by type of surgery and BCRL status.

QOL scores in the non-BCRL group: mastectomy vs reconstruction

Patients with breast reconstruction scored significantly higher on the physical functioning domain ($p=0.004$).

QOL scores in the BCRL group: mastectomy vs reconstruction

No statistically significant differences were found.

QOL scores of reconstruction patients: non-BCRL vs BCRL group

Patients in the BCRL group scored significantly lower on all EORTC domains, except for two: future perspective ($p=0.10$) and breast symptoms ($p=0.15$). The women in the BCRL group also reported significantly more complaints on all domains of the Lymf-ICF questionnaire.

Multivariate Analysis

We further assessed the QOL domains in the group of women who had undergone breast reconstruction in a multiple linear regression, taking into account the presence of BCRL, total number of lymph nodes removed, radiation treatment and use of chemotherapy. After adjustment of these

covariates BCRL was significantly associated with a lower score on the following domains: physical function ($\beta = -7.46$; $p=0.009$), role function ($\beta = -15.75$; $p=0.003$), cognitive function ($\beta = -11.56$; $p=0.005$) and body vision ($\beta = -11.62$; $p=0.007$). Furthermore, BCRL was also associated with significantly higher scores on all domains of the Lymf-ICF questionnaire.

Figure 1-4. Median quality of life scores per domain shown by breast reconstruction and BCRL status.

Figure 3. Lymph-ICF scores

Figure 4. Lymph-ICF scores

Blue bar: mastectomy patients with BCRL, Green bar: reconstruction patients with BCRL, Yellow bar: mastectomy patients without BCRL, Red bar: reconstruction patients without BCRL.

Discussion

In this cross-sectional study, we report on the impact of BCRL on the QOL of breast cancer survivors with and without breast reconstruction. We included women who underwent autologous-, implant- and a combination of implant and latissimus dorsi flap reconstruction in the same surgical session as the mastectomy or secondarily. Irrespective of having undergone breast reconstruction, our data suggests that BCRL has a negative effect on the QOL of breast cancer patients. This is an important observation, as in plastic surgery most surgical procedures are aimed at improving the health related quality of life. In other words, BCRL can undo

the positive effect on the overall well-being of breast cancer survivors that is achieved with breast reconstruction.²¹⁻²⁴ However, when we compared the QOL outcomes of the women in the non-BCRL group, those who underwent breast reconstruction only scored higher on the physical domain, as compared to the women who only underwent a mastectomy. The expected benefit of breast reconstruction on the psychological- and emotional well-being is not seen in this group. This may be related to the effect of the time that had elapsed since surgery, which was circa 52 months. A study by Metcalfe et al., in which the changes in psychosocial well-being of women who underwent breast reconstruction and mastectomy alone were monitored over a period of approximately 6 years, reported a significant improvement in QOL in both groups over time.²⁵

Quality of life questionnaires

Despite the fact that the EORTC QLQ-C30 and the EORTC QLQ-BR23 were not specifically designed to be used among patients who have undergone reconstructive breast surgery, these were the most suitable QOL questionnaires available at the time this study was performed. These are valid and reliable questionnaires that can be used among breast cancer patients, and give good insight on the QOL of the research population.^{15,16} Moreover, we also used the disease-specific Lymf-ICF questionnaire which is a reliable and valid questionnaire that is used to assess impairments in function, activity limitations and participation restrictions of patients with arm lymphedema after breast cancer surgery.¹⁸ Currently, there are a few validated patient-reported QOL questionnaires available that can be used among breast reconstruction patients. The QLQ-BRR26, a new validated EORTC module specific for breast reconstructive patients, is developed as a supplement to the EORTC QLQ-C30 and the EORTC QLQ-BR23. This model also makes it possible to make a comparison of QOL among different breast reconstruction techniques.³⁰ Furthermore, the BREAST-Q is another QOL questionnaire that can be used in breast augmentation, breast reduction and breast reconstructive patients. The questionnaire measures the surgery-related QOL and is specifically designed to measure the satisfaction among breast augmentation, breast reduction and breast reconstructive patients. A disadvantage of the BREAST-Q is that the questionnaire was not developed to be used among mastectomy patients³¹, which is why it was not used in this study. The Michigan Breast Reconstruction Outcome Study Satisfaction (MBROS-S) questionnaire and the Breast-Related Symptoms Questionnaire (BRSQ) are two other QOL

questionnaires that can be used among breast reconstructive patients, but have limited validation for all breast reconstructive techniques.³²

Strengths and limitations

One of the strengths of this study is the long mean follow-up time of more than 4 years, which excludes patients with acute lymphedema and physical complaints occurring directly post-operatively or related to adjuvant therapy, resulting in a study population of only chronic BCRL patients. Petrek et al. showed that in most patients the onset of BCRL will develop in the first 4 years after treatment, probably making this study population with a mean follow-up of more than 4 year a representative group.³ The measurement of BCRL by using the use of the water displacement method, which is the gold standard for the measurement of BCRL, is another strength of this study. Furthermore, our study is the first to evaluate the QOL of breast cancer survivors after mastectomy alone and reconstructive breast surgery that have developed BCRL. However, several limitations of our study should also be mentioned. As a result of the cross-sectional design, measurements of baseline parameters immediately after surgery were not performed, making it impossible to measure the change in QOL. Shi et al reported the importance of a baseline measurement and showed that there is a significant improvement of QOL during the first years after surgery.²⁴ Secondly, not all psychological and socio-demographic influences such as educational level, employment status, financial difficulties were incorporated into this study. The health related quality of life is a multi-dimensional entity. Disease related characteristics such as time since mastectomy, radiation, chemotherapy, hormone therapy and tumor stage are not the only important confounding factors. Lee et al. has reported on the relevance of socio-demographic characteristics as confounding factors for the QOL.³³

Future directions

Due to the large impact of BCRL on the QOL of breast cancer survivors, a growing interest is shown for microlymphatic surgery as a potential treatment option for BCRL.^{33,34} In a systematic review we investigated the outcome of microlymphatic surgery, including lymphatic vessel transfer, composite tissue transfer and derivate surgery, on symptoms, limb circumference, limb volume and improvement of the lymphatic function.³⁶ The available literature shows positive results with regards to limb volume/circumference reduction. Furthermore, few complications after

microlymphatic surgery are reported.³⁵ These findings underline the importance of future research to further assess the effectivity of microlymphatic surgery as a treatment option for BCRL.

Conclusion

In conclusion, this study implies that BCRL has a negative effect on the QOL of breast cancer survivors, potentially negating the positive effects on QOL reconstructive breast surgery has. It is therefore imperative for the quality of breast cancer survivorship that research is continued on the subject of curative BCRL treatment options, such a microlymphatic surgery.

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Chapter 7

Microsurgical techniques for the treatment of breast cancer related lymphedema: a systematic review

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Abstract

Background: Upper limb lymphedema is one of the most underestimated and debilitating complications of breast cancer treatment. The aim of this review is to summarize the recent literature for evidence of the effectiveness of lymphatic microsurgery for the treatment of breast cancer related lymphedema (BCRL).

Methods: A search was conducted for articles published from 2000 onwards. Only studies on secondary lymphedema after breast cancer treatment and those examining the effectiveness of microsurgery were included. The following data was extracted: surgical intervention type, population size, follow-up time, BCRL classification, duration of BCRL, arm volume/circumference reduction, lymph-flow improvement, symptom relief, post-operative conservative therapy discontinuation and complications.

Results: No randomized clinical trials or comparative studies were available; ten case-series met inclusion criteria. Three surgical techniques were described: (composite) tissue transfer (n=4), lymphatic vessel transfer (n=2) and derivative microlymphatic surgery (n=4). Limb volume/circumference reduction varied from 2%- 50% over a follow-up time ranging from 1 to 132 months. Post-operative discontinuation rates of conservative therapy were only reported after composite tissue transfer, ranging from 33 to 100% after 3 to 24 months. Little to no complications were observed in all surgical techniques. Clear selection criteria for lymphatic surgery and lymphatic flow assessment were absent in most studies.

Conclusion: We identified the important methodological shortcomings of the available literature. Evidence acquired through comparative studies with uniform patient selection is lacking. Consistent positive findings with regards to volume/ circumference reduction and limited complications are reasons to further explore these techniques in methodologically superior studies.

Introduction

Upper limb lymphedema is one of the most underestimated and debilitating complications of breast cancer treatment. Hitherto, lymphedema treatment options have mainly been based on the lifelong application of a combination of conservative techniques, such as compression garments/bandages and manual lymph drainage.¹⁻³ Conservative therapy is initially aimed at alleviating symptoms without curative intent; with such treatment, some patients may achieve sufficient limb volume reduction and symptom relief. In cases of inadequate disease management, lymphedema may progress: arm-swelling transforming from a predominantly fluid encompassing entity to fibrosis and fat.^{4, 5} Lymphedema in its late chronic phase is irreversible and accompanied by more symptoms and physical impairments, consequently compromising the quality of survivorship.⁶⁻¹⁰ An alternative treatment option could be beneficial for patients that aren't responsive to standard conservative therapy. Lymphatic microsurgery could be such a treatment option, if treatment would be applied before lymphedema reaches its chronic, irreversible phase.

Derivative (super) microlymphatic surgery

Microlymphatic repair for lymph edematous limbs emerged with the development of reconstructive microsurgery in the late 1960's. The very first experimental studies reported, were in obstructive canine models. In these studies communications were created between the lymphatic and venous systems to divert static lymph fluid away from the obstruction site in a technique called lymphatic venous anastomoses.¹¹ The canine studies reported low and inconsistent patency rates as the result of this intervention, triggering the further development of the derivative microlymphatic technique. Refinements were made in order to reduce the chances of venous back flow and consequently bypass stenosis. However, limitations in the available microsurgical technology hampered the long-term establishment of viable anastomoses, as the pressure gradient between the lymphatic- and venous systems were still too high. Until the beginning of this millennium there was little progression in lymphatic surgical techniques. In the contemporary clinical field of microvascular surgery anastomoses with vessels as small as 0.3mm in diameter are possible, this also known as "super microsurgery". Because of these technical refinements it is now possible to create multiple bypasses between lymphatic vessels (ranging from 0.3mm- 0.5mm) and venular vessels (0.5mm) found in the subdermal plane of a lymph edematous limb. Anastomosing smaller vessels of the two vascular systems is hypothesized to ensure better bypass patency due to the

minor intra-vascular pressure differences.¹² Over the years evidence has been reported of lymphatic repair being effective in patients with secondary lymphedema of both the upper and lower extremities using lymphatic venular anastomoses.¹³⁻¹⁵

Tissue Transfer

Another technique to improve lymphatic drainage is the vascularized lymph node transfer with or without simultaneous free flap reconstruction.¹⁶ Experimental studies on lymph node transplantation in small animal studies have reported promising results of lymphatic function restoration, and with that, the facilitation of lymphedema resolution.^{17,18} Moreover, an alternative approach is achieved through the interposition of autologous tissue (i.e. lymph vessel), in which an attempt is made to restore flow within a damaged lymphatic system by bypassing the site of blockage. The transplanted lymph vessel(s) can function as a bridge connecting the afferent and efferent lymphatic vessels from the obstruction site.¹⁹

The recent movement towards the incorporation of evidence-based medicine into plastic surgery²⁰ has stressed the importance of good quality research as the core of the clinical decision making process. The primary aim of this systematic review is to summarize the recent literature for evidence of the effectiveness of lymphatic microsurgery for the treatment of breast cancer related lymphedema (BCRL). Specifically, the effect of surgery on upper-limb volume/circumference reduction, symptom relief, lymph flow improvement and the discontinuation of compression therapy post-operatively will be evaluated.

Methods

Literature search

An electronic literature search was conducted in MEDLINE and PubMed for literature published from January 2000 onwards. Three independent investigators (TLP, NH, CI) performed the search. The following search terms were used: lymphedema, lymphoedema, microsurgery, surgical treatment, breast cancer, lymph node transfer, lymphovenous anastomoses, lymphaticovenular anastomoses and lymph vessel transplantation. The search was limited to English, Dutch, German and French literature, while we also hand-searched reference lists of the relevant articles found. Abstracts were

scanned for relevance. Only the studies providing data of patients with secondary lymphedema after breast cancer treatment and those examining the effectiveness of microsurgical intervention were eligible for inclusion. Data from studies on primary lymphedema, lower extremity lymphedema and mixed groups of lower and upper extremity lymphedema were excluded. All articles were evaluated for duplicate reporting on the same patient population and if so removed.

Data extraction

The following data were extracted if available: surgical intervention type (lymph node transplantation, lymph vessel transplantation or derivative lymphatic surgery), size of the patient population, mean follow-up time, BCRL classification and stage, mean duration of BCRL before surgery, arm volume or circumference reduction, lymph flow improvement as quantified by lymphoscintigraphy, symptom relief (self-perceived pain, heaviness and erysipelas), discontinuation of post-operative conservative therapy (compression garments/bandages or manual lymphatic drainage) and complications (donor or recipient site morbidity).

Quality assessment

A detailed methodological quality assessment was conducted independently by three investigators (TLP, CI, NH). The case series were assessed using an 8-question checklist from The American Society of Plastic Surgeons (ASPS) for therapeutic studies.²¹ Each affirmative answer was a point. Thus, a total score of 8 was the maximum to be assigned per case series. The quality scores were compared and disagreements resolved by consensus.

Data analysis

The median and range of the methodological quality rating of all the studies combined, as well as the studies per surgical technique are provided. We compared the median quality ratings using the Mann-Whitney U test. A p-value < 0.05 was considered significant. Data-analysis was conducted using SPSS for Mac 17.0 (SPSS Inc. Chicago, Illinois).

Results

There were no randomized clinical trials or comparative studies available, thus we were limited to the inclusion of case-series. A total of 19 case-series were identified. Nine²²⁻³⁰ were excluded as they described either lymphedema of only the lower extremity²²⁻²⁵, a mix of lower and upper extremity lymphedema²⁶⁻²⁹ or a mix of primary and secondary upper extremity lymphedema.³⁰ The remaining 10 studies were included for assessment (Table 1). In these studies, three types of micro lymphatic surgery were described: composite tissue transfer, lymphatic vessel transfer and derivative surgery. The number of patients per case-series was small ranging from 6 - 24 women. However, one study reported evidence on 127 women.³⁵ Follow-up time varied amongst the studies, ranging from 5 to 72 months in articles evaluating derivative lymphatic surgery and 6 to 132 months in that of (composite) tissue transfer. Different measures were used to assess treatment outcome. These included reduction of limb volume³⁵⁻³⁹, circumference^{31, 33, 34, 37, 40} or symptomatology^{31, 32, 38-40} and improvement of lymphatic function quantified by lymphoscintigraphy.^{31, 33, 34, 36, 38-40}

Quality assessment

The median methodological quality rating of the 10 studies was 4.5 [range 2-5] (Table 1). The studies on (composite) tissue transfer had a higher median quality score compared to that of derivative techniques, respectively 5 [2-5] VS 4 [range 3-5]. However, this difference was not statistically significant $p=0.567$.

Microsurgical techniques

We were unable to pool the results of the included studies due to a few restricting factors. Firstly, the outcomes of interest were reported in a variable manner in much of the studies. Secondly, the patient populations of the selected studies were of heterogeneous nature. We have therefore presented a schematic overview of the important data.

Table 1. Methodological quality assessment of the case series reporting on lymphatic microsurgery for the treatment of BCRL.

Ref	Appropriate selection	Consecutive cases	Confounders addressed	Intervention performed similarly	Procedures performed by 1 surgeon	Valid & defined criteria for	FU time sufficient to detect outcome	No conflicts of interest	Total score
31	-	+	+	-	?	+	+	+	5
32	+	?	+	+	?	-	+	+	5
33	+	?	+	-	+	+	+	?	5
34	+	?	+	+	?	+	+	?	5
35	-	?	-	+	?	-	+	?	2
36	-	?	-	+	?	+	+	?	3
37	+	?	-	+	?	-	+	+	4
38	+	?	+	+	?	-	+	+	4
39	+	?	+	+	+	+	+	?	5
40	-	?	+	+	?	-	+	?	3

Abbreviations: Ref; reference, BCRL; breast cancer related lymphedema, FU; follow-up.

1. (Composite) tissue transfer

A total of four retrospective case series (n=52) on composite tissue transfer for the treatment of BCRL were identified (Table 2.). Three (n=39) described a similar operative technique: lymph nodes harvested at the inguinal site with the vascular structures and fat surrounding the superficial circumflex iliac vessels set in the axilla of the affected limb using the thoracodorsal vessels as recipient vessels.³²⁻³⁴ Of these three, Saaristo et al modified the technique by combining it with a DIEP/msTRAM free flap for simultaneous breast reconstruction. The technique described by Lin et al. differed from the other three in that the recipient site was the dorsal wrist of the affected arm instead of the axilla. Circumference reduction rate was provided by one study³¹, stating an average reduction of 51% at 4.7 years follow-up. As for symptom improvement, Becker et al. reported a reduction of pain in all 6 patients direct post-operatively and Lin et al. a reduction of the incidence of cellulitis in 11 of the 13 patients. Of the studies providing quantitative lymph flow assessment improvement was reported in all three.^{31,33, 34} Three studies reported the discontinuation rate of post-operative compression therapy, ranging from 33-100% 3 months to 2 years after surgery.³²⁻³⁴ No donor site morbidity was reported. Two studies (n=139) were identified reporting on lymph vessel transplantation for the treatment of BCRL. The largest series (n=127), a retrospective assessment by Baumeister et al. reported an average volume reduction of 22% at a follow-up of 31 months.³⁵ The rate of post-operative discontinuation of compression therapy was not addressed. As for post-operative complications, one case of donor site edema was reported.

2. Derivative (super) microsurgical techniques

A total of four prospective case-series (n= 47), evaluating derivative (super) microsurgery for the treatment of BCRL, met the inclusion criteria (Table 3). Three of the four studies reported a volume or circumference decrease greater than 30% at a follow-up time ranging from 5 to 72 months.^{37, 38, 40} Results were less favorable in a study by Damstra et al, reporting a limb volume reduction of 2% with accompanying unchanged lymphatic flow, 12 months post-operatively.³⁹ Three of the four studies showed improvement of symptomatic complaints post-operatively.³⁸⁻⁴⁰ Although only addressed by two studies, no post-operative complications were reported.^{38,40} Post-operative conservative therapy in the form of compression therapy and/or bandaging was continued indefinitely in all case-series.

Discussion

In this review we summarized the available literature on lymphatic microsurgery for the treatment of BCRL. We were primarily interested in the efficacy of derivative lymphatic surgery and (composite) tissue transfer on upper-limb volume or circumference reduction, relief of symptoms related to BCRL, lymphatic function and the discontinuation of conservative therapy post-operatively. Data could only be acquired through a mix of pro- and retrospective case series, as randomized or comparative studies were not available. This resulted in level IV evidence. With respect to the methodological quality, the studies on composite tissue transfer rated best when compared to that of lymph vessel transfer and derivative surgery (Table 1). Two criteria were most often associated with a low methodological rating. The first is incomplete information on the patient selection procedure for surgery. As differentiating between early non-fibrotic lymphedema and chronic lymphedema is an important outcome-determining factor recording of these lymphedema stages when selecting study patients is essential. Secondly, the post-surgical outcome assessment should not only include limb volume or circumference measurements, but should also be complemented with monitoring of lymphatic flow. Unfortunately, it was not possible to pool the results of the different studies included in this review, due to incomplete data documentation, but most importantly because of the large difference between the studies with respect to the criteria used for selecting patients for surgery. For example, only four studies stratified patients into lymphedema clinical stages before ensuing surgery, while the others did not take the pathophysiological nature of lymphedema into account, resulting in a heterogeneous patient population.

Primary outcomes

All but one study³⁹ noted consistent reduction of upper-limb volume or circumference reduction from surgical intervention through derivative lymphatic surgery^{37,38, 40}, lymph node transplantation³¹⁻³⁴ or lymphatic vessel transfer.^{35,36} Damstra et al., reporting on results after lymphatic venous anastomosis, measured a disappointing mean volume difference of 2% after one year. There are, however, two aspects in the methodology of this study that might have affected the outcome. Firstly, a surgical procedure according to Degni-Cordeiro was applied. This is a rather outdated technique originating from the early 1980's⁴¹, a period in which derivative lymphatic surgery had proven low bypass patency due to the intravascular pressure gradient. Secondly, the selection

criteria for the group of patients that would undergo derivative lymphatic surgery have affected the outcome of this study. It is stated by the authors that complete limb volume reduction was achieved in nearly half of the patient population when circumferential suction-assisted lipectomy was performed after the initial LVA operation. This suggests a chronic lymphedema stage. The natural progression of lymphedema sees to the change of limb swelling composition, from an at first predominantly fluid containing entity to the addition of fibrosis, fat and protein. So, even if the static lymph fluid is relieved, swelling still remains in the form of excess fat and fibrosis.^{42, 43} Furthermore, chronic lymphedema also suggests a prolonged hypertensive state within the lymphatic system. This phenomenon causes irreversible damage to the lymph vessels i.e. degeneration of smooth muscle cells^{44, 45}, rendering the lymph vessels incapable of lymph fluid propulsion. Therefore failure is inevitable in the attempts of producing patent lymphatic venous bypasses.

Aside from limb volume or circumference reduction, surgery effectiveness can be determined by lymphatic function. Lymphoscintigraphy can visualize lymphatic flow, providing qualitative information on lymph transport in the affected limb. Only half the studies^{31, 33, 34, 36, 39} assessed in this review evaluated the effect of lymphatic microsurgery on the lymphatic function. This is a major methodological flaw, as the ultimate aim of every lymphatic surgery should be to repair the function of the damaged lymphatic system. Moreover, in derivative surgery it is important to monitor lymphatic-venular bypass patency. Until recently there were no means of doing so. The use of indocyanine green fluorescence lymphangiography appears promising in this respect.^{46, 47}

The effect of surgery on symptom relief was not a main focus for many of the studies in this review. A specific decrease in neuropathic pain and in cellulitis rates was reported in two small populations after lymph node transplantation.^{31,}

³² As for the effect of derivative lymphatic surgery, a subjective relief of symptoms was noted in 50-100% of the patients in three studies.³⁸⁻⁴⁰

The discontinuation of post-operative conservative therapy was realized, although in variable rates, three to 24 months after surgery in the three studies evaluating inguinal lymph node transfer to the axilla of the lymph edematous arm.³²⁻³⁴ As reported^{31, 33}, the results were better when the duration of lymphedema was the shortest before lymph node transfer suggesting that this surgery cannot only be used as an alternative treatment for conservative therapy-resistant BCRL, but also as a curative up-front approach for lymphedema.

Table 2. Summary of studies on (composite) tissue transfer and derivative (super) micro lymphatic surgery for the treatment of BCRL

Ref	Intervention	Post-operative conservative treatment	n	FU in mo	BCRL classification & stage	Duration of BCRL	Results	Complications
31	IFP & nodes set in wrist	Not mentioned	13	56 [6-96]	-	2.8 years [4-84 mo]	C: 12/13 had reduction, mean of 51% [0-71%]. L: in all flow improvement. S: 11/13 had decrease cellulitis incidence C/V: lymphedema resolved in 5/6 pts. S: 100% reduction in pain scale.	Wound infection (n=1), venous congestion (n=1), no donor site morbidity
32	IFP & nodes set in axilla	No CG, MLD discontinued after 3 mo	6	21 [13-38]	No specification on staging type: I (n=4), II (n=2).	-	C: 6 >50% reduction, 6 < 50% reduction, 10 returned to normal, 2 unchanged. L: 5/16 flow improvement.	No donor or recipient site morbidity
33	IFP & nodes set in axilla, 2 nd procedure (n=7) IFP set in elbow	No CG, 62.5% stopped MLD after 12 mo	24	100 [60- 132]	- I (n=6) early edema, <2 infectious episodes, <30% difference. - II (n=18) edema > 1 year, >2 infectious episodes, difference 30-50%	- ≥ 1 year average of 5.6 years (n=18) - <1 year, average 5 months (n=6)	C: 6 >50% reduction, 6 < 50% reduction, 10 returned to normal, 2 unchanged. L: 5/16 flow improvement.	Lymphorrhea (n=8)
34	DIEP/msTRA M & IFP & nodes set in axilla after WLSE	33% discontinued MLD & CG after 8-24 mo	9	6	-	43 months [6-120]	C: 7/9 had reduction L: 5/6 had flow improvement	No donor site morbidity
35	Lymphvessels set in upper arm/supraclavicular region	CG for 6 mo	127	31	-	-	V: 22% average reduction	DVT (n=1), donor site edema (n=1)

36	Lymphvessels set in upper arm/supraclavicular region	CG for 6 mo	12	96	-	-	V: Reduction 22-31% L: 11/12 significant flow improvement (p<0.01)	-
37	MLVI	CT for first 6 mo	9	17 [15-22]	-	7.3 years [1-13]	C: 77.8% had >50% reduction	-
38	LVA	CT & CG continued indefinitely	20	12	Campisi classification: stage II (n=10) & III (n=10)	4.8 years [1-17]	V: 65% had reduction, average 35% S: 80% long term improvement	NR
39	LVA	CG continued indefinitely	10	12	Campisi classification: stage III (n=10)	5.3 years [3-14]	V: average reduction of 2% S: 50% improvement after 6 mo L: no improvement	-
40	MLVI	CG continued indefinitely	18	24 [12-72]	-	7.1 years [1-23]	C: distal arm average reduction 54% [0-100%], proximal arm average reduction 45% [7.1-76.5%] S: 100% improvement	NR

Time of follow-up and duration of breast cancer related lymphedema presented as mean and range.

Abbreviations: IFP; inguinal fat pad, V, results measured by arm volume; C, results measured by arm circumference; L, results measured by lymphoscintigraphy; S, results measured by symptom assessment; CG, compression garments; CT, compression therapy; Pts, patients; MLVI, microsurgical lymphaticovenous implantation; LVA, lymphaticovenous anastomoses, NR; none reported, Mo; months, WLSE; wide local scar excision

Even though we were limited to level IV evidence, a preference can be given to the inguinal lymph node transfer based on the reviewed literature. Not only was this the only technique that made the discontinuation of post-operative conservative therapy possible, it was also the technique described in better methodological quality studies compared to that of the other techniques. Furthermore, because this surgical procedure can be combined with autologous breast reconstruction it might be easier to incorporate it into current breast cancer management programs.

Conclusion

An overview is presented of the current evidence base for the effectiveness of lymphatic microsurgery for the treatment of BCRL. We have identified important methodological shortcomings of the available literature. Evidence acquired through comparative prospective studies with uniform patient selection is lacking. The consistent positive findings with regard to limb volume/circumference reduction and limited to no complications reported after microlymphatic surgery are, however, reasons to further explore these techniques in methodologically superior studies, perhaps answering the question as to when is the most appropriate time in the disease process for lymphatic surgery. We believe that the true contribution of micro lymphatic surgery for the treatment of BCRL will only be elucidated through protocolized treatment initiation by experienced micro surgeons. In our institution we are currently in the process of setting up a prospective study: an integrated care program in which breast cancer patients are prospectively screened for lymphedema and are structurally treated with conservative therapy followed by lymph node transplantation or derivative surgery in conservative treatment-resistant cases.

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Chapter 8

The changing role of axillary treatment in breast cancer: Who will remain at risk for developing arm morbidity in the future?

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Abstract

Introduction: Primary aim is to give an overview of changes in axillary staging and treatment of breast cancer patients. Secondly, we aim to identify patients with a high arm/shoulder morbidity risk, and describe a strategy to improve early detection and treatment.

Methods: Recent and initiated studies on axillary staging and treatment were evaluated and clustered for clinically node negative and clinically node positive breast cancer patients, together with studies on pathology, detection and (surgical) prevention and treatment of lymphedema.

Results: For clinically node negative patients, the indication for axillary lymph node dissection in sentinel node positive patients is fading. On the contrary, clinically node positive patients are routinely subjected to an axillary lymph node dissection, in combination with other therapies associated with an increased lymphedema risk, such as mastectomy, adjuvant radiation- and (taxane-based) chemotherapy. Techniques for prevention, early detection and (surgical) treatment of lymphedema are being developed.

Conclusion: Axillary staging and treatment in breast cancer patients with a clinically node negative status will become less invasive, thereby reducing the incidence of morbidity. Nevertheless, in patients with a clinically node positive status, aggressive treatment will still be required for oncologic control. For these patients, a surveillance program should be implemented in order to apply (curative) surgical treatment for lymphedema.

Introduction

Breast cancer treatment is in the process of moving towards an era of more conservative axillary treatment. Studies have shown that in selected patient populations, less extensive axillary surgery does not increase the regional recurrence rate, nor does it decrease overall survival.¹⁻³ The main advantage of a conservative approach towards axillary surgery is the reduction in treatment-related morbidity. Of all, lymphedema has the highest incidence amongst axillary treatment related morbidities in breast cancer and is perceived as disabling. Swelling of the affected arm, symptoms of heaviness, paresthesia and decreased range of motion contribute negatively to the quality of life.^{4,5} Studies have revealed several patient- and treatment related risk factors for breast cancer related lymphedema (BCRL), with most evidence pointing towards the axillary lymph node dissection (ALND) as an important risk factor. Other risk factors include greater number of dissected lymph nodes, mastectomy, high body mass index, adjuvant radiation therapy, and taxane-based chemotherapy.^{4,6}

For a long time, ALND was considered standard treatment for all breast cancer patients. Fifteen years ago, the sentinel lymph node biopsy (SLNB) replaced the ALND in patients with a clinically node negative status, resulting in significantly lower axillary morbidity rates, without compromising regional recurrence rates and overall survival.^{7,8} Completion ALND was up until shortly considered the standard treatment in patients with a positive sentinel lymph node (SLN). Currently, there is a decline in the indication for completion ALND in patients with SLN metastases, and the clinical relevance of the SLNB in certain patient groups is being debated.

The primary aim of this paper is to give an overview of current and expected future changes in axillary staging and treatment, and to estimate the impact of these changes on the incidence of arm/shoulder morbidity, and of BCRL in particular. Secondly, we aim to identify the group of patients still high at risk for BCRL and to describe a strategy to improve early detection and treatment.

The changing role of axillary staging and treatment

Clinically node negative breast cancer patients

The standard preoperative lymph node staging consists of physical examination of the axilla, and according to the ESMO breast cancer guideline, combined with an axillary ultrasound.⁹ If negative, a patient is considered clinically node negative, an SLNB is performed, and until recently, followed standardly by a completion ALND in patients with a positive SLN. The reported BCRL rate after completion ALND is 20%, and 6% after SLNB-only.⁴ Several randomized trials have been performed with the aim to investigate whether completion ALND in patients with metastatic SLNs could be replaced by less invasive treatment or even omitted. In the AMAROS trial, clinically T1-2N0 breast cancer patients with SLN metastases were randomized to completion ALND or axillary and periclavicular radiation therapy.³ This trial has demonstrated that axillary and periclavicular radiation therapy provided a five-year regional recurrence rate of 1.03% that is comparable to 0.54% in the completion ALND group. Most patients were treated with breast conserving therapy (82%) and received adjuvant systemic therapy (90%). At five years, the BCRL rate following axillary radiation therapy was significantly lower than following completion ALND based on clinical signs (11 vs. 23%; $p < 0.0001$), as well as based on an arm circumference increase of $\geq 10\%$ (6% vs. 13%; $p = 0.0009$). The higher BCRL rate in the completion ALND-arm might partly be explained by the fact that 6% of these patients underwent axillary and periclavicular radiation therapy as well, compared to 2% of patients in the radiation therapy-arm that received both therapies.³ In this subgroup of patients, the BCRL rate was 58%. Further, it is uncertain whether the stated advantage for axillary and periclavicular radiation therapy will persist over time, as side effects of radiation therapy evolve over a more prolonged time course than surgical side effects.¹⁰

In the ACOSOG Z0011 trial, clinically T1-2N0 patients with 1-2 macrometastatic SLNs treated with breast conserving therapy were randomized to completion ALND or no completion ALND.² Results revealed a regional recurrence rate of 0.9% at five years after treatment for patients in whom the completion ALND was omitted compared to 0.5% in the completion ALND group, while it was estimated that 27% of the patients had residual nodal disease.² Furthermore, overall survival was not compromised by not performing a completion ALND in this patient population. However, adjuvant systemic treatment was administered to 96% of the patients. Side effects such as seroma, paresthesia or

lymphedema, were reported in 70% of patients in the completion ALND-arm, and in 25% after SLNB alone in the first year after randomization ($p \leq 0.001$).¹¹

The IBCSG 23-01 trial also randomized clinically T1-2N0 patients to completion ALND or no completion ALND, though only in case of a micrometastasis in the SLN.¹ Breast conserving treatment was performed in 91% of the patients, mastectomy in 9% and adjuvant systemic treatment was administered to 96% of the patients. The ALND-specimen of patients in the control arm contained additional lymph node metastases in 11% of the cases, but again, the regional recurrence rate after omitting the completion ALND was low (1.1%) and comparable to the completion ALND group (0.2%).

The AMAROS, ACOSOG Z0011 and IBCSG 23-01 trial were underpowered, as events occurred less common than anticipated.¹⁻³ Nevertheless, these trials suggest that for clinically node negative breast cancer patients, a completion ALND is no longer indicated in case of 1-2 macrometastatic SLNs when treated with breast conserving therapy and adjuvant systemic treatment,² and neither in the case of a micrometastatic SLN when treated with mastectomy and adjuvant systemic treatment.¹ Furthermore, axillary- with or without periclavicular radiation therapy instead of a completion ALND might be beneficial in terms of morbidity risk for mastectomy patients with a macrometastasis in the SLN.³ Thus, the incidence of BCRL in the clinically node negative patient group is likely to decrease in the coming years due to omitting completion ALND in the majority of patients with SLN metastases. The incidence is expected to decrease even further in the future when results of several ongoing randomized trials become clear. One of these trials is the Dutch BOOG 2013-07 trial that randomizes clinically T1-2N0 breast cancer patients with macrometastatic SLNs treated with mastectomy, to completion axillary treatment or no further axillary treatment.¹² Several other independent randomized controlled trials are investigating the safety of omitting the SLNB in clinically T1-2N0 breast cancer patients with negative axillary ultrasound findings who are treated with breast conserving therapy: the Dutch BOOG 2013-08, the Italian SOUND, and the British SNIPE trial.¹³⁻¹⁵ The hypothesis that the SLNB could be safely omitted in this patient population derives from the fact that residual lymph node metastases in 11-27% of patients in the ACOSOG Z0011 and IBCSG 23-01 trials in whom completion ALND was omitted, did not result in a worse regional recurrence- and overall survival rate.^{1,2} Despite the developments of minimizing or even no longer performing invasive staging and treatment of the axilla, we should remain mindful that patients with a clinically node negative status could still develop BCRL with the risk ranging from 6 to

20%.⁴ As described earlier, type of breast surgery, a high body mass index, and adjuvant therapy could influence this risk.^{4,6}

Clinically node positive breast cancer patients

Breast cancer patients with preoperatively biopsy-proven nodal metastases or with palpable lymph nodes that are highly suspicious for malignancy, are considered clinically node positive.¹⁶ In most of these patients an ALND should be performed according to ASCO and ESMO guidelines.^{9,17} These patients are consequently at a high risk for developing severe BCRL, especially since a clinically node positive status is associated with a larger primary tumor, more often requiring a mastectomy, adjuvant chemotherapy and radiation therapy. Adjuvant chemotherapy is frequently indicated in patients with nodal metastases and in patients without nodal metastases but with poor prognostic factors based on primary tumor characteristics, such as tumor grade and diameter. Nowadays, chemotherapy schedules containing taxanes are standard of care. Several studies have shown that taxanes are associated with generalized edema during treatment that can persist and increase the risk of BCRL.¹⁸⁻²⁰ The indication for adjuvant radiation therapy of the chest wall, axilla and periclavicular region is based on the risk of disease relapse and type of breast surgery, but in case of a pathological node negative or N1 status, there is no consensus amongst European and North-American guidelines. Varying risk factors are used in the guidelines to indicate the need for adjuvant chest wall irradiation in mastectomy patients, such as large tumor size, a grade 3 tumor, angio-invasive growth and age below 40 years. Independent from the type of breast surgery, adjuvant periclavicular radiation therapy (combined with breast/chest wall) is recommended in patients with ≥ 4 lymph node metastases. A prospective study concluded that patients treated with radiation therapy of the breast/chest wall, axilla and periclavicular region have, after only two years of follow-up, a risk of BCRL ranging from 21% to 25% when combined with ALND.²¹ Remarkably, the one-year BCRL rate after completion ALND and axillary and periclavicular radiation therapy was much higher in the AMAROS trial, to note 59% and after five years 58%.³ This large difference in BCRL rate between these studies might partly be ascribed to different BCRL definitions and measurement methods. In the AMAROS trial, an increase in arm circumference of at least 10%, or any recorded sign of lymphedema was defined as BCRL,³ while Warren et al. only used standardized arm volume measurements to define BCRL as an arm volume increase of at least 10%.²¹

Furthermore, a difference in the lateral border of the axillary radiation field could also play a role. In the AMAROS trial, the axilla was irradiated with a broad anteroposterior field, and a smaller, laterally-localized, posteroanterior radiation field. In the study of Warren et al., it seems that periclavicular nodes were irradiated with a much smaller anteroposterior field, with sometimes an additional medially-localized posteroanterior field to treat axillary level 3. This corresponds with a study of Graham et al., who found that there was no increased risk of lymphedema if the lateral border of the supraclavicular field did not extend laterally from the coracoid process.²² BCRL due to radiation therapy is thought to develop by increasing fibrosis over the years, resulting in progressive obstruction and infiltration of lymphatic structures. The risk of BCRL is obviously further increased when lymph nodes and vessels are removed at surgery.

So, patients with a clinically node positive status and a large tumor size who are subjected to ALND, combined with mastectomy and radiation therapy of the chest wall, axilla and periclavicular region, and adjuvant chemotherapy should be considered as patients with a high risk for developing BCRL. Especially the combination of ALND and axillary radiation therapy seems to increase the risk of BCRL, but no randomized data are available on this specific issue. For these women, it is imperative that clinicians anticipate the development of severe arm morbidity and treat accordingly in order to maintain an acceptable quality of life. Although this “high-risk” group of women might be small in numbers when comparing to the women who will benefit from less extensive axillary treatment, arm lymphedema is a chronic disease that in most cases calls for lifelong treatment, loss of quality of life and potentially resulting in a substantial economic burden.²³

Pathology and early diagnosis of BCRL

Little is known about the exact pathophysiology of lymphedema and the time it takes for disease progression to take place, but what is clear is that progression is driven by hydrostatic and osmotic changes in the lymphatic system and accelerated by inflammation and infection.^{24,25} This leads to irreversible structural changes, such as interstitial fibrosis or atrophy of smooth muscle cells within the lymphatic walls, rendering the lymph vessels incapable of lymph fluid propulsion.²⁶ Nevertheless, early diagnosis and treatment initiation has proven to be more effective at reducing limb-volume.²⁷ The aforementioned points

substantiate the move from the current so-called impairment (symptom)-based model, in which the patient is the initiative taker, towards a surveillance-based model for diagnosing and treating upper-limb morbidities.²⁸ For BCRL this entails pre-operative distribution of precautionary information and limb-volume assessment. Even though there are no results of randomized trials available yet, the efficacy of such a surveillance model has been assessed in a prospective population-based study.²⁹ Pre- and postoperative upper-limb volume assessment allows the start of early lymphedema treatment, presumably resulting in more effective treatment and less cases of chronic lymphedema. Implementation of a breast cancer related arm morbidity surveillance program into standard care could reduce the burden and should find its base in appropriate clinical investigations.

Surgical interventions for lymphedema prevention and treatment

Axillary surgery is the biggest predictor for the development of lymphedema. In the hopes of limiting lymphatic damage in the upper-extremity, axillary reverse mapping (ARM) has been proposed as a technique to further refine axillary surgery.^{30,31} By mapping out the afferent lymphatic system of the upper-extremity using blue dye, a radioisotope, or indocyanine green as a tracer agent in conjunction with standard SLNB/ALND procedures, the lymph nodes draining the breast can be selected and removed. In theory, the ARM-procedure facilitates preservation of the lymphatic system draining the upper-extremity, thus reducing the risk of BCRL. An anatomical study assessing the relationship between the breast and the upper-extremity lymphatic drainage, reported a close relationship of the two systems with shared connections in 24% of the cases.³² This phenomenon is seen in clinical studies in which crossover of SLNB/ALND and ARM-nodes are reported, rightfully raising doubts on the oncological safety of the ARM technique.³³ Moreover, the efficacy of sparing ARM-nodes for reducing the incidence of BCRL has yet to be confirmed in long-term follow-up studies.^{34,35} As previously stated, achieving oncological radicality with preservation of the ARM-nodes is debatable. With that in mind Boccardo et al. developed the Lymphatic Microsurgical Preventative Healing Approach (LYMPHA) to be performed in conjunction with the ARM-procedure. In cases where crossover of SLNB/ALND and ARM-nodes are present in the axillary dissection plain, lymphatic venous anastomosis are made after dissection in order to restore the upper-extremity lymphatic drainage system. After a 4-year

follow-up, the Boccardo group reported a lymphedema incidence rate of 4% (3/74).³⁶ Although it concerns only a small study, these results are quite promising, when compared with the incidence of BCRL after ALND and SLNB, 20% and 6% respectively.⁴

For a long time, treatment of BCRL consisted of symptom control and maintenance with manual lymphatic drainage and compression garments. The Dutch breast cancer guideline suggests compression stockings for three months in case of a 5-10% limb-volume increase. The addition of compression therapy as part of complete decongestive therapy could induce significant limb-volume reduction.³⁷ When maximum limb-volume reduction is achieved, compression stockings should be worn to retain achieved results. These treatment strategies are without curative intent, which for most patients means lifelong treatment and a constant reminder of the breast cancer period. Published evidence for restoring normal lymphatic function in the damaged limb through microsurgery has triggered the idea that a curative approach to BCRL is possible. The most promising is the vascularized autologous lymph node transfer with or without simultaneous free flap reconstruction.³⁸ Once again, if lymphatic surgery could indeed repair the flow of a damaged lymphatic system after breast cancer treatment, surgery would need to be done when lymphatic vessels are still viable, with the aim of eliminating the need for life-long conservative treatment and making BCRL a disease less prevalent.

Conclusion

In conclusion, axillary staging and treatment in breast cancer patients with a clinically node negative status is becoming increasingly less invasive, thereby reducing the incidence of lymphedema of the arm, and increasing quality of life. Nevertheless, in some patients with a clinically node positive status, aggressive treatment will still be required for optimal oncologic control. For these patients, a surveillance program should be implemented in order to apply surgical treatments that are being developed to curatively treat lymphedema at an early stage.

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Chapter 9

General discussion

General discussion

Upper-limb lymphedema is one of the most debilitating chronic morbidities that can develop as a result of breast cancer treatment. Yet, there is little interest for this treatment-related complication amongst clinicians. Thankfully, the increase in focus on the quality of breast cancer survivorship has stimulated research on this topic. It is the opinion of the authors that both the detection of breast cancer related lymphedema (BCRL) and its treatment warrant improvement. This belief formed the driving force behind the initiation of the studies described in this thesis. In this thesis we focus on several important aspects of BCRL, such as the problems associated with its diagnosis, its effect on quality of life, and the possible role of reconstructive (breast) surgery in the pathophysiology and treatment.

Diagnosing Lymphedema

The research presented in this thesis is based on two separate cohorts of breast cancer survivors and on two overviews of recent literature. The women in the study cohorts were not prospectively assessed pre- and post-operatively after breast cancer surgery for the presence of BCRL, but the post-operative contralateral limb volume was used as a control for diagnosing BCRL. This outcome was combined with patient reports of self-perceived complaints known to be associated with BCRL. It is our opinion that with this method the patients with clinically relevant BCRL were identified, which ultimately is the target group for treatment. We understand that the lack of consensus regarding the diagnosis of BCRL is an important limitation in the research base of BCRL. An observation made when assessing the available BCRL literature is that it seems as if each researcher has adopted his/her preferred mode of lymphedema measurement as rule of law, as there are many available methods for measuring lymphedema. The consequence of this is described in Chapter 2, in which we demonstrate varying BCRL prevalence rates in one patient cohort when using four different modes of measurement. With this we underline the necessity for a consensus on the diagnostic criteria for BCRL. Furthermore, it is true that lymphedema assessment provides some challenges. This is in part due to differences in intra-observer reliability of the measurement techniques, the dynamic nature of the pathophysiology of lymphedema and also due to the discrepancy sometimes seen between patient perception and limb volume measurement. Volumetry, either being the classic water displacement method or the optoelectronic volumeter (Perometer), is considered the most reliable method for the assessment of lymphedema.¹ The optoelectronic volumeter is

gaining interest as the new gold standard for lymphedema assessment; Deltombe et al. have shown a slightly better intra-observer reliability for the Perometer when comparing it to the water displacement method.² Moreover, the usage of infrared light instead of water, results in a convenient and faster limb volume assessment. These points make the Perometer an attractive substitute for the water displacement device. However, the advantage of the water displacement method is that it is more cost-effective and the most applied method and readily available device in Dutch institutions. Also, there is sufficient evidence reporting comparable (high reliability) results with that of the Perometer.³⁻⁵ Our research group has assessed three-dimensional imaging as a novel approach for limb volume measurements. In this study the validity and reliability of the 3D camera was assessed by measuring arm volume in healthy volunteers and by using water volumetry as the gold standard.⁶ 3D measurements appeared to be as reliable as water volumetry, with a high intra- and inter rater reliability of both 0.99.⁶ But, as in case with the Perometer, and unlike the water displacement technique, the hand is not incorporated into the volume measurements by 3D imaging. Not having the hand included in the 3D limb volume measurement does not necessarily have to be problematic, as it can be combined with a simple circumference measurement of the dorsum of the hand. 3D imaging is yet to be validated in patients with lymphedema.

In the clinical evaluation of lymphedema the focus should not only be put on volume changes. Although volume is important and is the most objective current clinical measure, using only volume may overlook a few important points, such as: tissue texture changes and the symptoms that patients experience. Firstly, the latent stage of lymphedema preceding the increase in volume can go unnoticed if one only focuses on volume changes.⁷ Ideally, to objectively determine the stage, lymphedema assessment should also take place on a histological level. In Chapter 4 the possible role of the Cutometer device for testing and monitoring biomechanical changes in the lymphadematous skin was evaluated. The results of this study show a significantly lower elasticity of the skin in upper-limb lymphedema. In healthy women no difference was found in the skin elasticity of both arms. This finding is supported by the theory that there is an increase in volume of the subcutaneous tissue in BCRL that affects the skin by increasing its tension at rest.¹⁵ It is hypothesized that the proportional changes within the tissue result in modification of the intermolecular bridging and thickening of the collagen bundle.¹⁶ The clinical use of the Cutometer as a diagnostic or follow-up tool warrants further investigation in a prospective setting with a larger population. A tool currently being used in the assessment of the early stages of BCRL when

swelling predominately consists of extracellular lymph fluid⁸⁻¹⁴ is the bioelectrical impedance spectroscopy (BIS), as it can accurately differentiate extracellular fluid from tissue. Secondly, because there is poor agreement between patient perception and objective measures¹⁷⁻²⁰, patient perceptions should be investigated for their relationship with the pathophysiology of BCRL. The discrepancy between complaints and symptoms could for example be explained by sensory changes in the treated limb due to neurological damage caused by (even limited) axillary surgery or radiation treatment.²⁰ Thus, questions that remain to be answered are: how do we differentiate sensory neuropathy as a consequence of surgery/radiation from that of numbness and tingling experienced by patients with lymphedema? Furthermore, does the inflammatory process activated by tissue injury as seen in BCRL^{21, 22} also cause dysfunction of the sensory nerves located in the epidermis? Currently, there are no studies that explore the symptoms caused by sensory nerve dysfunction in the context of the pathophysiology of BCRL.

Burden of disease

One of the most important risk factors for the development of BCRL is the axillary lymph node dissection (ALND).²³⁻²⁶ For a long time, ALND was considered standard treatment for all breast cancer patients. Around 15 years ago, the sentinel lymph node biopsy (SLNB) replaced the ALND in patients with a clinically node negative status, resulting in lower axillary morbidity rates, without compromising regional recurrence rates and overall survival.²⁷⁻²⁹ However, BCRL rates after SLNB are not negligible. One of the largest RCT's comparing morbidity rates between SLNB and ALND reported a BCRL incidence rate of 7% after three years in patients having undergone SLNB.³⁰ Furthermore, a review of SLNB procedure specific BCRL incidence rates by Shah et al. reported a range of 3% -23%.³¹ In Chapter 3 the long-term health-related quality of life (HRQOL) of breast cancer patients with BCRL surviving more than 5 years after diagnosis, was assessed using the EORTC QLQ-C30 and QLQ-BR23 in the SLNB-era. Half of the women in this cohort underwent a SLNB (76/145). Of these 76 women, five were diagnosed with BCRL, which equals to a 6.6% rate in the SLNB patients. After adjustment for BMI and age, the women with BCRL scored lower on the social functioning scale when compared to the women without BCRL. Moreover, the presented cohort as a whole scored lower on a majority of the functioning scales, compared to scores in the general Dutch population. However, it was only the BCRL group that

scored significantly lower on role- and social functioning. A prospective study comparing the long-term HRQOL of patients undergoing SLNB alone versus ALND observed that women reporting arm lymphedema themselves, both in the presence of or without objectively measured lymphedema, scored lower on all HRQOL domains.¹⁷ Thus, clinicians should be perceptive of and receptive to subjective reports of symptoms which might be related to lymphedema. This is a further plea for investigating the relationship between patient perceptions and the pathophysiology of BCRL.

In plastic surgery most surgical procedures are aimed at improving HRQOL. There is evidence that reconstructive breast surgery has a positive effect on the overall wellbeing of breast cancer survivors.^{32–36} However, it is of interest to know if this positive effect is also present in patients with BCRL after breast reconstruction. In a cross-sectional study in chapter 5, we reported on the impact of BCRL on the HRQOL of breast cancer survivors with and without breast reconstruction. We included women who underwent autologous reconstruction, an implant-based reconstruction and a combination of an implant and latissimus dorsi flap reconstruction in the same surgical session as the mastectomy, or secondarily. Irrespective of having undergone breast reconstruction, our data suggest that BCRL has a negative effect on the QOL of breast cancer patients. Thus, it goes without saying that BCRL has a negative impact on the HRQOL of breast cancer survivors. However, some believe that BCRL will be a problem of the past as breast cancer treatment is in the process of moving towards an era of increasingly conservative axillary treatment. Many patients have already benefited from the introduction of the SLNB and many more patients with clinically node negative breast cancer are likely to benefit from developments aimed at further reducing axillary treatment. Results of Z0011 trial suggest that a completion ALND is no longer indicated in case of 1-2 macrometastatic sentinel lymph nodes (SLN) when the patient is treated with breast conserving therapy and adjuvant systemic treatment³⁷, and neither in the case of a micrometastatic SLN when the patient is treated with mastectomy and adjuvant systemic treatment.³⁸ Furthermore, axillary radiotherapy with or without periclavicular irradiation, instead of a completion ALND was reported to be beneficial in terms of the morbidity risk for mastectomy patients with a macrometastasis in the SLN.³⁹ However, it is uncertain whether the stated advantage for axillary and periclavicular radiation therapy will persist over time, as side effects of radiation therapy tend to evolve over a more prolonged time course than surgical side effects.⁴⁰ Furthermore, patients with a clinically negative axillary status are still at risk of developing BCRL, with percentages ranging from 6 to 20%.²⁶ The type of breast surgery, a high body mass index,

and use of radiotherapy and adjuvant systemic therapy can influence this risk.^{26,41} A further specific subgroup which will remain at a significant risk of developing BCRL are the patients with clinically positive axillary lymph nodes. These patients usually present with large tumors, more often requiring a mastectomy, adjuvant hormonal treatment and/or chemotherapy^{42–44} and radiation therapy^{45–47} of the chest wall, axilla and periclavicular region. Especially the combination of ALND and axillary radiation therapy is known to increase the risk of BCRL.⁴⁶ For these women, it is imperative that clinicians anticipate the development of severe arm morbidity and treat accordingly in order to maintain an acceptable quality of life. Thus, we must move away from the current so-called impairment (symptom)-based model, in which the patient is the initiative taker, towards a surveillance-based model for diagnosing and treating BCRL.⁴⁸ This should entail pre-operative distribution of precautionary information and pre- and postoperative limb-volume and symptom assessment.^{49–52} The Implementation of a BCRL surveillance program into standard care could reduce the burden and should find its base in appropriate clinical investigations.

Reconstructive surgery and lymphedema

Reconstructive breast surgery is now clearly established in the arsenal of breast cancer management. Currently, autologous and implant based reconstructions are widely performed either in the same (oncologic) surgical session or secondarily. The wide application of reconstructive breast surgery has raised the question whether these procedures might have an effect in the development of BCRL. Current literature provides some evidence for a protective effect of breast reconstruction on the development of BCRL.^{53–56} Our findings in Chapter 5 are in line with the current body of evidence; after multivariable analysis breast reconstruction was associated with a lower risk of having BCRL. Although, there are also studies that have reported no effect of reconstructive breast surgery on the incidence of BCRL.^{57,58} Moreover, it is most unlikely that a randomized study will ever be performed with the aim to determine the effect of reconstructive breast surgery on the risk of developing BCRL.

Studies on reconstructive surgery in the context of a potential curative treatment option for BCRL is of interest, especially for patients who are not responsive to standard conservative therapy. A variety of techniques is described in the literature, such as derivative microsurgery in the form of lymphatic venular anastomoses^{59–64} and composite tissue transfers containing vascular structures and lymph nodes^{65–70} with varying outcomes on limb volume/circumference. Evidence acquired through comparative prospective studies with uniform patient selection is lacking. The consistent positive findings with regard to limb volume/ circumference reduction and limited to no complications reported after microlymphatic surgery are, however, reasons to further explore these techniques in methodologically superior studies, perhaps answering the question as to when is the most appropriate time in the disease process for lymphatic surgery. We believe that the true contribution of micro lymphatic surgery for the treatment of BCRL will only be elucidated through protocolized treatment by experienced micro surgeons.

Concluding Remarks

In this thesis we focused on lymphedema of the arm. However, experience gained through conducting the studies presented in this thesis has taught us that swelling of the trunk, breast and axilla is also considered problematic by those who experience it. Means of objectively measuring and monitoring lymphedema in these anatomical locations is technically challenging. Hopefully in the future, as our knowledge grows on the exact etiology and pathophysiology of BCRL we will be able to provide a solution for this problem. Perhaps the Cutometer device will find its place, after further confirmation of the before described results (chapter 4) in larger clinical studies, in the diagnosis of lymphedema of the trunk, breast and axilla.

With regards to the management and treatment of BCRL, a structured approach is lacking in the national breast cancer standard of care. In most hospitals patients have to take the initiative themselves to seek help of a lymph therapist, as the treating physician often pays little attention to post-breast cancer treatment arm morbidities. Saying this, an integrative BCRL surveillance program that combines pre- and post-operative limb measurements and patient education on lymphedema symptoms should be implemented in standard breast cancer care to assist in the early identification^{49–52} and treatment of lymphedema, especially for high-risk patients. Pre-operative limb measurements are especially important to allow the identification of early

symptoms and of small post-operative changes in limb volume.^{71,72}

Furthermore, the effectivity of lymphatic microsurgery to prevent or treat BCRL warrants further investigation in a randomized controlled trial (RCT) comparing it to the current gold standard of conservative therapy. With this, we will also be able to retrospectively formulate clinical criteria to select patients who will benefit mostly from new treatment strategies, including lymphatic microsurgery.

Implementing a multidisciplinary BCRL screening program into standard of care and setting up a RCT are costly and not possible without the help of external funding. Unfortunately, the opinion that BCRL is and will remain a relevant problem amongst breast cancer survivors is not shared amongst the majority of those in charge of distributing national grant funding for research. It is the goal of the authors to further pursue research on the topic of BCRL and ultimately obtain enough evidence to enthuse these non-believers.

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Summary

Summary

Summary

In **chapter 1**, an introduction on breast cancer related lymphedema (BCRL) is provided as well as the outline of the thesis. Focus is placed on certain important aspects of BCRL, such as issues associated with its diagnosis, its effect on the quality of life, and the possible role reconstructive (breast) surgery plays in its treatment and pathophysiology. The aim of this thesis was to gain better insight on the above-mentioned aspects in order to substantiate the need for improvement of lymphedema management amongst breast cancer survivors.

Chapter 2 describes the long-term prevalence of BCRL using four different commonly used measuring methods in a cohort of breast cancer survivors five years after oncological surgery. The prevalence varied significantly depending on the method used for lymphedema assessment. This data underlines the necessity for consensus on the diagnostic criteria for BCRL.

In **chapter 3** data are presented that show that the health related quality of life (HRQOL) of long-term breast cancer survivors with BCRL is significantly lower compared to breast cancer survivors without BCRL and also significantly lower compared to normative data representing the Dutch speaking population in the Netherlands within the same age category. The women in the study cohort were all treated in the sentinel lymph node biopsy (SLNB) era. These results demonstrate the clinical relevance of BCRL as a morbidity of the upper-limb, despite of the less invasive axillary surgery performed in the SLNB-era.

Ultra-structural research has given insight on the progressive nature of BCRL: tissue injury induces the accumulation of inflammatory cells, which ultimately leads to fibrosis and degeneration of smooth muscle cells in the lymphedematous tissue. The above-described pathogenesis process implicates a role of biomechanical skin changes within the development of BCRL. In **chapter 4** the biomechanical skin changes of patients with BCRL are presented using a Cutometer® for assessing skin-elasticity and visco-elasticity, and the Corneometer® for the assessment of skin-hydration. Data of this study give evidence of a reduced elasticity of the skin of the affected limb in BCRL, suggesting the use of the Cutometer® device in the diagnostic evaluation of BCRL in which a continued decrement in the skin elasticity may be an indication of further progression of lymphedema.

Breast reconstruction is an important component of rehabilitation after ablative breast surgery. These procedures do not only provide good aesthetic results,

Summary

but have also been demonstrated beneficial with regards to quality of life and body image without interfering with cancer management. The wide application of reconstructive breast surgery has raised the question whether it should be considered as a risk factor or protective factor for the development of. **Chapter 5** investigated whether women who underwent breast reconstruction, as part of their breast cancer treatment, were less likely to develop BCRL. 130 women who underwent unilateral mastectomy and axillary lymph node dissection (ALND) with or without immediate or delayed breast reconstruction between January 2006 and December 2010 were included in this study. After multivariable adjustment breast reconstruction was associated with a significantly lower BCRL risk, this being of interest for the surgical decision making process.

In **chapter 6** data are presented that show that the HRQOL of breast cancer survivors who have undergone breast reconstruction and have BCRL is significantly impaired, negating the positive effects reconstructive breast surgery might have on the HRQOL.

Chapter 7 presents a systematic review that was undertaken to give an overview on currently available literature on the effectiveness of lymphatic microsurgery for the treatment of BCRL. In this review it was concluded that composite tissue transfer and derivative microlymphatic surgery may be a promising treatment option that provides limb volume/circumference reduction. This systematic review identified the important methodological shortcomings of the available literature.

In **chapter 8** an overview of the changes in axillary staging and its implications on the development of arm morbidity for the future is given. It was concluded that clinically node negative breast cancer patients would have a reduced risk due to less invasive axillary staging and treatment. Nevertheless, in patients with a clinically node positive status, aggressive treatment will still be required for oncologic control. These patients should be considered at high risk for developing BCRL.

Finally, **chapter 9** provides the general discussion with conclusions following from this thesis.

Summary (in Dutch)

Summary (in Dutch)

Samenvatting

In **hoofdstuk 1** wordt de opzet van het proefschrift beschreven en een introductie over “breast cancer related lymphedema (BCRL)”, oftewel lymfoedeem van de arm na behandeling van borstkanker, gegeven. Enkele belangrijke aspecten van de pathofysiologie en de behandeling van BCRL worden besproken, zoals problemen omtrent de diagnose, het effect op de kwaliteit van leven en de mogelijke rol van reconstructieve (borst-)chirurgie. Het doel van dit proefschrift was om een beter inzicht te verkrijgen in bovengenoemde aspecten en zodoende een verbetering van de zorg van borstkanker patiënten te waarborgen.

In **hoofdstuk 2** wordt de prevalentie van BCRL, vijf jaar na de behandeling voor borstkanker, beschreven. In een cohort van 145 borstkankerpatiënten, werd de aanwezigheid van lymfoedeem gemeten met behulp van vier verschillende meetmethodes: volumetrie, omtrek meting, som van arm omtrek metingen en subjectieve klachten patroon. De prevalentie van BCRL varieerde significant, afhankelijk van de methode die werd gebruikt om het lymfoedeem te bepalen. De gepresenteerde data benadrukken het gebrek en de behoefte aan een consensus omtrent diagnostische criteria voor BCRL.

In **hoofdstuk 3** wordt aangetoond dat de kwaliteit van leven, oftewel de quality of life (QOL) van borstkanker patiënten mét BCRL significant lager is dan die van overlevenden zónder BCRL en tevens significant lager is dan de QOL van vrouwen in de algemene Nederlandse populatie in dezelfde leeftijdscategorie. De vrouwen in het studiecohort zijn allemaal in het sentinel lymfklier biopsie (SNB) tijdperk behandeld en hebben dientengevolge minder uitgebreide okselchirurgie ondergaan. Ondanks de beperkte okselchirurgie, bevestigen deze resultaten dat, de morbiditeit van BCRL in het SNB tijdperk substantieel is.

De ontwikkeling van lymfoedeem en de progressieve aard van de aandoening wordt gekenmerkt door een aantal opeenvolgende pathofysiologische processen. Het proces wordt geïnitieerd doordat weefselschade activatie van inflammatoire cellen veroorzaakt, wat uiteindelijk fibrosering en vervolgens degeneratie van gladde spiercellen en oedemateuze huid veroorzaakt. Het hierboven beschreven proces impliceert het optreden van biomechanische huidveranderingen in de pathogenese van BCRL. In **hoofdstuk 4** worden deze biomechanische huidveranderingen van patiënten met BCRL gepresenteerd met behulp van de Cutometer® voor bepaling van huidelasticiteit en visco-

elasticiteit en de Corneometer® voor bepaling van de hydratatie van de huid. Data van deze studie hebben aangetoond dat er een significant verminderde huidelasticiteit aanwezig is in de aangedane arm bij patiënten met BCRL. Dit impliceert het gebruik van de Cutometer® als een diagnosticum bij de evaluatie van BCRL, waarbij een progressieve vermindering van de huidelasticiteit mogelijk duidt op het ontstaan of progressie van het lymfoedeem.

Tijdens of na de behandeling van borstkanker kiezen steeds meer vrouwen voor een borstreconstructie, waardoor de reconstructieve chirurgie een belangrijk onderdeel van de borstkankerbehandeling is geworden. Deze ingrepen zorgen niet alleen voor een verbeterde esthetiek, maar blijken ook een gunstig effect te hebben op de QOL en het lichaamsbeeld van deze patiënten, zonder hierbij te interfereren met de oncologische behandeling. De brede toepassing van reconstructieve borstchirurgie heeft geleid tot de vraag of er een associatie is tussen borstreconstructie en de ontwikkeling van BCRL. In **hoofdstuk 5** is de invloed van borstreconstructie als onderdeel van borstkankerbehandeling op het ontwikkelen van BCRL onderzocht. Honderddertig vrouwen die een unilaterale mastectomie met een okselklierdissectie (OKD) hebben ondergaan, met of zonder reconstructieve borstchirurgie, tussen januari 2006 en december 2010 werden geïnccludeerd in deze studie. Multivariate analyse toonde een protectieve associatie tussen borstreconstructie en BCRL. Deze interessante bevinding is van belang voor de chirurgische besluitvorming en verdient verder onderzoek.

In **hoofdstuk 6** wordt aangetoond dat de QOL van borstkankeroverlevenden die reconstructieve borstchirurgie hebben ondergaan en daarbij BCRL hebben ontwikkeld significant verminderd is ten opzicht van borstkankeroverlevenden zonder BCRL na reconstructieve borstchirurgie. Deze data impliceren dat BCRL het mogelijke positieve effect van borstreconstructie op de QOL teniet doet.

Hoofdstuk 7 is een systematische review welke de huidige literatuur omtrent de effectiviteit van lymfatische microchirurgie als behandeling voor BCRL behelst. Deze review concludeert dat gemengde weefseltransplantaties, welke dus onder andere lymfeklieren bevatten, alsook lymfe-veneuze anastomoserings mogelijke behandelingsopties zijn die voor volume-/omtrekreductie zorgen van ledematen aangedaan door BCRL. Tevens identificeert deze review de belangrijke tekortkomingen van de huidige literatuur en dientengevolge de behoefte aan research op dit gebied.

In **hoofdstuk 8** wordt een overzicht gegeven van de huidige veranderingen die plaatsvinden in de borstkankerbehandeling met betrekking tot de oksel. Er is momenteel een trend naar minder invasieve okselchirurgie ter stadiering en behandeling van borstkanker patiënten. Diverse studies naar de oncologische veiligheid en de verwachte gevolgen van minder invasieve okselchirurgie op de ontwikkeling van BCRL zijn opgezet en de resultaten zullen over enkele jaren bekend zijn . In hoofdstuk 8 wordt geconcludeerd dat het risico op BCRL zal afnemen bij borstkankerpatiënten die klinisch geen axillaire metastasen hebben. Toch zullen vrouwen met positieve axillaire lymfeklieren een agressieve behandeling moeten ondergaan met het oog op behoud van oncologische controle. Deze patiëntengroep moet beschouwd worden als een hoog risicogroep op het ontwikkelen van BCRL.

Hoofdstuk 9, tenslotte, bevat de algemene discussie met de uit deze thesis voortvloeiende conclusies.

Summary (in Dutch)

Valorization

Introduction

Approximately one in eight women in the Netherlands will develop breast cancer during her lifetime. Fortunately, due to the implementation of population based screening programs, advancements in treatment options and increased awareness, a large proportion of these women will go on to survive the initial treatment phase. The fact that more women are successfully being treated for breast cancer has caused a shift of attention towards the period after active cancer treatment, also known as the period of survivorship. Survivorship refers to the end of active cancer therapy, a period in which late effects of cancer treatment are prevalent. In saying this, the management of the late effects of breast cancer treatment is imperative for maintaining an acceptable long-term quality of life. In the scope of upper-arm morbidities as part of the late effects of breast cancer treatment, lymphedema has the highest incidence and is perceived as disabling. Swelling of the affected arm, symptoms of heaviness, paresthesia and decreased range of motion contribute negatively to the quality of life. Between 6% - 43% of breast cancer survivors develop breast cancer related lymphedema (BCRL). Studies have revealed several patient- and treatment related risk factors for BCRL, with most evidence pointing towards the axillary lymph node dissection (ALND) as an important risk factor.

In this chapter the focus is put on the economic and societal benefits of the knowledge acquired through the studies gathered in this thesis.

Relevance of scientific results

This thesis addressed several important aspects of BCRL, such as the problems associated with its diagnosis, its effect on quality of life, and the possible role of reconstructive (breast) surgery in the pathophysiology and treatment.

Most importantly, we were able to conclude that BCRL is and will remain a relevant problem amongst breast cancer survivors. Currently, axillary staging and treatment in breast cancer patients with a clinically node negative status is becoming increasingly less invasive, thereby reducing the incidence of lymphedema of the arm. Nevertheless, in patients with a clinically node positive status, aggressive treatment will still be required for optimal oncologic control. Although this “high-risk” group of women might be small in numbers when

comparing to the women who will benefit from less extensive axillary treatment, BCRL is a chronic disease that in most cases calls for life long treatment, decrease in quality of life and potentially resulting in a economic burden. Therefore, we advice implementing a BCRL surveillance program into standard breast cancer care in order to facilitate early lymphedema treatment.

With regards to the treatment of BCRL, a structured approach is lacking in the national breast cancer standard of care. In most hospitals patients have to take the initiative themselves to seek help of a lymph therapist, as the treating physician often pays little attention to post-breast cancer treatment arm morbidities. Saying this, an integrative BCRL surveillance program that combines pre- and post operative limb measurements and patient education on lymphedema symptoms should be implemented in standard breast cancer care to assist in the early identification and treatment of lymphedema, especially for high-risk patients. Pre-operative limb measurements are especially important to allow the identification of early symptoms and of small post-operative changes in limb volume. Furthermore, the effectivity of lymphatic microsurgery to prevent or treat BCRL warrants further investigation in a randomized controlled trial (RCT) comparing it to the current gold standard of conservative therapy. With this, we will also be able to retrospectively formulate clinical criteria to select patients who will benefit mostly from new treatment strategies, including lymphatic microsurgery.

Target population

The results of this thesis are relevant for investigators in the medical field with special interest in breast cancer, morbidities related to breast cancer, lymphedema and quality of life. In addition, this thesis is of interest to (surgical) oncologists, plastic surgeons, lymphedema therapists, dedicated nurses and lymphedema-patient platforms.

Knowledge utilization and innovation

As previously mentioned, a multidisciplinary BCRL screening program should be implemented in breast cancer standard of care. This will especially be important for “high-risk” patients. Through this approach of secondary prevention of BCRL we will not only be able to treat lymphedema more

effectively but also learn more about its pathophysiology. The idea of moving away from the current so-called impairment (symptom)-based model, in which the patient is the initiative taker, towards a surveillance-based model is an innovative concept in Dutch breast cancer care. In the US a few hospitals have already adopted this approach as standard of care with evidence of being potentially cost saving compared to the traditional treatment of BCRL.

The place of lymphatic microsurgery in the treatment of BCRL is yet to be established in comparative prospective studies with a uniform patient group. This is ultimately one of the most important goals of our research group.

Appendix

Scientific output

Acknowledgements (in Dutch)

About the author

Scientific output

TR Lopez Penha, B Botter, EM Heuts, AC Voogd, MF von Meyenfeldt, RRWJ van der Hulst. Quality of life in patients with breast cancer related lymphedema and reconstructive breast surgery. *Journal Reconstr Microsurg* (submitted)

RC Killaars, **TR Lopez Penha**, EM Heuts, AA Piatkowski de Grzymala, RRWJ van der Hulst. Biomechanical properties of the skin in breast cancer patients with upper-limb lymphedema compared to healthy individuals. *Lymphat Res Biol* 2015. Sep;13 (3):215-21.

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Het is eindelijk af!

About the author

Tiara Rebecca Lopez Penha was born the youngest of three siblings on March 11th 1986 in St.Maarten, Netherlands Antilles. In June of 2004 she graduated from the Milton Peters College with a VWO diploma. Subsequently, she moved to the Netherlands to pursue her secondary education at the Maastricht University.

She received her medical degree at the Maastricht University in September 2010. During her final year at university she did a research internship on the subject of Breast Cancer-related lymphedema under the guidance of Prof.dr. M.F. von Meyenfeldt, of which would lay the basis for the current dissertation.

Tiara started her career in September 2010 at the Surgical department of the Maastricht UMC as a resident not in training and shortly thereafter (February 2011- January 2013) as a PhD-student.

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