Determining the Size of the Problem: A Validation Study to Improve the Assessment of Mid-line Breast Cancer Related Lymphoedema

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Abstract

Background: Lymphoedema can develop after treatment for breast cancer due to damage caused to the lymphatic drainage affecting the arm, breast and or chest wall. Most of the research on this topic has focused on the incidence and outcomes of breast cancer related lymphoedema (BCRL) of the arm. Despite the significant amount of research in this area, there is still much debate over the diagnostic criteria and the assessment techniques used.

Lymphoedema can also affect the breast or chest wall but this area of BCRL does not appear to be as well studied. Although mid-line BCRL is recognised in the clinical setting the initial assessment and the techniques used to monitor the effectiveness of treatment currently rely on subjective assessment and patient report.

Aims: The overall aim of this thesis was to improve the assessment and recognition of mid-line BCRL.

The first objective included completion of two systematic literature searches and comprehensive reviews. These were undertaken to examine the available literature on the incidence, assessment and development of mid-line BCRL plus evaluation of the quality of life (QoL) tools currently available. This led to the development of the clinical study.

The second objective involved the design and completion of the clinical study. This was developed to validate the objective assessment techniques identified from the literature, a patient completed symptom report tool and a QoL tool.

Methods: A systematic search was performed. A review of the literature was completed to identify the incidence of mid-line BCRL, specifically when and how commonly it occurs and to evaluate the assessment techniques that have been utilised. The second review was

undertaken to ascertain whether the QoL tools currently available were designed and validated for patients with mid-line BCRL.

A clinical study was undertaken which recruited 89 women who had undergone breast cancer treatment and included those with and without breast BCRL. Blinded clinical assessment was used as the gold standard technique and overall determinant of the presence or absence of breast lymphoedema. Measurement of skin thickness by ultrasound scanning, local tissue water by tissue dielectric constant (TDC) and tissue indentation by tonometry was recorded. Breast cancer treatment and demographic details were documented. Participants each completed two QoL questionnaires and a breast lymphoedema symptom report tool.

Results: The two reviews identified 116 unique papers, of which 27 focused on the incidence and assessment mid-line BCRL and 89 on QoL.

The majority of the studies focussed on breast BCRL. There is a paucity of literature that included chest wall BCRL. The incidence of breast BCRL was presented in 9 studies and ranged from 9.6% to 75.5%. The range in the incidence reported is reflective of the variety in the study methodologies applied; including the sample size, the objective and subjective assessment tools utilised and the frequency and duration of the study assessments.

A range of objective assessment techniques were identified. These included techniques that are commonly used to assess and monitor lymphoedema of the arm. It was apparent from the review why there currently isn't a gold standard tool for assessment of mid-line BCRL and that further research needs to be undertaken.

The QoL search identified 89 papers, which had utilised 24 different QoL tools. Most of the studies undertaken focused on arm BCRL and the impact of this on QoL. The literature demonstrated that BCRL is associated with reduced QoL. The QoL tools used in the studies varied

and included generic and disease / condition specific QoL tools. Only two studies directly examined QoL in patients with mid-line BCRL. The review identified that the EORTC-QLQ-BR23 tool does include questions pertaining to breast symptoms, however, this has not been tested in patients with breast BCRL.

In the clinical study, breast lymphoedema was confirmed in 40 women (44.9%) with the lower half of the breast most commonly affected. Of this group, it had been previously undiagnosed in 29/40 (72.5%). Increased BMI, larger Bra size, increased number of positive lymph nodes, axillary surgery, receipt of chemotherapy and increased NPI were all associated with the presence of breast lymphoedema ($p<0.05$).

Ultrasound and TDC measurements were significantly higher in the lymphoedema group ($p<0.05$). No differences were seen in the tonometer measurements. Receiver Operator Characteristic (ROC) curves demonstrated that ultrasound and TDC measurements were able to distinguish between oedematous and non-oedematous breasts. Threshold levels were produced which demonstrated good levels of sensitivity and specificity.

The number of clinician identified and patient reported signs and symptoms were higher in women with breast BCRL, although women without lymphoedema did report the presence of some of the symptoms. The breast lymphoedema symptom questionnaire (BLSQ) appears to be a valid tool and has potential to be used as a screening tool for breast BCRL.

QoL using the EORTC-QLQ-BR23 and the LYMQOL-Breast was lower in those with breast BCRL. Analysis undertaken confirmed the newly developed LYMQOL breast to be a valid tool.

Implications: The findings in this thesis have the potential to improve the assessment and recognition of breast BCRL. Ultrasound and TDC measurements can be used to enhance the diagnosis of breast BCRL.

In addition, the BLSQ and TDC could be used in breast cancer clinics as screening tools to identify patients who might have breast BCRL and warrant referral and assessment by a lymphoedema specialist.

Use of the signs and symptoms, applied by the clinical expert in this study, by lymphoedema therapists in routine clinical practice would improve the consistency of patient assessment.

LYMQOL-Breast can be added to the arm and leg versions available and used in clinical practice to assess QoL associated with breast lymphoedema.

Future research is required to test further the threshold levels proposed, test the reliability and responsiveness to change of these and the LYMQOL-Breast. A prospective longitudinal study using these tools and assessment techniques would provide more accurate information on the incidence of breast BCRL, the time course for development and potential resolution.

Chapter 1. Introduction and Background.

1.1. Introduction.

This chapter provides an overview of lymphoedema, particularly breast cancer treatment related lymphoedema (BCRL) and background information on how and why the research question developed. The definition, diagnosis and assessment of lymphoedema are considered. The aims and objectives of the thesis are introduced and how they will be met proposed.

1.2. Lymphoedema.

Lymphoedema or chronic oedema are terms that are used interchangeably which describe failure or inadequacy of the lymphatic system (1). Oedema is often the most recognised consequence of lymphoedema, but other effects include skin and tissue changes and a predisposition to infection. Lymphoedema arises when there is an imbalance between capillary filtration and lymphatic drainage from the interstitial spaces which can be due to a variety of causes (1). Broadly lymphoedema is defined as primary, due to a genetic abnormality of the lymphatic system which is present from birth, or secondary due to damage to a normally functioning lymphatic system. Lymphoedema that develops following breast cancer treatment is one recognised type of secondary lymphoedema. Lymphoedema is also related to the presence of advanced cancer and has been recognised to develop or worsen in this group of patients. This is associated with lymph node involvement of the cancer. Worsening lymphoedema despite appropriate treatment can be an indication of recurrent cancer. Investigation and referral back to the cancer team are undertaken to rule this out.

A recent international review of lymphoedema specialist services, which included UK clinics, identified that the overarching cause of

lymphoedema seen in these clinics results from cancer treatment with the upper or lower limb(s) most commonly affected (2). This finding reflects the focus of the majority of lymphoedema research that has been and is currently undertaken, which look at the incidence and treatment of lymphoedema that developed as a result of cancer treatment.

There is disparity between the various diagnostic criteria currently used to define the presence of lymphoedema and as a result no agreed gold standard assessment technique for defining lymphoedema exists. A consequence of this is that often the methodologies and results from studies vary significantly making it difficult to compare studies and to draw conclusions that relate to the wider population.

There are many outcome measures used in the assessment of the lymphoedema treatment. These include limb volume measurement, incidence of infection, presence of wounds, quality of life, range of movement / function, limb shape and skin or tissue changes (3,4). There is debate on the importance and relevance of the outcomes reported and work is currently being undertaken to provide consensus on this.

In addition to the physical changes to the lymphoedematous area, quality of life has been recognised as being lower in patients with lymphoedema compared with the general population (5). There are several condition specific quality of life questionnaires that have been designed and validated for use in this patient group (6, 7,8). One study comparing functional and physical well-being in patients with and without lymphoedema following breast cancer treatment, reported significant reduction in quality of life in those patients with breast cancer related lymphoedema of the arm (9).

During the evaluation of these quality of life tools and in subsequent studies it has become evident that the extent of measurable oedema does not correlate with the change in quality of life (7, 10, 11). It has

been postulated that in the comparison of limb volume measurements with quality of life scores, individuals with larger limb volume measurements (more significant oedema) would have a lower quality of life, however, this relationship has not been proven (7, 10, 11). This finding highlights the importance of recognising and assessing quality of life in all patients with lymphoedema.

1.3. Breast Cancer Related Lymphoedema.

Lymphoedema can develop after treatment for breast cancer due to damage caused to the lymphatic drainage affecting the arm, breast and or chest wall. The majority of research on this topic is focused on the incidence and outcomes of BCRL of the arm. This type of lymphoedema is recognised as different to lymphoedema associated with the presence of active or advanced breast cancer. This is because the treatments provided, the aim of treatment and expected outcomes may not be the same between these two groups.

The clinical presentation of arm lymphoedema is commonly recognised as the presence of pitting oedema in the hand and / or along the arm (12). In addition, there may be skin thickening and tissue changes present. When the dorsum of the hand becomes oedematous the knuckles are less defined. There can be a loss of visible veins and tendons on the dorsum and at the wrist. The shape of the hand or arm can change, and visible enlargement seen. This can be confirmed by physical measurement of the arm circumference or volume or by patient report, due to change in clothes fitting. Early lymphoedema is often characterised as heaviness, tightness or aching in the affected limb (12). Over the past 10 years consideration has been given to the development and recognition of sub clinical lymphoedema or International Society of Lymphology (ISL) stage 0 lymphoedema for BCRL affecting the arm (13, 14). Figure 1 displays the different ISL stages. It has been recognised that there is a relationship between the early detection and treatment of BCRL of

the arm with improved outcomes (15). Recognising sub clinical lymphoedema adds further to the complexity in the diagnosis of BCRL as it is in such an early stage that significant limb volume increase has not yet occurred, and volume changes can be small, such as 3% in one study (15). Often the diagnosis of sub-clinical BCRL of the arm is reliant on patient reported symptoms (13). Currently randomised studies are being undertaken to study this phenomenon further, specifically whether early intervention can prevent or delay more significant swelling (16).

Figure 1 ISL staging

Stage	Desciption
0 or Ia	Represents a latent or sub- clinical condition where swelling is not yet evident despite impaired lymph transport, subtle alterations in tissue fluid/composition, and changes in subjective symptoms.
I	Represents an early accumulation of fluid relatively high in protein content (e.g., in comparison with “venous” edema) which subsides with limb elevation. Pitting may occur. An increase in various types of proliferating cells may also be seen.
II	Limb elevation alone rarely reduces the tissue swelling and pitting is manifest. Later in Stage II, the limb may not pit as excess subcutaneous fat and fibrosis develop.
III	Encompasses lymphostatic elephantiasis where pitting can be absent and trophic skin changes such as acanthosis, alterations in skin character and thickness, further deposition of fat and fibrosis, and warty overgrowths have developed.

The reported incidence of arm BCRL varies throughout the literature. The prevalence of arm BCRL is around 25-28% although it has been reported as low as 6-7% (17). The incidence of BCRL is dependent on the diagnostic criteria applied by each individual study and the length of follow up undertaken. The majority of BCRL occurs in the first few years after treatment but there is a recognised pattern of oedema with delayed onset that can occur several years after treatment (18).

Baseline or pre-treatment assessment of limb volume or circumference measurement improves the accuracy of diagnosis and is perceived as best practice baseline measurement enables the assessor to calculate relative volume change over time. This also corrects for natural limb differences that would skew assessments if comparisons were made between the “at risk” to the “control” limb measured only at the time of swelling presentation.

A difference of 10% between limbs obtained by limb volume measurement, circumferentially or using perometry has conventionally been used as the diagnostic criterion in lymphoedema research. Other common definitions include a 200ml volume difference or a difference of 2cm in a single circumferential measurement. The variety in the reported incidence of BCRL of the arm is demonstrated in one study that identified a range of 21-70%, at 12 months follow up, when four different diagnostic criteria were applied (18). The diagnostic criteria included patient report, volume change and circumference change (18). At all assessment points a 2cm change in any one circumferential measurement of the arm identified the highest occurrence of lymphoedema. This difference persisted and the incidence at 60 months ranged from 43- 94%. (19). In this study pre and post-operative assessments were undertaken, and relative limb volume change calculated. Furthermore, in a separate study a statistically significant difference was demonstrated when four measurement techniques / diagnostic thresholds were compared. In this study the techniques considered were; water displacement

volumetry, the sum of circumferential measurements, change in a single measurement point and patient self-report. The incidence was lowest, 8%, using water volumetry and highest, 31%, using a 2cm change at a single circumferential measurement point ($p<0.01$) (20). This study assessed participants only once post-surgery and compared the affected to the unaffected arm. Comparison of the methodologies and assessment techniques of these two studies which appear to be similar emphasises the differences between them and the difficulty in determining the true incidence of BCRL.

Studies designed to consider the time course of BCRL with assessments at multiple time points, pre and post treatment, have identified that patients who develop a mild or small increase in limb measurements may progress to develop more significant lymphoedema at follow up assessments (21, 22). Recently a more liberal criterion of an increase from baseline measurement of 3-5% has been suggested as indicative of BCRL (23, 24). However, caution has been raised regarding measurement error in the techniques used and the time of assessment for lymphoedema following breast cancer treatment to prevent resolving post-operative swelling or measurement error being misdiagnosed as true lymphoedema (25, 26).

The literature has an abundance of recognised risk factors pertaining to the development of BCRL; however, there is inconsistency in the significance reported for each of the individual risks. These include; surgery with axillary lymph node dissection, radiotherapy, post-surgical complications including wound healing, infection, seroma formation and cording (axillary web syndrome), raised body mass index (BMI) and weight change during treatment, taxane chemotherapy, skin puncture and having a predisposition to the development of BCRL (27, 28).

Since the introduction of the sentinel node biopsy (SNB) the reported incidence of arm lymphoedema has reduced but is still present. Radiotherapy continues to be a recognised risk factor for BCRL. In a

systematic review 32 studies were identified that explored the prevalence and severity of upper limb problems following breast cancer radiation. The authors of the review calculated that patients who received surgery and radiotherapy had an increased odds ratio of 1.46 of developing lymphoedema of the arm compared with patients who received surgery alone (29).

Post-operative problems including wound infections, cording and seroma formation are also felt to increase a patient's risk of developing BCRL (30). There is a growing awareness that axillary web syndrome or cording is not always an immediate post-operative problem (31).

There is evidence that the chemotherapy agents of the taxane group, specifically Docetaxel, may cause generalised oedema. A meta-analysis of 19 studies produced an odds ratio of 6.61 for developing oedema, reported as a grade 3 or greater toxicity, following taxane chemotherapy compared to non-taxane chemotherapy (32).

The theory behind the mechanisms of BCRL are being re-examined particularly to try and explain why some patients develop regional lymphoedema only, where often an area such as the hand is spared. Imaging of lymph flow and drainage has demonstrated that lymph flow is raised in both the subcutis and the muscle of both the operated and unoperated arm post operatively of those who go on to develop BCRL (33). This suggests that some patients may be predisposed to developing BCRL.

1.4. Mid-Line Breast Cancer Related Lymphoedema.

There is a lack of consensus concerning the definition and diagnostic criteria used in the assessment of BCRL of the arm. This inconsistency contributes to the difficulties in studying this area. Furthermore, these criteria are even less clear for breast and chest wall

lymphoedema. Conceivably this is one reason for why there are fewer reported studies of mid-line BCRL.

Lymphoedema affecting the mid-line, occurring after breast cancer treatment is seen in the clinical environment, and is recognised in patients with and without arm lymphoedema. At present it is assessed following clinical examination, patient report and on occasion the use of pre and post treatment photographs. There is not currently a recognised objective assessment technique for quantifying the degree of, or presence of oedema in the chest wall or breast. In addition, the risk factors pertaining to mid-line lymphoedema are not as well studied and confounding results have been presented.

There appears to be a paucity of studies of mid-line BCRL and this area often is omitted when lymphoedema following breast cancer treatment is considered. The reasons for the lack of research in this area are not known. Breast conserving surgery (BCS) was first proposed as an alternative to mastectomy in the late 1960's and wide local excision followed by post-operative radiotherapy to the breast has been found to be as effective as a total mastectomy when comparing overall breast cancer survival (34). In 2007 the proportion of breast cancer patients undergoing BCS was higher than those who received a mastectomy, 57% compared with 43% (35). In addition to the developments in the treatment of breast cancer, the initiation and uptake of the NHS National Breast Screening Programme in 1988 is acknowledged as a factor in the reduction in mortality particularly when the continued increase in breast cancer diagnosis is considered (36 ,37). Breast screening programmes enable earlier diagnosis of breast cancer which will influence the treatment required, enabling more women to be treated with BCS. Therefore, the proportion of women who are at risk of mid-line lymphoedema, particularly breast lymphoedema, is considerable. Oedema of the breast has been reported in several studies, since as early as 1982, but does not appear to be as well recognised clinically or researched as frequently

as arm BCRL (38). In addition, the reported prevalence varies dependent on the methodology and diagnostic criteria of the study, but has been reported to be as high as 75.5% (39)

Therefore, further research is required to improve the recognition of this type of BCRL.

1.5. Breast Cancer Related Lymphoedema in Clinical Practice.

In 2014 the Derby Lymphoedema Services was receiving approximately 350 referrals per year and of these 14% were for patients with BCRL. The proportion of patients presenting with BCRL had risen over the previous four years from 10.4% to 15.7% following the introduction of pre and post-operative lymphoedema monitoring. Since 2010 all patients due to undergo surgery for breast cancer have been seen by the lymphoedema research team pre-operatively and baseline limb volume measurements obtained. Patients undergoing axillary node clearance are offered post-operative re-assessment. All patients are provided with information about the development of lymphoedema and can contact the research team through the breast care nursing team if they have any concerns and seek referral to the lymphoedema service. Any patients with measurable or clinical signs of lymphoedema of the arm or chest are then assessed by a lymphoedema specialist.

Since working more regularly with breast cancer patients at risk of developing lymphoedema and because of the pre and post-operative monitoring two areas of potential research focus have evolved. The first is that we recognise that more patients have clinical signs of arm lymphoedema without exceeding one of the measurable diagnostic criteria for lymphoedema. This finding has made us question and rethink whether a limb volume change of 10% as the diagnostic criteria for BCRL of the arm is too conservative. The second is that more patients are presenting with breast or chest wall lymphoedema than was expected. At the follow up assessments, patients are asked

to identify any concerns about swelling. As a team we are involved in two large multi-centre studies exploring the assessment of BCRL of the arm and the effect of early intervention on mild or sub-clinical arm lymphoedema. These studies do not include assessment of recognition of breast or chest wall lymphoedema. At present we do not know the best method for the assessment and diagnosis of lymphoedema of the breast or chest wall and as a result cannot objectively monitor the effect of our treatments. It is this area that will be the focus of this thesis and it is hoped that the findings will provide a positive contribution to the scientific community.

1.6. Overarching Aim and Objectives.

The principal aim and focus of this thesis was to increase the understanding of mid-line lymphoedema and provide evidence that would improve the assessment and recognition of lymphoedema to this area. It was hoped that the results would enable practitioners to accurately assess for the presence of breast lymphoedema using validated objective assessment techniques where available. Assessment of quality of life would help improve the understanding of how this condition affects individual patients and help evaluate the interventions provided.

The first objective of this work was to determine the current evidence base for the assessment of mid-line lymphoedema. This was achieved by undertaking two literature searches and completing comprehensive reviews. The methodology and findings for the two reviews are presented in Chapters 2 and 3. The systematic reviews of the available literature established the current level of evidence, helped shape the research methodology and determined whether any of the objectives of this thesis have already been met.

The first literature search and review focused on the incidence and assessment of mid-line lymphoedema. It explored the reported incidence of mid-line lymphoedema and evaluated the methodologies

utilised in these studies. Factors similar to those pertaining to arm lymphoedema were considered in their relationship to the development of mid-line lymphoedema. Signs and symptoms associated with the presence of mid-line lymphoedema were identified. The review determined that the objective measurement techniques currently used in the assessment of lymphoedema of the limbs have not been validated in the assessment of mid-line lymphoedema.

The second literature review appraised that quality of life tools that have been used for patients who are / have undergone breast cancer treatment and also those with lymphoedema, specifically focusing on those that have been studied in mid-line BCRL.

As a result of the reviews, a clinical research study was designed and conducted with an overall goal of producing evidence that would improve the assessment of mid-line BCRL. The study included validation of the objective assessment techniques, a lymphoedema specific quality of life tool and a patient completed symptom questionnaire. The aims and objectives of this study are introduced after the reviews, in Chapter 4.

The proposed study will provide substantial information on the assessment of mid-line lymphoedema which should have relevance to develop and advance clinical practice. It is hoped that by improving the assessment of mid-line lymphoedema patient care will be enhanced.

Chapter 2. Literature Search and Review 1: The Incidence and Assessment of Mid-line Breast Cancer Related Lymphoedema.

2.1. Introduction.

This chapter presents the first of the two literature searches and reviews that were undertaken. This review was undertaken to determine the current level of evidence on the incidence and risk factors for mid-line BCRL development. In addition it sought to ascertain what objective assessment tools had been used to measure lymphoedema of the breast and chest wall. Examination of how they had been applied and the validation they had undergone considered.

This chapter describes the literature search process that was undertaken including the search databases that were used and the search terms that were applied. Rationale for the choices relating to the search terms, age and type of papers that were selected provided.

The papers identified were carefully and systematically reviewed. This process where able used the critical appraisal skills programme (CASP) checklists which provided questions and guidance to help interpret the study methodology, results and implications for practice (40). This structured approach enabled a consistent appraisal of the current research.

The findings were used to confirm what is known about the incidence and assessment of mid-line lymphoedema and where additional research is needed. This helped to focus the research questions and formulate the objectives of the proposed clinical study.

2.2. Literature Search Methods.

A systematic search of online search databases was undertaken. These included Ovid, PubMed, and Medline. An online search of the Cochrane library was also undertaken. A broad search was undertaken to obtain a wide selection of papers so there was no limit on the date of publication, however, only papers published in English and studies with female participants were included.

The initial searches were not limited to research studies only, however, subsequent more detailed searches were limited to randomised controlled trials, clinical trials, comparative studies, evaluation studies and validation studies.

Due to variation in the spelling of lymphoedema around the world both spellings were included during the searches. This was achieved by spelling lymphoedema using a $ in place of the first o, as it enabled results to be identified that included both spellings.

The flow chart of the search is shown in figure 1. In the first search the search terms used were lymphoedema / lymphedema, breast cancer, arm, breast, chest wall and measurement. In both searches these were combined to narrow down the number of results obtained. In the first search initially 6540 articles were identified from the different databases utilised. Restricting the search to the research terms and removing the duplicated papers 3295 abstracts were reviewed. Tables 1-3 display the search terms used and the numbers of papers identified and selected for review.

Figure 2. Literature Search Flow Chart

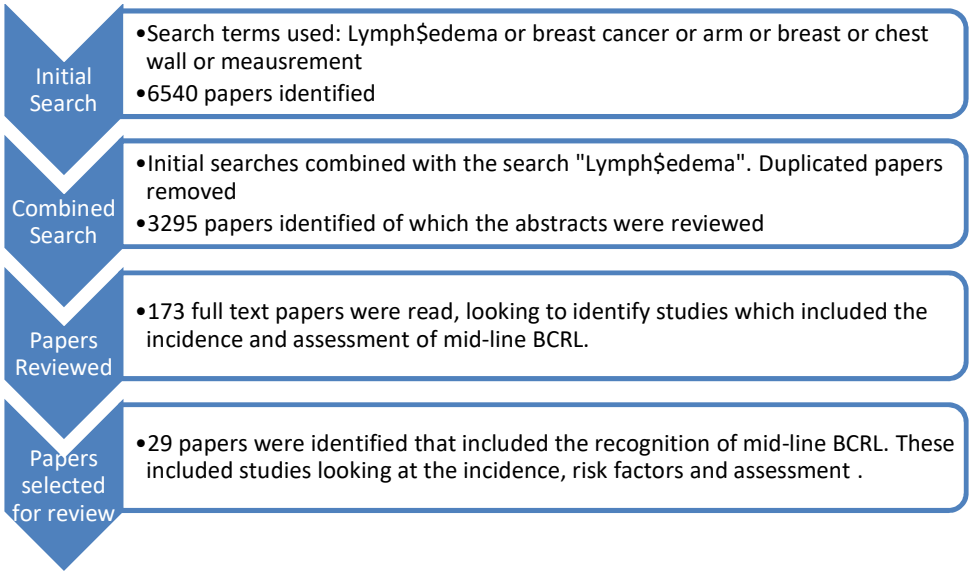


Figure 3 Inclusion Criteria for Reviewed Papers

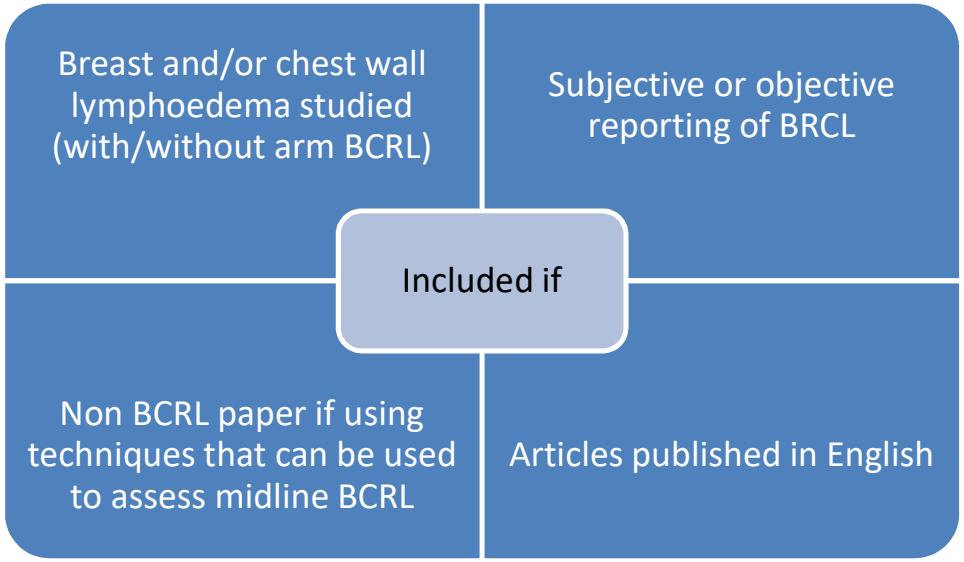


Table 1. Literature search results – Lymph$edema and chest wall

Database	Lymph$edema AND chest wall	Restricted to research terms	Selected following abstract review
Ovid (including AMED, BNI, Embase and Medline)	401	401	4
PubMed	73	8	5

Table 2. Literature search results – Lymph$edema and breast cancer and arm

Database	Lymph$edema AND breast cancer AND arm	Restricted to research terms (removing duplicates)	Selected following abstract review
Ovid (including AMED, BNI, Embase and Medline)	2518	1136	80
PubMed	1540	220	36

Table 3. Literature search results – Lymph$edema and measurement

Database	Lymph$edema AND measurement	Restricted to research terms	Selected following abstract review
Ovid (including AMED, BNI, Embase and Medline)	1733	1295	46
PubMed	275	235	57

Of the 173 unique papers identified from the first literature search 29 focused on the incidence and assessment of breast, chest or truncal lymphoedema. The majority of the 173 papers identified focused on lymphoedema of the arm only and were not included unless they also incorporated the assessment of mid-line lymphoedema.

The searches and review process was undertaken between 2013 and 2014. The papers identified dated from 1982 to 2014 and were published in a range of nursing and medical journals. Older papers were included but the surgical, radiotherapy and chemotherapy regimens utilised were considered to determine whether they were applicable in this patient population. If the breast cancer treatment was not reflective of current practice, then the incidence of lymphoedema and significance of the findings may not be relevant.

The searches also considered whether a lack of published papers on a particular subject may be a result of publication bias since studies with non-significant or undesirable results are not always published. Therefore, national research registries and conference proceedings were reviewed in an attempt to obtain comprehensive information on the search topics.

The studies identified varied in the number of participants included. Some of the papers were small case studies describing the measurement technique and how it had been used. These were included in the review as they were developed to examine novel applications of the techniques.

The sample size was considered in the review including consideration of whether a formal sample size calculation had been undertaken and if the statistical analysis undertaken was appropriate for the sample size and methodology of the study.

The search identified studies that followed patients up prospectively, using the assessment techniques to identify the incidence of lymphoedema, also some papers that had undertaken retrospective analysis from data sources including medical note reviews or previously collected data. Retrospective data collection from medical notes could result in bias in the information reported as this would be reliant on the health care professionals being consistent on the assessment and documentation undertaken and how records were interpreted by the researchers. Prospective studies that applied a consistent and agreed approach would result in more accurate and reliable data.

There was a difference in the length of study follow up. This was not unexpected as the time from breast cancer surgery to presentation of lymphoedema is debated and would influence the incidence reported. It is reported that the majority of patients who develop lymphoedema of the arm after breast cancer treatment will do so in the first 12-30 months after treatment (41, 42) but later onset of up to 5 years is reported in the literature (20). Therefore, not all of the studies reviewed provided sufficient follow up periods to enable the true incidence of BCRL to be observed. Some of the studies reviewed assessed participants once, at a set time after treatment and some prospectively followed participants up at regular intervals. The adjuvant treatments offered to patients can take several months to

complete, especially if chemotherapy and then radiotherapy undertaken, therefore depending on the time scale of follow up assessment(s) this could influence the incidence of lymphoedema reported.

The more recent papers reflected the change in research methodology and included a pre-treatment or baseline assessment that is used to calculate and identify changes at subsequent assessment times. It has been acknowledged especially in arm lymphoedema that using the unaffected arm as comparator is not accurate as the arms are not symmetrical pre-treatment, due to differences in arm shape and size related to arm dominance (26). As the techniques for assessing breast lymphoedema are not as commonly researched the pre-treatment differences between the affected and unaffected breast is not known.

Rather than specifying individual assessment techniques "measurement" was the search term used. This was preferred as it was hoped that more studies would be included in the search results. Some studies did not apply an objective assessment technique but relied on clinician or patient reported symptoms / examination. These papers were included in the review. Reliance on subjective assessment increased the risk of bias compared to the studies that applied objective assessment techniques. The aim of the search and review was to identify techniques that can be replicated in the assessment of mid-line BCRL. It was felt that those which applied techniques that had been validated, both objective and subjective assessments would provide stronger evidence.

Seven of the papers identified in both searches were review articles and were included to ensure that they didn't refer to any relevant papers that hadn't been identified from the searches.

In the first search one paper was included although the sample did not include patients that had undergone treatment for breast cancer. This study used ultrasound to assess oedema in patients with systemic

sclerosis (43). One study was included that used mammography to assess mammary skin oedema and compared this to recurrent breast cancer rates (44). One study was included that used tonometry to assess tissue changes following implant insertion in patients without oedema (45). Other papers that were included focused on the treatment of breast and trunk lymphoedema used quantitative assessment techniques. These included bioimpedance spectroscopy (BIS) (46), caliper creep to measure truncal skinfold thickness (47), circumferential measurement of the chest (48) and 3D imaging (49).

2.3. Results from literature search 1: The incidence of mid-line lymphoedema.

2.3.1. The presence of mid-line lymphoedema in the literature.

There was a paucity of literature focusing on this type of breast cancer related lymphoedema (BCRL) with the majority of available literature designed to assess the incidence and treatment outcomes of arm lymphoedema.

Despite the lack of agreement between limb measurement techniques and diagnostic criteria there are several tools commonly used for monitoring arm lymphoedema. These same tools, however, cannot be or have not been used in assessing mid-line lymphoedema. In both clinical practice and the research studies reviewed mid-line lymphoedema was often identified subjectively by; patient self-report, following clinical assessment or photographic comparison. This may influence the incidence of lymphoedema reported (50-53, 38) and increased the potential for bias to influence the findings. However, in three studies that applied subjective assessment multiple assessors

were used which was felt to improve the strength and consistency of the study findings (50, 53, 38).

Similar to arm BCRL, the reported incidence of mid-line lymphoedema differed between studies. These differences may be related to the diagnostic criteria / techniques utilised, the surgical procedure undertaken, adjuvant therapies received, and the length of study follow up. Advancement in breast conserving surgical techniques, the introduction of the sentinel node biopsy (SNB) and development in the precision of radiotherapy regimes may have influenced the reported incidence of lymphoedema and these factors were considered.

Adding to this complex subject is the relationship between mid-line lymphoedema and delayed breast cellulitis (DBC). As part of the literature search three papers exploring this phenomenon were identified (54, 55, 56). The symptoms of DBC include diffuse breast erythema, oedema and tenderness which are also reported in breast lymphoedema. The similarities between the two conditions, the lack of positive bacterial cultures and the poor response to antibiotic treatment question whether they are two conditions or whether the patients in these papers had breast lymphoedema.

2.3.1.1. The incidence of mid-line lymphoedema following treatment for breast cancer.

Table 4 displays the studies that reported the incidence of mid-line BCRL. The diagnostic criteria applied and length of study follow up is included.

Table 4. Incidence of mid-line lymphoedema reported in the literature.

Study Authors	Year	Incidence	Diagnostic criteria	Sample	Length of follow up
Adriaenssens et al (39)	2012	**75.1% breast**	Self report questionnaire (>1/80 = lymphoedema)	131 pts, single assessment point	One assessment within 5 yrs breast cancer diagnosis
Back et al (50)	2004	**20.5% breast**	Retrospective review of medical notes. Oedema recorded as present / absent	223 pts. Medical note review.	≤4 weeks post RT
Clarke et al (38)	1982	**41% breast**	Clinical examination by 3 assessors	74 pts (76 breasts) prospective study	Median 23 months (range 12 – 90)
Degnim et al (51)	2012	**31% breast**	Clinician report – sub group had 3 assessors	124 pts, prospective study	Median 11 months (range 3 – 14). Assessments undertaken at 1,3,6 and 12 months.

Goffman et al (52)	2004	**9.6% breast**	Medical note review	240 pts, retrospective review	Single review of medical notes at 1.5 years
Liljegren et al (53)	1993	**59.8% breast @ 12 months**	Clinician report, self-report, photographic review	381 pts, prospective study	36 months. Assessments undertaken at 3,12,24,36 months
Pezner et al (57)	1985	**27.7% breast**	Clinical examination	45 pts (47 breasts)	12 months post RT
Roberts et al (58)	1995	**57.1% trunk**	Aim to validate caliper creep as diagnostic tool	14 pts with arm LE	Single assessment.
Ronka et al (59)	2004	**34% breast**	Clinical report, USS	160 pts, prospective study	Single assessment. Median 12.6 months post op (range 11.3 – 18.8)
Wratten et al (60)	2007	**45% breast @12 months**	Clinical report, cutaneous oedema measurement by USS	54 pts, prospective study	Assessments: pre RT, during, 2,6,16,26,52,104 weeks

The incidence of mid-line lymphoedema identified in the literature ranged from 9.6% to 75.5% of breast lymphoedema following breast conserving surgery with or without adjuvant therapy and 57.1% of the sample assessed for truncal lymphoedema following a mastectomy (table 4). There does not appear to be a relationship between the age of the study and the incidence of lymphoedema reported, suggesting that breast lymphoedema remains a consequence of breast cancer treatment. However, it may be postulated that surgical techniques and radiotherapy regimens undertaken in the earlier studies may have been more invasive and would inadvertently damage healthy lymphatics, thus resulting in an increase in the incidence of mid-line lymphoedema.

The majority of studies used subjective reporting to identify the presence of breast lymphoedema, however, not all studies presented the signs and symptoms they used, in some papers breast lymphoedema was reported as present or absent (50, 53, 60).

The CASP checklists identify that studies which do not clearly describe the methods that were used for detecting the condition being studied could result in bias in the results. In addition, this increased the difficulty in reviewing the accuracy of the outcome and whether they were reflective of the true incidence of mid-line lymphoedema.

Some studies did include how lymphoedema was subjectively reported, this included a grading of mild/moderate/severe oedema and erythema in each quadrant of the breast when assessed on multiple occasions, however, the definition of each grading was not given (51). This study did undertake sub-group analysis with 46 patients having an additional assessment by a breast surgeon or lymphoedema therapist and good levels of agreement were produced when comparing the specialist and the nurse undertaking the study assessments were produced, Kappa = 0.76 and 0.75 respectively. In another study three assessors were used, and a mild, moderate and severe grading system applied (38). This grading system included the

symptoms that were considered and these included; reporting of heaviness and or pain, degree of skin changes (peau d'orange) and cosmetic appearance. The study did not report the levels of agreement or how disagreement between assessors was recorded and resolved. A third study applied a retrospective review of notes and identified reports of arm lymphoedema and breast lymphoedema separately (52). Breast lymphoedema was recorded if the assessing physician or nurse or patient recognised swelling or changes to the tissues including hyperaemia and peau d'orange appearance. In one study a patient rated subjective symptom tool was developed and used to diagnosis the absence or presence of breast lymphoedema at one assessment within 5 years of breast cancer treatment (39). Lymphoedema was diagnosed if the participant scored >1/80 on completion of the tool. This consisted of eight symptoms with a range of scores from 1-10 for each, with the maximum score possible being 80. The authors did identify that using subjective assessment only was a limitation of their study and in addition the sample were self-selected which may add bias to the high incidence of breast lymphoedema that has reported 75.5%. Additionally, a similar study identified that not all patient reported symptoms (including oedema and erythema) were consistent with a clinical diagnosis of breast lymphoedema (51). In that study 11.6% and 13% of participants respectively reported oedema and erythema but were not found to have breast lymphoedema on clinical examination.

Therefore, the incidence of mid-line BCRL from studies that included a subjective assessment only, particularly those that didn't provide the criteria used and those which used retrospective reviews of medical notes annotation were susceptible to bias and produced weaker results than those who applied objective assessments, diagnostic criteria and multiple assessors.

Due to the variety in study methodologies it was not possible to compare the incidence of mid-line lymphoedema and produce any meta-analysis or overall incidence.

2.3.2. The Time Course of Mid-line Lymphoedema.

The time course of breast lymphoedema was considered in some of the reviewed studies.

Pre-radiotherapy assessment identified that in some cases breast lymphoedema preceded the initiation of the radiotherapy (51, 38, 60). The length of follow up and number of assessments differed between individual studies but there was consensual agreement that for the majority of patients' breast oedema developed within the first 6 months of study follow up. However, as the studies differed between when follow up commenced, post-surgical intervention or post radiotherapy, comparison of the exact time course of breast lymphoedema cannot be inferred. It was acknowledged in one study that follow up assessments undertaken at 1-year post operatively meant that the group who received adjuvant chemotherapy and then radiotherapy were assessed on average at 3 months earlier following radiotherapy completion than the group who received adjuvant radiotherapy only (59). This may have influenced the incidence of lymphoedema reported in this study as the group of patients who had undergone both chemotherapy and radiotherapy had the largest reported incidence of breast oedema in this study.

The significance of this limitation is amplified as the studies that included multiple follow up assessments and those with longer follow up periods reported that in some cases breast lymphoedema is self-limiting and resolved over time.

Two studies reported that patients with breast lymphoedema were referred for and treated with manual lymphatic drainage (MLD) (51, 52). However, some studies did not report treating the lymphoedema but had continuing assessments after it had been recognised. The assessment of breast lymphoedema both subjectively and using ultrasound measurement demonstrated that for some patients this was a transient phenomenon, that the oedema improved and, in some cases, resolved over time (53, 38, 60, 57). There were differences in the reported incidence of breast lymphoedema when the presence of visible parenchymal breast oedema was compared to epidermal thickness measured by ultrasound scanning (60).

2.3.2.1. Presence of Breast Lymphoedema and Length of Study Follow Up.

The length of study follow up ranged from 4 weeks post radiotherapy up to 5 years post treatment and breast lymphoedema was reported as present at this initial assessment and at the repeated assessment at 18, 20, 24 and 36 months (52, 53, 38, 60). The sustained presence of breast lymphoedema over time and the associated negative impact on quality of life as well as symptoms such as; heaviness, discomfort, redness and visible swelling that were reported by patients' questions whether breast lymphoedema should be left untreated to resolve over time (51). This considered alongside the results of an early intervention study of mild arm lymphoedema following breast cancer treatment (15). In this study a compression sleeve was applied when limb volume increase (compared with pre-operative baseline) rose to above 3%. The compression sleeve was worn daily for 4 weeks and then on an adhoc basis, during exercise or if the patient felt their arm was swollen. The analysis demonstrated that the limb volume measurement decreased significantly ($p<0.05$) which is making the lymphoedema world rethink not only when to treat lymphoedema but

whether a short period of early intervention can delay or even prevent breast cancer related lymphoedema. This study had limitations as there was no control group and it was not clear how many or how frequently patients continued to wear the compression garment after the 4 week period. Current studies have been developed to provide further information on the diagnostic thresholds and early treatment of arm BCRL.

2.3.3. Risk Factors Associated with Mid-line Lymphoedema.

There are several risk factors that are associated with the development of BCRL of the arm and these include; increased body weight and body mass index and post-operative problems including wound infections, cording and seroma formation.

Comparable to the literature on arm BCRL different risk factors that were identified with the development of breast BCRL the study methodology specifically, the sample studied, the diagnostic criteria applied, and the length of study follow up were felt to influence the significance or lack of significance for some results.

2.3.3.1. Axillary Surgery and the Incidence of Mid-line Lymphoedema.

Despite the age of the studies reviewed, the results demonstrated that more patients who underwent invasive axillary procedures developed breast lymphoedema (38, 51, 57, 59), although this relationship did not demonstrate statistically significant differences in all of the studies reviewed (57). Of the 147 patients who underwent ANC 50% were identified in the individual studies as having breast lymphoedema compared to 36% of 136 patients who had a SNB (38,

51, 59). This finding is supported when the studies which included participants who had not undergone axillary procedures were considered. Three studies included patients that did not have axillary procedures and of the 131 participants only 3 (2.3%) developed breast lymphoedema (51, 52, 38). Patients who underwent an axillary node clearance (ANC) or axillary lymph node dissection (ALND) were more likely to have breast lymphoedema than those undergoing SNB or axillary sampling (AS) (38, 59, 60). In one study, however, the proportion of patients with breast lymphoedema was similar for those who had ALND and SNB although the sub-group for ALND included only 11 patients (51).

Two studies identified that patients who had lymph node positive disease and therefore received more invasive surgery that included a level II lymph node dissection or ANC and then lymph node irradiation were more likely to develop breast lymphoedema (59, 60). This finding was strengthened in both studies as they used quantitative objective measurement of breast tissue by ultrasound and comparison of the sub-group measurements was significantly different, X^2 p=0.0290 (59, 60). Most of the lymphatic drainage from the breast takes place through the deep and superficial lymphatic vessels which lead directly to the axillary lymph nodes, therefore, invasive surgery and radiotherapy to this area could result in damage to the drainage pathway of the breast (62).

2.3.3.2. Relationship of Radiotherapy and the Incidence of Mid-line Lymphoedema.

The majority of patients sampled in all of the reviewed studies underwent radiotherapy to the breast as part of their treatment regime. The area(s) treated and dose fractionation varies. Some include radiotherapy to the breast only with some including patients who received radiotherapy to the breast, including boost to the

tumour bed plus radiotherapy to the regional lymphatics (38, 50, 53, 60). This difference may be reflective of the age of the papers and the different countries that the research was undertaken in. One study compared radiotherapy to the cosmetic outcome following breast cancer surgery (53). Follow up was undertaken on multiple occasions and the presence of breast lymphoedema recorded as non-existent, moderate or severe when compared to the contralateral breast by the patient and two health care professionals. The health care professionals were involved in the patients care and therefore aware of the treatment they had undergone, which could influence the assessments. Breast lymphoedema was identified in both groups at all assessment time points including at the final assessment at 36 months, however, the incidence was significantly higher at each time point in the radiotherapy group. The study authors identified that the surgical procedure undertaken in this study was more extensive than the surgical procedures in similar studies designed to evaluate cosmetic results. The sector resection procedure they described involved dissecting the mammary gland down to the pectoral muscle and included the pectoral fascia in the sample. As the drainage of the breast lymphatics travel through the pectoral lymph nodes this may be associated with the high incidence of breast lymphoedema in both the radiotherapy and no radiotherapy group reported in this study (53).

In one early study (38) no correlations were found between lymphoedema of the breast and radiotherapy fractionation scheme, use of bolus or radiotherapy close to the breast. The time over which patients had been recruited was seven years and therefore during this time the radiotherapy doses and fractionation schemes had evolved. Breast lymphoedema was assessed by the 3 of the 4 members of the study team and classified as mild, moderate or severe. The study team assessing the presence of breast oedema were medics from the radiotherapy department, however, the paper did not specify levels of agreement between the individuals or whether there were differences in the oedema classifications and if so how this was resolved.

Univariate and multivariate analysis identified a statistically significant difference when axillary dissection, sampling or no axillary surgery were considered, p = 0.001. 78% of the sample who had undergone axillary node dissection developed breast lymphoedema compared to 25% of those who underwent axillary sampling and 6% of those who had no axillary surgery. One third of the sample who experienced breast lymphoedema did so prior to the initiation of radiotherapy treatment. This led the authors to the conclusion that breast lymphoedema is a complication of the axillary staging procedure primarily rather than a complication of radiotherapy.

A retrospective notes review of radiotherapy toxicities recognised post-treatment complications which included post-operative oedema, and wound infections or cellulitis that required antibiotic therapy, to be significantly associated with the presence of breast oedema at the end of radiotherapy, X^2 $p<0.028$ and $p=<0.002$ respectively (50). Modelling analysis designed to understand the time course of cutaneous breast oedema identified that the occurrence of a post op wound infection had a significant interaction with dissection type and this relationship differed between SNB and ALND (60). Epidermal thickening was greatest in the group who had undergone an ALND and excluding the group of patients who had experienced a post-operative infection following SNB there was no difference in epidermal thickness between those who had a SNB and those who did not have axillary surgery (60).

Epidermal thickness measured by ultrasound demonstrated that infection was associated with an increased level of cutaneous oedema prior to radiotherapy commencement and this increased over time (60). Cellulitis is a recognised complication of lymphoedema generally. It is not known if the relationship between development or worsening of lymphoedema and cellulitis occurrence is one of cause or effect (63).

2.3.3.3. Body Mass Index & Tumour Location Related to Mid-line lymphoedema.

Univariate regression analysis identified increased body mass index (BMI) and location of the tumour in the breast to be significantly associated with the development of breast lymphoedema, p=0.0058 and p=0.0042 respectively (52). In this study the group who developed breast lymphoedema had a higher BMI (mean =29.26Kg/m^2) and tumour located in the upper outer quadrant of the breast. The identification of breast lymphoedema is this study was following a retrospective notes review and patients were considered to have lymphoedema if swelling and skin changes to the breast were documented as present by the health care professional or self-reported by the patient.

Conversely tumour location was not found to influence the presence of clinically or ultrasound detectable breast lymphoedema in a further study (59). In addition, patient's weight did not correlate to the development of breast lymphoedema in a prospective study using multiple clinician assessment (38).

Reasons for these conflicting findings may be due to the methodologically differences and the age of the study in that the treatment provided in the 1970's different and more aggressive that in the late 1990's. The study that did identify that there appeared to be a relationship had completed a retrospective review of the medical notes and it appeared identified patients with significant breast lymphoedema. This was highlighted as several of the patients had received antibiotic treatment for presumed mastitis or diagnostic biopsies to rule out inflammatory recurrence in the breast (52). They did acknowledge that the incidence of lymphoedema reported may be an underestimate as formal screening was not undertaken. Median BMI of the large sample (n=240) was 29.26 Kg/m^2 indicating that this patient group were overweight. This was further supported as 10%

patients were classed as extremely obese. The second study reported a much higher incidence of breast lymphoedema, this was up to 79% in those who had undergone ALND (38). No description of the BMI or weight range of the sample was provided so it is difficult to compare the two groups. However, this study did complete a detailed assessment of patients at each assessment including a mild, moderate and severe rating of breast oedema. Three of the four authors, all Doctors working in the radiation department undertook the assessments. Another difference in the findings is that for the nearly all of the patients found to have breast lymphoedema this was reported as mild (28/31) and resolved over time. Therefore it could be inferred that the severity of breast lymphoedema increases with increased weight / BMI rather than the incidence of the condition.

2.3.3.4. The Relationship between Mid-line Lymphoedema and Bra Size.

There were conflicting findings on the relationship between breast or bra size and the development of breast lymphoedema. One study identified no relationship. In two other studies breast size was associated with the development of breast lymphoedema, however, the results from these are conflicting (53, 57). Both were prospective studies using clinician report to determine the presence of lymphoedema. One study concluded that women with small breasts had more breast lymphoedema (53) where the other identified a statistically significant, lower incidence of breast lymphoedema in patients with a smaller bra cup size of A or B when compared to the larger C, D or DD cup size ($p<0.003$) (57).

2.4. Delayed Breast Cellulitis.

From the literature search three papers were identified that explored delayed breast cellulitis (DBC) following breast conserving surgery. The concept of DBC replicates many of the signs and symptoms of breast lymphoedema including diffuse breast erythema, oedema, tenderness and warmth. Additionally, the time course following breast cancer treatment to the development of symptoms is similar for both conditions (54-56). For cases of DBC presented in these papers, there was lack of systemic "flu like" symptoms which are usually associated with acute infective cellulitis and this criterion had been used to differentiate the two conditions. The lack of positive bacterial cultures and poor response to antibiotic treatment raises the question of whether these studies are describing breast lymphoedema and this is the same condition as DBC. The timescale reported for the development of DBC was between 3 and 10 months after breast surgery, this was similar to the studies presenting the epidemiology of breast lymphoedema. Of significance was the relationship of DBC commonly occurring on the dependent portions of the breast and some improvement in symptoms after patients were supine. This pattern of oedema improvement or for some patient's oedema resolution is well recognised in early, mild lymphoedema (12). A proportion of patients in each study were treated with intravenous (IV) or oral antibiotics with varying levels of success in resolving the symptoms. In one study the mean time to resolution was 7.5 months (56). DBC reoccurred in 22% of patients during the 3 year follow up and 4% of patients went on to have a mastectomy for intractable breast pain (54).

In a retrospective review of 601 breast cancers in 580 patients over a 20-year period the incidence of DBC was 8%. Univariate analysis found obesity, post-operative infections, increased number of lymph nodes removed, radiotherapy boosted by electrons and coincident

lymphoedema of the arm to be significantly associated with DBC (54). Breast size was not included as a variable and therefore not analysed. These significant risk factors are similar to those that have been associated with the development of breast lymphoedema. All three studies suggested that DBC is related to lymphatic impairment or occlusion, that this stagnant fluid provides a medium for bacterial culture. However, this model for cellulitis in other types of lymphoedema is no longer favoured. The authors associated the cumulative damage from breast conserving surgery plus radiotherapy to the lymphatics in the upper outer quadrants of the breast interrupted the major draining pathways of the breast to the axilla.

2.5. Diagnosis of Mid-line lymphoedema.

There are several methods used in the identification and monitoring of lymphoedema affecting the limb(s) and often in unilateral limb lymphoedema these methods compare the affected or at-risk limb to the contralateral limb. The diagnostic criteria and recommended thresholds vary throughout the literature and include a 200ml limb difference or increase from baseline, a 10% difference or increase from baseline and a 2cm difference or increase at one circumferential measurement point. A significant development has been the recognised importance of baseline (pre-treatment) measurements and the difference in limb shape and size that exists naturally between limbs often due to limb dominance recorded (25, 26). Very few studies have assessed mid-line lymphoedema using quantitative objective measurement techniques and this is not common practice. Table 5 presents the studies that were identified in the literature search, including the measurement technique(s) applied and details of the sample.

The quantitative measurement techniques for assessing mid-line lymphoedema utilised in the selected papers include bioimpedance spectroscopy (BIS) (46, 61), skin thickness by ultrasound assessment (39, 59, 64, 60), tonometry (61), caliper creep using skinfold thickness (47, 58), local tissue water by tissue dielectric constant (TDC) (65) and chest circumference measurements (48). Some of these studies are novel applications of the measurement techniques and therefore the sample sizes are small which may limit the generalisability of the findings to the larger population (66). Only one paper reported that a sample size calculation had been undertaken strengthening that the significant outcomes hadn't occurred as a result of chance (66). A sample size calculation will identify the number of participants required for a study to ensure that statistically significant differences, interactions and relationships can be detected. The other studies did not provide rationale for why those numbers of participants were included. There was little information given that enabled the reader to ascertain that the statistical tests undertaken were appropriate to the size of the sample and the distribution of the data.

Table 5. Overview of the measurement techniques, sample and results from the studies identified in the literature search.

Author (year)	Assessment technique	Sample	Results
Shukla et al (1984) (44)	Skin thickness by mammography, prognostic indicator for recurrent disease. Comparing treated and untreated breast.	N=220 pts. BCT between 1972-77. End point = recurrence by 60 months	Oedema of <1.5mm = freedom from recurrence whilst >3mm equally high likelihood of recurrence.
Bosman and Piller (2010) (46)	Breast bioimpedance spectroscopy as an outcome measure for treatment of seroma using kinesio tape.	N =9, pre & post op measurement of breast quadrants. Equation to calculate ECF volume.	Bioimpedance similar in both groups pre-op. Bioimpedance and extra cellular fluid (ECF) calculation changed at repeated measurements.
Moseley and Piller (2008) (61)	Reliability of bioimpedance spectroscopy and tonometry to measure breast tissue.	N=14 women previous breast cancer treatment (BCT) >12months.	Repeated measurements for each breast quadrant. Good between subject reliability concluding techniques consistent and reliable.

Mulder and Nicolai (1990) (45)	Report on the use of a tissue tonometer for the accurate measurement of capsule formation.	Report includes measurements from 116 patients with breast implants and displays the tonometer readings over time of 3 patients.	Provides information on the limitations of this technique including patient positioning and measurement position. Recognises the natural difference in breast tissue tone related to age. Compares the difference in measurements to the clinical assessment of breast tissue following reconstruction.
Hesselstrand et al (2008) (43)	High frequency USS comparison with palpation in systemic sclerosis.	N=106 pts. with systemic sclerosis. USS mmts. including chest undertaken	Inverse correlation between skin thickness and echogenicity, thicker skin initially caused by oedema. USS mmts. demonstrated chest skin thickening but not always identified on palpation.

Wratten et al (2000) (64)	Pilot study to determine what qualitative and quantitative changes in treated breasts can be measured using USS.	N=11 women having or had Radiotherapy (RT), clinical examination 4 had breast oedema. Majority had repeated mmts.	Mean thickness treated breast >untreated breast. Both breast medial mmt >lateral mmts. Pre-treatment scans demonstrate thickening in treated breast. Large inter-patient variation in mmts. of treated breast.
Wratten et al (2007) (60)	Full study. Aimed to identify factors that can cause breast oedema, mmt using high frequency USS and clinical assessment.	N=54 women, multiple assessments pre and post RT upto 24 months.	Small increases in mmts. post RT but peaked between 4-6/12 post RT returning to B/L mmts by 12 months. USS did not predict prolonged parenchymal oedema any better than clinical assessment at start of RT.
Jahr et al (2008) (49)	Comparison of MLD with/without deep oscillation. Measured using 3D scan and VAS for pain and swelling.	N=22 with known breast oedema.	Difficulty obtaining accurate imaging – inspiration / expiration. Further evaluation in humans required. 3D imaging demonstrated reduction in treated breast and increase in control group post treatment but not at 8/52

Mayrovitz et al (2008) (65)	Comparison of tissue dielectric constant in anatomically paired sites including axilla and thorax.	N=22, 10 healthy controls and 12 pts. pre breast cancer treatment. Triplicate mmts. undertaken at each site.	BCT group > control group pre-treatment mmts at forearm, bicep and axilla. No difference at thorax. No difference between dominant / non-dominant limbs. Comparing all 4 sites TDC highest at axilla.
Ronka et al (2004) (59)	USS and clinical assessment of breast tissue post BCT, comparing SNB with ANC.	N=160 consecutive pts. follow-up mmts at 12months post op.	No difference between thickness or interstitial fluid (ANC or SNB) making USS a feasible method for evaluating breast oedema. Increased skin thickness, s/c oedema and fluid collection more common in ANC than SNB, however, less time post completion of treatment in ANC than SNB.

Finnerty et al (2010) (48)	Audit of the treatment of breast oedema using kinesio tape, chest circumference mmt. as outcome measure.	N=10, 8 with clinical or self-reported breast oedema.	General decrease in chest wall mmts reported. Difficulty in obtaining accurate mmts. difference between therapist. Effect of time of day, abdominal bloating etc. on mmts.
Williams et al (2002) (47)	RCT comparing MLD and SLD in the treatment of BCRL of the arm, caliper creep of the chest and USS used as outcome measures.	N=31 with known BCRL of the arm.	Not all pts. able to have caliper creep mmts. undertaken. No significant difference in pre/post MLD mmts. using USS or caliper creep. Increase in unaffected side measurements post treatment.
Roberts et al (1995) (58)	Aim to develop an objective measurement of truncal oedema using skinfold thickness and caliper creep.	N=14 with known BCRL of the arm. Repeated measures comparing to unaffected side as control.	Comparing to control, 8 pts had >10% (2SD) difference with 2 having clinical oedema. Rate of creep more sensitive indicator than skinfold thickness alone.

Johanssen et al (2014) (67)	Aim to investigate tissue water content (TDC) in skin and upper subcutis following surgery and radiotherapy for breast cancer	N=118. Measurements obtained pre-RT, during RT and at 2 and 4 wks post RT. Measurements of both breasts undertaken and ratio calculated.	Treated breast demonstrated higher mmts. (more fluid) at all time points. Proposed ratio of >1.4 indicative of breast oedema. Rate of oedema increased at all time points and was highest (62.6%) at 4 weeks post RT.

2.4.1. Ultrasound.

Looking at the techniques utilised, ultrasound was the most commonly applied method for assessing breast lymphoedema and had been used in five studies, including one that assessed oedema occurring in patients with systemic sclerosis (43).

In a pilot and the subsequent full study (64, 60) difficulty in distinguishing the individual layers of the skin was recognised and as a result total cutaneous thickness was recorded. In one study, further to the measurement of skin thickness alone, change in echogenicity and visibility of the different layers of the tissues and visualisation of interstitial fluid accumulation were considered in the characterisation of lymphoedema (59).

Measurements using ultrasound scanning were undertaken of the affected and also of the contralateral breast. This enabled comparisons between the affected and unaffected sides to be made. All four studies identified that skin thickness increased in the affected side when compared to the unaffected breast and in the studies that undertook assessments on multiple occasions that this difference was present prior to radiotherapy commencement (47, 59, 60, 64).

One study compared the incidence of breast lymphoedema following ANC or SNB and found that median breast skin thickness at one-year post surgery to be thinnest in patients who had undergone SNB only and thickest in patients with node positive disease who had undergone an ANC. This measurement difference was statistically significant for each of the four breast quadrants (59). The difference in skin thickness at the selected measurement sites highlighted a need for a detailed assessment protocol to ensure that measurements are undertaken at the same site. None of the studies undertook pre-surgical ultrasound assessments but multiple assessments at different time points were included in three of the studies reviewed (47, 64,

60). Multiple assessments enable changes in the condition over time to be determined and repeated abnormal measurements increased confidence in the diagnosis of the condition being studied,

The mean variation reported in one study following repeated ultrasound measurements of the treated breast was 1.05mm and the mean coefficient of variation was 13.9% (64). Consideration of the thickness of the area being measured and that in another study skin thickness measurement of greater than 2mm was considered indicative of oedema. This variation in ultrasound measurement is significant when considering the reliability of the results obtained and the application of this technique in the assessment of breast oedema.

Ultrasound assessments were used in the prediction of parenchymal breast oedema at the start of radiotherapy but following regression analysis this was not found to improve predictions of clinical assessment alone (60). There was disparity between the ultrasound assessment and clinical assessment of breast and chest tissue in two further studies (43, 64). Some patients were not deemed to have oedema following clinical assessment, but skin thickening was identified on ultrasound assessment.

2.4.2. Skin Thickness Assessment by Mammography.

Skin thickness measured by mammography was studied and used as a predictor of disease recurrence in one study (44). Mean skin thickness measurement at each of the four breast quadrants and the areola were undertaken and the difference between these and measurements from the contralateral breast were calculated. The difference in mean skin thickness between the two breasts was taken to represent oedema. It was proposed that using this technique measurements could be produced reliably to 0.25mm. 220 patients

were followed up for at least 60 months and the results identified statistically significant differences in skin oedema measurements and the incidence of local and systemic recurrence at 60 months. The group that did not develop recurrent disease had the lowest mean skin thickness and the group with systemic recurrence the highest. The age of this study, published in 1984 and the time over which the study was undertaken 1972 to 1977, reflect a time when the surgical techniques and treatments utilised are different from those used today, and therefore the recurrence rate now would be different and hopefully lower. However, mammography continues to be undertaken at regular intervals both pre and post treatment and therefore could be used to assess and monitor changes in the treated breast.

2.4.3. Bioimpedance spectroscopy.

Bioimpedance spectroscopy (BIS) of the breast has been undertaken in two studies, both measuring segmental bioimpedance of each of the four quadrants of the breast (46, 61). The first was a reliability study designed to determine the accuracy of bioimpedance and also tonometry in the measurement of breast tissue (61).

Bioimpedance analysis is the measurement of the opposition or impedance to the flow of a small, harmless alternating current through a region of the body, which is used as a measure of extracellular fluid in the area being assessed. When used to monitor unilateral arm lymphoedema following breast cancer treatment electrodes are placed at the same points on the affected and unaffected arm and an unaffected foot. Impedance is inversely related to volume. Bioimpedance spectroscopy measures impedance over a range of applied frequencies and uses data modelling to predict the impedance at zero (R0) and infinite (R_∞) frequencies. At zero frequency the current would pass through the extracellular fluid. As volume increases, R zero decreases proportionately.

Comparing the ratio of the affected and unaffected limb once corrected for dominance or by interpreting the L-Dex, an indication of change in extracellular fluid can be made. Bioimpedance has been compared to other methods of assessing lymphoedema of the limbs including circumferential measurements, water displacement and perometry. It has been established that bioimpedance can be undertaken faster, consistently and is sensitive to change (68).

Bioimpedance of the breast quadrants has also been used as an outcome measure in the assessment of kinesio taping used in the treatment of seroma formation following breast cancer surgery (46). This small RCT applied kinesio tape to half of the sample post operatively, n=4, and the other half received standard treatment. Bioimpedance spectroscopy was undertaken pre-operatively and on repeated occasions post operatively. The resistance values obtained were used to estimate extracellular volume. The results demonstrated that in the treated breast extracellular fluid increased significantly post operatively but by the end of the study, 16 days post-surgery, the readings were lower than at baseline. It was not reported whether there was a difference in the bioimpedance of the four quadrants measured. The sample also included four patients who had undergone a modified radical mastectomy of which three developed a seroma. The method describes the four quadrants being divided from the nipple which may make reproducibility difficult, particularly in patients who have undergone mastectomy or when post-operative swelling is present measurements as bioimpedance is reliant on accurate electrode placement. If the electrodes are not placed at the same points each time, then the size of the area measured changes and this may affect the readings produced.

2.4.4. Tonometry.

Tonometry is a technique that was designed to measure the resistance of the tissues to pressure at a measured point. The tonometer consists of a weighted plunger which is placed on to the skin and the depth of depression into the tissues measured. Depending on whether the tissues being assessed are oedematous or fibrotic this will affect the result obtained. Tonometry has been used as an outcome measure for assessing lymphoedema treatments but due to the differences in desired outcomes i.e. softening fibrotic tissue and therefore aiming for an increased tonometer value or reducing oedema and therefore aiming for a reduction in tonometer value a "normal" range for measurements has not been produced. The tonometer has recently been developed further and an indurometer produced by the same company. This has been validated against the tonometer and as a result the indurometer is being modified with the aim of improving the repeatability of measurement (69).

Repeated measurements of bioimpedance spectroscopy and tonometry in a sample of patients who had undergone breast conserving surgery and adjuvant radiotherapy, without lymphoedema, produced low covariance ranging from 1.29% to 3.25% for tonometry and 0.20% to 0.86% for bioimpedance. The authors concluded that the results demonstrated between subject reproducibility and that these techniques could be considered as consistent and reliable (61). This study assessed both breasts but did not compare the measurements to explore whether measurements obtained for the "at risk" breast were similar to or differed from the contralateral side. They did not describe either whether the measurements obtained at each quadrant were similar or whether the individual quadrants of the breast differed in local fluid and tissue fibrosis as has been recorded in the ultrasound studies of breast tissue. The sample size in this study was small, n=14 and there have not been further studies which have

included either of these measurement tools since this study was published.

A report using a tissue tonometer for the measurement of capsule formation identified some limitations of this measurement technique (49). This study was designed to measure intramammory pressure for objective references of capsule contracture after breast augmentation and reconstruction. Patient positioning was identified as important as the breast shape and size changes dependent on whether the patient is recumbent, supine or upright. The natural changes and differences in skin and subcutaneous tissue could affect the results. They reported that the level of indentation increased in a young firm breast compared to a soft ptotic breast. Despite the range in tonometer readings being large in the operated and un-operated population, 4 to 14mm and 4-10mm respectively, the authors concluded that when used alongside clinical examination this was a useful technique that could be used as an objective measurement of the breast. This paper was presented as a report and did not provide statistical analysis to compare the tonometer measurement changes or the correlation between the tonometer measurements and clinical examination.

2.4.5. Tissue Dielectric Constant.

Another instrument designed to assess local tissue changes is the moisture meter (Delfin Technologies). This assesses local tissue water by measuring the tissue dielectric constant (TDC) at a range of depths at any chosen point. An electromagnetic wave is directed into the tissue by an open ended coaxial probe, creating an electromagnetic field in the tissue. Depending on the relative permittivity of the tissue, or dielectric constant of the tissue, the alterations in magnitude and phase of the electromagnetic wave that travel through the tissue vary. The dielectric properties of a tissue responsible for

this wave shift are directly influenced by the total amount of water in a tissue. Therefore, the amount of fluid in the area being assessed will affect the result produced. An increase in skin / tissue fluid will result in a higher TDC value produced.

This technique has been validated in the assessment of local tissue water in the forearm in patients with breast cancer (70). Measurements of forearm local tissue water have been obtained in different patient groups including; pre and post-menopausal women, varying body mass index (BMI), those with and without breast cancer and without or without lymphoedema (70, 71).

In an early study TDC was not found to correlate with limb volume calculated using circumferential measurements. However, as the moisture meter measures water content within the tissue at the depth of the probe being used therefore it may not reflect whole limb volume measurements. The maximum measuring depth of the probes used was 5mm compared to the mean radius of the limb being 45.8mm, thus it was felt that similar TDC values could be obtained in limbs with varying levels of oedema (70). In a later study, using a smaller TDC probe which measured to 2.5mm, it was found that TDC ratio of the "at risk" arm to the contralateral arm correlated significantly with both the whole and segmental arm ratio (71). The author suggested that a TDC ratio between the "at risk" and contralateral limb that exceeds 1.26 could be used as a threshold for determining sub-clinical lymphoedema.

There have been several studies that have used this technique to assess and quantify lymphoedema in the arm following breast cancer treatment but only one that looked at other areas at risk, including the axilla and thorax (65). This study compared TDC values in a group of patients with breast cancer prior to any surgical intervention and also in a control group. Triplicate measurements were obtained at each site and the analysis demonstrated statistically significant, higher readings in the forearm and bicep. The measurements at the

axilla were different but this was not statistically significant and the measurements obtained at the thorax were very similar. It is not clear from this paper whether the measurements obtained were compared to the measurements undertaken on the control group as it would be interesting to understand whether there were any differences between the two breasts. When the TDC values for the individual sites were compared the axilla demonstrated the highest readings for both the control and breast cancer group. It was proposed that as this area is a known portal for lymphatic drainage that this would have a higher TDC.

More recently TDC has been used to determine the presence of breast oedema after breast cancer surgery specifically the incidence before, during and after radiotherapy (72). TDC readings were obtained for both breasts in all four quadrants and a ratio comparing the affected and unaffected produced. A ratio of >1.4 was deemed to represent breast oedema. This was determined from calculating the mean plus 2 standard deviations of a group of healthy volunteers (n=15). Of the 118 participants who had undergone surgery for breast cancer, 31.4% had a ratio of >1.4 prior to starting radiotherapy and this increased at each of the study time points to 62.6% with breast oedema determined by TDC at 4 weeks after radiotherapy.

2.4.6. Skinfold thickness.

Measurement of truncal skinfold was undertaken in two studies. The first was a study aiming to develop an objective measure of truncal swelling using modified skinfold calipers (58). The second compared manual lymphatic drainage (MLD) to simple or self-lymphatic drainage (SLD) in the treatment of BCRL. In this study skinfold thickness was used as an outcome measure (47).

Skinfold thickness was measured using a standardised technique on a healthy subject on twelve occasions over fifteen days and then in 14 patients with known BCRL of the arm. Once the calipers were applied a reading was taken at 10 seconds and then again at 60 seconds. This enabled caliper creep to be determined; this was the difference between the two readings. The purpose of measuring caliper creep was that this was felt to be analogous to the "pitting" test that is routinely used to determine the presence of oedema in tissues and would quantify this. Measurements were obtained on the affected and unaffected sides and statistically significant differences were reported. It was found that the rate of creep was higher on the affected side, therefore more pitting was present. Repeated measurements undertaken on 5 patients on two consecutive days produced high correlation coefficients of 0.998 for the affected side and 0.993 for the unaffected side. Eight of the fourteen patients had more than a 10% difference compared to the measurements from the unaffected side with only two having clinically obvious truncal swelling. The authors concluded that this technique offered a portable, reliable and reproducible method for assessing truncal oedema. The authors did acknowledge that the initial calipers had to be modified as the pressure exerted by the unmodified calipers varied by 14%. This study was published in 1995 and it may be that the calipers in production now overcome this limitation, however, this is not currently a commonly used tool in lymphoedema assessment.

A further limitation of this technique identified in the second study was that not all patients could have skinfold thickness measurements undertaken (47). A quarter of the 31 patients studied could not have caliper measurements completed due to; obesity which caused difficulty with holding the calipers in place, and tolerance of the measurement due to scarring and skin sensitivity to the affected area as a result of radiotherapy and infective episodes. After MLD caliper creep was lower in the affected side but had increased in the unaffected side, neither result demonstrated statistical significance

but both showed a trend towards this. This relationship was felt to reflect the movement of lymph during MLD towards a draining pathway.

2.5. Conclusions and Summary of Findings.

2.5.1. Conclusions from literature search 1: The incidence and risk factors for the development of mid-line lymphoedema.

Although the literature available on the incidence and assessment of mid-line lymphoedema following breast cancer treatment is limited it is apparent that this is a problem for a significant proportion of patients and that similar to arm lymphoedema it can result in discomfort and reduced quality of life. Critical appraisal of the study methodologies identified that most demonstrated a potential for biased results and a lack of information on the subjective criteria used when determining the presence or absence of mid-line lymphoedema. Limited information was presented to provide rationale for the statistical tests applied and the sample size included, in several studies the number of participants recruited was small.

Despite the searches being broad with an aim to identify studies on the topic of mid-line lymphoedema, compared to the number of studies that have been published with a focus on arm BCRL, there has been limited research undertaken. There was a particular paucity of literature that focused on the incidence and assessment of chest wall BCRL.

The key findings of the review are highlighted below:

- Incidence:

There was a wide range in the reported incidence of mid-line oedema, from 9.6% to 75.1%. The incidence of lymphoedema was influenced by the definition used in the study, the measurement / assessment techniques applied and the length of study follow up.

- Time Course:

The length of study follow up varied from 4 weeks to 5 years. The time point of the first assessment also varied, including before and after radiotherapy. Mid-line lymphoedema was present in some participants before the administration of radiotherapy. There was consensual agreement in the literature that mid-line oedema generally developed within the first 6 months of study follow up.

- Is breast lymphoedema a self-limiting condition?

It may be inferred from some of the studies undertaken that breast lymphoedema was a transient problem that resolved, in some cases without treatment, over time. This pattern was recognised in studies that utilised either subjective or objective assessment. It was recognised in the longitudinal studies that reassessed participants at 12 and 18 months that for some the oedema had resolved and measurements returned to the baseline levels. However, in some patients, oedema was still present at 36 months post-surgery which raises uncertainty whether breast lymphoedema is self-limiting for all patients. The papers reporting delayed breast cellulitis described similar symptoms to that of breast lymphoedema and the lack of response to antibiotics raises the question whether they are the same condition.

- Risk Factors:

The risk factors identified pertaining to mid-line BCRL were similar to those recognised with arm BCRL. However, not all risk factors demonstrated a statistically significant relationship with mid-line lymphoedema in every study and in several studies conflicting results were found.

  - There was a difference in the incidence of breast lymphoedema reported depending on the type of surgery that the patient underwent. Axillary node surgery, (ANC or ALND) increased a patient's risk compared to sentinel node biopsy (or axillary sampling) or no axillary surgery, however, breast lymphoedema was reported in all groups.
  - Several studies considered the relationship of radiotherapy in the development of breast lymphoedema and it is felt that adjuvant radiotherapy increased the risk of developing breast lymphoedema. Some studies included a pre-radiotherapy assessment and breast lymphoedema was recognised in some patients at this assessment point. In the studies that compared the incidence of breast lymphoedema for those who did and did not receive radiotherapy breast lymphoedema was recognised in both groups, but the incidence was higher in those who had received radiotherapy.
  - Increased BMI was found to be significant in one study investigating the incidence of breast lymphoedema. Univariate analysis demonstrated a BMI of greater than 44 was associated with the development of breast lymphoedema. Participant weight or BMI was not reported in any of the other studies. Obesity was also associated with the development of delayed breast cellulitis.
  - Tumours located in the upper outer quadrant were associated with the occurrence of breast oedema in one study. This study used subjective reports of oedema by clinicians as part of a retrospective notes review. Conversely, tumour site was not

found to be associated with breast oedema in two other studies that used clinical examination and ultrasound scanning.

- Bra size was non-significant in one study and significant in two studies, however, one study identified that women with small breasts were more likely to develop breast lymphoedema and the other women with large breasts.
- Cellulitis and post-operative wound infections were identified in two studies to be statistically associated with the presence of breast oedema. It has been recognised that infections such as cellulitis can damage the lymphatics and can cause or worsen lymphoedema in other parts of the body.

2.5.2. The Objective Measurement of Breast Lymphoedema.

The limitations identified from the techniques that are available or have been adapted to assess mid-line BCRL demonstrate why there currently isn't a gold standard tool for assessment. The lack of a gold standard technique for diagnosing lymphoedema makes the validation of new or additional assessment techniques more difficult. This may be why the methodologies of the reviewed studies vary significantly. Some of the assessment techniques have been utilised in breast lymphoedema studies, however, some of these includes only a small number of participants. In addition, few studies repeated measurements or complete sequential assessments over time. In addition little is known about these measurements in a "normal" breast. Of the tools that have been studied there does not appear to be a "normal range" and as such, diagnostic thresholds for mid-line BCRL have not been proposed.

It is felt that despite the limitations there is potential in the measurement techniques considered in this review to improve the objective assessment of BCRL.

The majority of the studies reviewed assessed for the presence of breast lymphoedema following breast conserving surgery. In these studies comparisons of the measurements were compared to a pre-treatment baseline or to the contralateral breast. These comparisons cannot be made for patients who undergo a mastectomy. Overall this review identified that chest wall BCRL has not been as well studied and appears more difficult to determine the absence or presence of oedema to this area.

Table 6. Advantages, disadvantages and limitations of the measurement methods reviewed.

Method	Application	Advantages in assessment	Limitations in assessment
Ultrasound	Longitudinal follow up and assessment of breast oedema. Recognition of changes in breast tissue prior to RT and resolution of oedema over time. No pre-surgery USS measurements obtained but pre and post RT, up to 24 months.	Can be used to compare to unaffected breast. Can measure and assess each breast quadrant separately. Most commonly studied assessment technique.	Difficulty distinguishing between the layers of the skin therefore total cutaneous thickness recorded. Mean coefficient of variance = 13.9%. Assessment not always correlated with clinical examination.
Tonometer	Reproducibility study undertaken. Used as an outcome measure in the identification of capsule formation post breast reconstruction. Not used in a longitudinal study for assessing breast oedema.	Successfully tested for reproducibility in the assessment of breast oedema. Measures local tissue changes / differences with contralateral points.	Not studied difference between affected/ unaffected breast or breast quadrant measurements. Breast shape changes depending on position, natural differences in shape and tone of breast.

Tissue Dielectric Constant (TDC)	Publications to date on the assessment of local tissue changes of the limbs.	Has been used to measure local fluid changes / differences, therefore could measure individual breast quadrants.	Normal or reference values published for specific measurement points on the arm and the ratio of 1.26 identified as indicative of the presence of oedema. More recently a ratio of >1.4 has been proposed as indicative for the presence of breast oedema.
Bioimpedance Spectroscopy (BIS)	Reproducibility study undertaken. Used to assess seroma formation and resolution after breast cancer surgery. Measurements used to estimate breast volume.		This technique for assessing breast lymphoedema has not been fully studied and it is not known whether the electrode positions reported will accurately measure bioimpedance in this area.

Caliper creep / skinfold thickness	Validation study to develop an objective measure in the assessment of truncal oedema. Used as an outcome measure in the comparison of MLD and SLD in patients with BCRL of the arm.	Repeated measurements (12 over 14 days) demonstrated high levels of correlation. Identified that the rate of creep, pitting, was a more sensitive indicator of oedema than skinfold thickness alone. Compares differences between the affected and unaffected side.	Variability in the pressure exerted by the calipers resulted in them being adapted for use in the validation study. Difficult to undertake in certain patients (obese, sensitive skin, scarring, RT reactions).

2.5.3. Implications for Future Research.

This review has highlighted that there is a need for producing a standardised clinical assessment for assessing mid-line BCRL and validating this alongside objective measurements and patient reported symptoms. The results of this would improve the holistic assessment and recognition of mid-line BCRL in clinical practice.

From the available literature it is apparent that there is a need to validate an objective measurement technique or techniques that can be used to monitor and identify the development of breast and chest wall lymphoedema. The techniques that are available and have been studied have limitations in their application which may be why this area of lymphology has many unanswered questions. Currently this type of lymphoedema is assessed subjectively by the patient and or the clinician. Having an objective measurement technique to use alongside clinical judgement and a patient completed symptom report would improve this. A patient reported symptom assessment validated alongside clinical mid-line BCRL and validated objective measures would support clinicians who do not have access to objective assessment tools to improve accuracy of the diagnosis of mid-line lymphoedema.

The literature review identified two new concepts. The first being delayed breast cellulitis and the second being the self-limiting effect of breast BCRL. The clinical signs of delayed breast cellulitis appear very similar to breast lymphoedema and the lack of positive blood cultures in the studied papers raise the question whether they might be the same condition. In the clinical environment patients present with leg lymphoedema who also have venous hypertension. In these patients the limb appears red, inflamed and swollen. Clinically this pattern is also recognised in patients with breast lymphoedema, often in the patients with larger breasts who have not been able to wear bras with enough support for the breast.

To observe the true time course of breast lymphoedema and to observe whether it is self-limiting presents ethical considerations if intervention was not offered. Clinical experience and the literature report significant levels of discomfort when breast lymphoedema is present. If breast lymphoedema does follow the same pattern as other types of lymphoedema, untreated lymphoedema increases the risk of cellulitis and the development of chronic skin changes that do not respond as well to the available conservative treatments.

A future study which would include pre-treatment / baseline assessment and follow up assessments over a period of at least 12 – 30 months is recommended to assess fully the true incidence of mid-line BCRL and potentially whether it is self-limiting.

Chapter 3: Literature Search and Review on Quality of Life and Mid-line Lymphoedema.

3.1. Introduction.

The assessment techniques described in the previous chapter focused on identifying physical changes in the body part(s) "at risk" of developing lymphoedema and did not examine the functional, emotional and psychosocial impact of lymphoedema. The literature reports that lymphoedema can negatively impact a patient's quality of life and that this relationship is not purely linear, in that quality of life does not decline as the severity of measured lymphoedema increases (7, 8, 10, 73). Therefore, it cannot be inferred that by assessing lymphoedema using physical measures only can holistically assess the impact of this condition on the patient.

There are many tools available that have been designed to assess quality of life (QoL) and are distinguished by those developed for generic use, disease specific tools and condition specific tools (74). All three types of tool have been used in research studies that were designed to explore the relationship between lymphoedema and quality of life. It can be debated whether the use of a generic or condition specific tool is most appropriate. The generic tools may explore the impact on quality of life from an overall view but may not capture the impact of the condition being studied. The condition specific tools look at the impact of the condition but may not be able to differentiate between the impact of the condition being studied or other comorbidities.

The search methodology that was presented in Chapter 2 was used in this search, but different search terms were applied. Again, the CASP methodology for critically appraising the selected papers was utilised to provide a consistent approach.

The search considered the use of generic QoL tools, disease and condition specific tools to enable a broad review to be undertaken. The overarching aim of the review was to determine whether there was a current validated tool that should be used to measure QoL in patients with mid-line BCRL or whether there is scope for this to be developed.

3.2. Literature Search Results.

The second search used the terms lymph$edema and quality of life. In the second search initially 2398 articles were identified once duplicates had been removed (table 7). This resulted in 89 papers that were included in the formal review (figure 4).

Figure 4. Literature Search Flow Chart – Quality of Life and Lymphoedema.

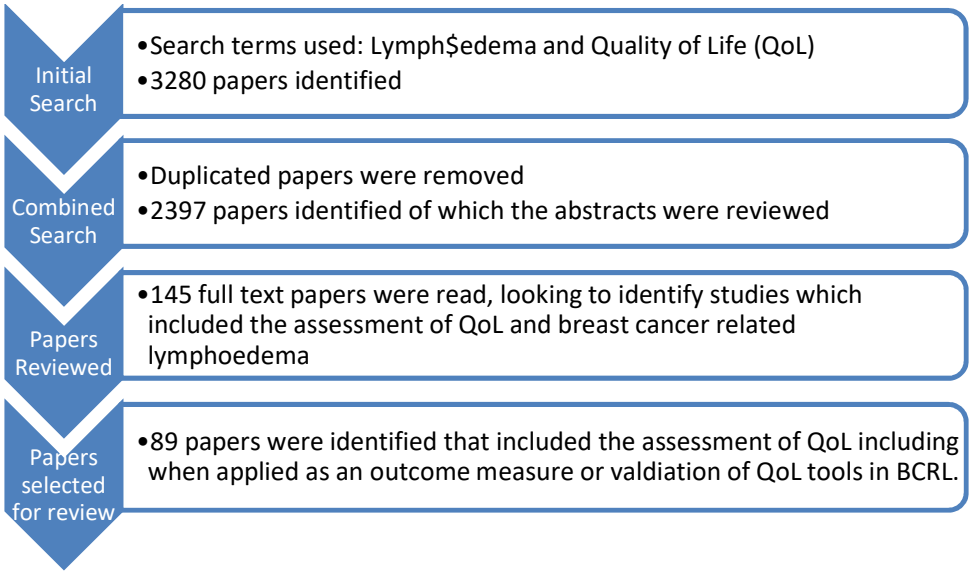


Table 7. Literature Search Results – Quality of life and breast cancer related lymphoedema.

Database	Lymph$edema and quality of life	Restricted to research terms	Selected following abstract review
Ovid (including AMED, BNI, Embase and Medline)	2267	2248	90
PubMed	131		55

The second search identified 89 unique papers. This search identified three conference presentations and abstracts that had been published in conference proceedings. These were considered to enable further investigation to be undertaken with the aim of determining if full papers detailing the study outcomes had been published or to identify ongoing research.

This search identified more papers overall than the search described in chapter 2. This may have been due to the broadness of the topics searched. Studies were included if they explored quality of life in patients with BCRL, it wasn't specified that the papers needed to include quality of life in patients with mid-line BCRL.

There were several topic themes that arose from the papers that were identified in this search and these included:

- the development and validation of quality of life tools (8, 75, 76, 77, 78)
- studies that were designed to explore QoL following breast cancer treatment with or without post treatment interventions.

Participants with BCRL were included in the sample and sub group analysis or comparisons between patients with and without BCRL were undertaken (21, 39, 79-88)

- studies that had been designed to assess the impact on QoL life in people with BCRL (89, 90, 91),
- studies designed to measure QoL as one of several outcomes following a treatment or an intervention for BCRL (92-98)
- studies that looked at QoL in patients with different types / causes of lymphoedema which included patients with BCRL (99, 100, 101, 102).

3.3. A review of the most commonly utilised quality of life tools identified in the literature review.

From the literature search 24 different QoL tools or versions of tools were identified from 89 papers. The majority of the papers identified looked at QoL in patients with arm BCRL and seven of the papers were reviews on QoL assessment in patients with lymphoedema.

The papers included validation studies of the disease and condition specific tools and studies that evaluated the impact of different interventions on quality of life. Table 8 describes the most commonly utilised tools identified in the search and details their development, validation and use by others.

Table 8. Overview of the QoL tools identified in the literature search.

Tool	Development and use	Validation details
Functional Assessment of Cancer Therapy – Breast (FACT B)	Developed by the Facit group from the FACT-G (general) tool (103). FACT G was originally developed and validated using a 5 stage validation process for evaluating QoL in patients receiving cancer treatment. Supplementary sections developed since look at specific diseases, conditions, treatments and side effects. Tool completed using a 7 day recall and 5 item likert scale (not at all = 0 to very much = 4). Self-reported item with additional subscales. Three generic sections in all questionnaires: physical wellbeing, emotional wellbeing and functional wellbeing. Total score calculated alongside individual domain totals.	FACT G validated in large multi centred study with patients receiving cancer treatment for different types of cancer. Tested alongside other validated tools including FLIC, ECOG. FACT B was validated in 2 samples, n=47 tested twice to assess sensitivity to change. Cronbach's α coefficient on total and subscale scores, test-retest reliability, convergent, divergent and known group validity n=295 (104)

FACT B +4 (for people with lymphoedema)	Developed as a symptom specific measure (75). Consists of FACT-B with 4 additional questions looking at arm symptoms (pain, range of movement, numbness and stiffness).	Validated in the ALMANAC study (21) in patients with known BCRL. Face validity tested by focus group. Moderate to high internal consistency. Test-retest reliability tested on treated BCRL group (oedema stable) correlations high for arm subscale (r=0.93). Discriminant validity confirmed as matched groups of patients compared – BCRL vs. no BCRL, significant differences between groups. BCRL scored lower on each QoL subscale except emotional wellbeing than no BCRL group (75). Sensitivity to change over time assessed in ALMANAC group comparing consecutive assessments. Significant decrease in QoL at 4weeks post op than pre-op (p=0.001). Scores improved but not back to pre-op level by 12 months post op (21).

SF-36 (Short Form)	A generic measure developed from the Medical Outcomes Study as a multipurpose, short form questionnaire to assess functional health, wellbeing and health status. Used to compare relative burden of disease (105). 36 items are split into three levels: 36 items (individual questions), 8 scales (consisting of items within the same area) and summary measures (scales combined to measure physical or mental health). Can be administered in several formats (self, telephone, computer and in-person interviewer). Completed using 1- or 4-week recall. Scores from each scale transformed to 0-100 scale, lower score = more disability. SF6D calculated from the SF36 enables economic evaluation, allowing cost utility analysis and quality of life affected years (QALYs) to be calculated.	Reported to be the most extensively validated and used health survey instrument for appraising quality of life (106). Reliability, specifically internal consistency and test-retest published statistics with rare exceptions exceed the minimum standard of 0.7 with the majority exceeding 0.8. Validity confirmed through extensive application. Reports content, concurrent, criterion, construct and predictive evidence of validity. Recognised limitations include the ceiling and floor effect (improved in version 2) and the loss of precision compared to longer surveys. This limitation is debated taking into consideration respondent burden and high response rates.

Euroqol 5D (107)	Designed as a simple generic measure of health. Is a standardised instrument used as a measure of health outcome. Provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. Designed to complement generic and disease specific quality of life tools. Consists of 5 questions with a 3 or 5 item likert scale plus visual analogue scale for self-reported health state. Simple to complete. Scoring system developed using all of the combinations of responses from the 5 questions (243 combinations).	Validated in several different languages and patient groups including healthy populations to patients undergoing high dose chemotherapy for breast cancer. Responsiveness to clinically large changes associated with high dose chemotherapy confirmed, however, some discrepancy reported in the effect size, medium to large effect sizes was reported for the breast cancer sample undergoing chemo. Smaller effect size produced when compared to generic quality of life tools in patients with knee surgery, sleep apnoea and prostate cancer (106).

EORTC- QLQ – BR23	The QlQ-C30 was designed as an international trials QoL tool for patients with cancer. The core instrument was designed to be supplemented by additional subscales to assess aspects of QoL of particular importance to specific subgroups. The core instrument consists of 30 questions. The BR23 subscale 23 additional questions. Question recall of the last 1 or 4 weeks. Responses use a 4 point likert scale. BR23 includes 2 symptom scales assessing arm and breast symptoms. In the Dutch version the breast questions are omitted for patients who did not undergo breast conserving surgery but these are kept in the English version to enable symptoms in the area of the affected breast (mastectomy site) to be recognised.	Developed with patients and medical specialists from 3 countries. Tested in a 3 country study (108). Content and construct validity testing undertaken, along with internal consistency analysis. Cronbach's α varied between the 3 groups but was >0.7 for the majority of the items, however, for the Spanish sample was <0.7 for the breast symptoms at both time points. Responsive to change was demonstrated when comparing different treatment groups (chemotherapy vs. radiotherapy).

Functional Living index Cancer (FLIC)	Developed to assess overall functional QoL of cancer patients “day to day” lives. Consists of 22 item questionnaire with 5 dimensions (physical wellbeing, emotional, sociability, family situation and side effects of treatment. Each item has a 7 scale response. Overall score ranges from 22-154.	Initial validation confirmed moderate to good levels of reliability and correlation coefficients with the SF36 ranged from 0.5 to 0.62. Further reliability study using more in-depth testing confirmed reliability in a prospective study which involved patients undergoing breast cancer treatment (109).

Nottingham Health Profile (NHP)	Developed as a self-administered tool designed to give a brief indication of perceived physical, social and emotional health problems (110). It was originally intended for use in primary care and not intended as an outcome measure for clinical trials. Its emphasis is on respondent's subjective assessment of health status. It consists of two parts; the first includes 38 items grouped into 6 sections (physical disabilities, pain, sleep, social isolation, energy levels and emotional reactions). Each question within a section is weighted with the maximum score for each section = 100. The second part is optional and is designed to identify handicap from 7 items.	The tool was first developed in 1981 and has been used widely in a range of settings and with different groups of patients with a range of conditions. Reference data for healthy population and specific groups of patients is available. The tool has undergone reliability and validity testing in several studies. It has been correlated against the SF-36 and the McGill Pain Questionnaire with satisfactory levels of correlations being reached. It has demonstrated discriminant validity comparing healthy controls and different patient / treatment groups. One limitation reported is the ceiling effect and the lack of sensitivity to change for people with good levels of health or minor levels of disability.

Lymphoedema functioning, disability and health questionnaire (Lymph ICF)	Developed to assess impairments in function, activity limitations and participant restrictions related to lymphoedema developed after axillary dissection for breast cancer (76). Recalls past 2 weeks, responses use a 100mm visual analogue scale (not at all – very much). Two different 4 point response scales: patient situation scale (totally not agree – totally agree) and patient importance scale (very unimportant to very important). The score for each statement is the product of the scores on both scales (range 1-16). For mean overall score higher = more problems. Mean domain scores also calculated (5 domains: physical, mental function, household activities, mobility activities, life and social activities). Original questionnaire developed in Dutch but has been translated into English using the WHO guidelines.	Developed following discussion with 20 patients to identify impairments. No impairments in mental function were therefore were included that were identified in the literature. Reliability and validation study undertaken of the pilot questionnaire; strong test-retest reliability, strong internal consistency and good construct validity. Content validity not acceptable as 38% participants felt the scoring system was not clear and 38% mentioned missing complaints relating to their oedema. Pilot version developed into final questionnaire. Final version tested for reliability and validity in 30 patients with breast cancer and in 60 patients with BCRL (30 with objective BCRL and 30 subjective BCRL). Questionnaires completed x3 occasions along with SF36. Test-retest correlations moderate to strong for the different domains (ICC 0.65 for life and social activities to >0.9 for physical function and household activities). Internal consistency ranged from moderate to very strong.

		Patients with BCRL had significantly higher score on 26/29 questions, similar scores for patients with subjective and objectively assessed lymphoedema. Limitations acknowledged included the responsiveness of the tool had not been tested, English version not validated and the relatively small sample sizes in the both validation studies.

Upper Limb Lymphoedema (ULL-27)	Quality of life scale in upper limb lymphoedema developed in 3 stages (111). The first being a qualitative survey of patients and health care professionals to identify themes. Thematic analysis of the 24 interviews identified 70 items. A preliminary questionnaire was administered to 154 patients to select the most relevant items and following the analysis the number of items reduced to 27 for the final questionnaire. The questions are divided into three domains: physical functioning, psychological dimension and social dimension.	ULL validated in a sample of 301 patients with BCRL. BCRL severity graded using limb volume measurement (77). ULL was completed alongside limb volume, SF36, VAS of arm comfort, Global Symptom Index (GSI) and Global Clinical Impression (GCI) at 2 time points (day 0, day 28). Reliability confirmed ICC >0.8 and Cronbach's α >0.8 for all 3 domains. Correlation coefficients for each item and the dimension they belong >0.4 confirming that they are correlated. Comparison of ULL scores to BCRL severity demonstrated significant differences for the physical and social dimensions but not the psychological dimension. However, this finding was not confirmed in the validation of the Dutch ULL-27. No differences were found in the total or domain scores of the different groups (8). Responsiveness was measured comparing the change between first and second visit. Patients who improved clinically had significantly different ULL scores (Paired Wilcoxon test $p<0.001$). Acknowledged that responses for some items were omitted.

LYMQOL	Condition specific quality of life tool. Developed with service users, designed as a self-completed tool for assessing quality of life in people with lymphoedema of the arm(s) or leg(s) (7). Designed to be used by people with a range of the cause or type of lymphoedema. The final validated version contains 27 items (LYMQOL leg) and 28 items (LYMQOL arm). There are four domains in each version: function, appearance, symptoms and mood as well as an overall quality of life rating (VAS 0 poor -10 excellent). Each item has a four point response (not at all to very much). The mean scores for each domain are calculated. The higher the score the lower quality of life.	Validation study undertaken of the first version of the tool to test the validity, reliability and responsiveness. Sample included people with arm and or leg oedema, n=209, recruited first visit to the lymphoedema service. Face validity confirmed by subjective assessment on the presentation of the questionnaire. Content validity confirmed by subjective assessment and a separate phenomenological interview study (112). 20% patients asked felt important areas were missing although 92% felt that no questions could be left out. Criterion validity confirmed using the EORTC-QLQ-C30, good levels of correlation with the comparable domains were found (all ICC >0.6). Cronbach's α >0.8 for all of the domains in both questionnaires confirming internal consistency. In split half testing reliability was good or adequate except symptoms domain of LYMQOL arm. Good levels of correlations found on test-retest analysis of patients with leg oedema. However, the number of patients was small (n=15). Construct validity was not confirmed as there was no significant correlations between limb volume and quality of life.

		Responsiveness was not confirmed in the arm questionnaire, but statistically significantly lower scores were found post treatment for the appearance domain and overall QoL increased.
Freiburg Life Quality Assessment – lymphoedema (FLQA-l)	Developed from the previously validate FLQA vein questionnaire with the aim of developing a standardised QoL questionnaire specific for lymphoedema (113). Aimed to be used for patients with primary and secondary lymphoedema. The questionnaire consists of 92 questions referring to physical status, everyday life, social life, emotional wellbeing, treatment, satisfaction and profession / household.	Validated on 392 patients. Crohnbach's α was identified as >0.75 in all the domains. No floor to ceiling effect reported. Test-retest reliability, sensitivity to change and convergent validity satisfactory. Patients with lymphoedema had lower QoL compared to patients with early venous insufficiency and were comparable to patients with venous leg ulcers.

Lymphoedema Quality of Life Inventory (LYQLI)	A Lymphoedema specific quality of life tool. Original tool developed and tested in Australia for people with upper and lower limb lymphoedema (114) Developed in three stages: firstly, qualitative interviews with women with lymphoedema and content analysis undertaken identifying four dimensions. It was then tested for clarity, face validity, content validity and internal consistency in a group of women and health care professionals with experience of treatment of lymphoedema. Thirdly 196 patients with lymphoedema completed the tool to assess internal consistency and concurrent validity. The questionnaire is divided into four domains; physical, emotional, social and practical. Each item is followed by 3 sub items with 4 answer alternatives. The final 2 questions include a general quality of life question and a quality of life question specific to lymphoedema. The Swedish version consists of 183 items and takes approximately 30 minutes to complete.	Further validation undertaken following translation into Swedish (78). Validity assessed by experts to identify statements commonly used by patients to describe lymphoedema. Face validity confirmed by 19 patients to determine understanding and relevance. As a result, 3 questions were added and the time period of recall increased from 1 week to 1 month. Test-retest analysis was undertaken without any intervention between questionnaire completion (looking to measure the same experience). Kappa coefficient ranged from fair to very good for each domain. However, measurement error was shown and the authors concluded that the tool should be used to assess QoL at one time and not to look for changes post intervention. It was recognised that not all patients completed the questionnaire at the first or on both occasions. The median age of non-completers was older, and it was suggested that the length of the questionnaire may deter completion.

		Correlations between SF-36 and SLYQLI were moderated (r>0.5) for quality of life and the practical, physical and social dimensions. It was questioned whether the SLYQLI was of use in patients with primary lymphoedema who had experienced oedema for many years as it was felt that they may have adapted to the condition.

Wesley Clinic Lymphoedema Scale (WCLS) (115)	This tool is an adaption of the FLIC questionnaire to create a condition specific tool (73). The 5 questions in the FLIC that specifically ask about "illness or "cancer" were substituted for "lymphoedema in particular". The WCLS is scored in the same way as the FLIC (see above). In the WCLS there are 22 items each with a 7 point scale.	No details of validation or reliability testing published. The tool has been used in one study to assess the effect of lymphoedema treatment (n=25). Measurements were taken pre and post intensive treatment and then at one, six and twelve months. Overall QoL improved slightly at the end of the intensive phase and this trend continued over the 12 month study period, however, the lymphoedema subscale demonstrated a decrease in QoL at the post treatment assessment. At the follow up assessment points QoL increased to just above the baseline level at 12 months. The linear trend was significant but not the quadratic trend. The relationship looking at changes in WCLS score did not reflect the direction of change in lymphoedema measurements.

3.4. Strengths and Limitations of the Available Quality of Life Tools.

Table 8 emphasises the variety in the tools available. The papers that detailed the validation undertaken for the tools all acknowledged limitations in their use. All demonstrated some of the characteristics required to be considered valid and reliable, but no single tool met all of the requirements. This may reflect why there is no current gold standard QoL tool and why new tools are still being developed and tested.

The methods used to validate the tools varied; some underwent more rigorous assessment than others. In addition to the CASP checklists standards have developed to appraise health related outcome tools, with a specific focus on the validation process. The COSMIN (COnsensus Standards for the selection of health Measurement INstruments) consensus and checklist were developed following an international Delphi study (116). The guidance identifies the measurement properties that a tool should have to be able to be described as reliable, valid and responsive. The checklist provides questions that help to determine whether the tool has been designed and tested appropriately. The questions from the COSMIN checklist were considered during the appraisal of the different QoL tools (table 9).

The involvement of patients and health care professionals in the development and testing of the questions is recognised in the content validity. Completion of this enables the readability and understanding of the questions to be confirmed. It also encourages additional questions to be suggested or those not felt to be relevant to the subject or patient group removed. This process was explicitly described for several of the QoL tools (7, 76, 78, 103, 108, 111). As a

result of this process, the number of questions or content of the tools were amended to the final, tested version.

Information was not always provided on how the sample size used in the studies was determined and whether the analysis undertaken was appropriate.

Construct validity is tested by comparing the newly developed tool with other established measures. Consideration was made looking at the similarities or differences between the tools in question and how this would be reflected in the analysis. The SF36 was most commonly used, and comparisons made against 5 other tools during the validation studies (76, 77, 78, 109, 110). The SF36 is reported to be the most extensively validated and used health survey instrument for appraising quality of life (106). It is a generic tool that was developed to assess functional health, wellbeing and health status. It focuses on the relative burden of disease. The QoL tools that have been compared to the SF-36 varied and included generic tools and lymphoedema specific tools.

Some of the limitations identified included missing responses or non-completion of questionnaires. This may be reflected in the length of the tool or the frequency of completion (7, 78). If a tool is too lengthy, or some of the questions are not felt by the patient to be applicable they may not be completed. It was recognised in the validation of the EORTC-QLQ-BR23 that sensitive questions were not completed by all patients (108). If questionnaires are issued too frequently especially by post or due to be returned by post the patient may feel fatigued by this and not complete or return the questionnaire.

Assessment of the measurement error or reliability of the tool is made after assessment of how and when the tool is administered. The test-retest analysis of some tools was undertaken without intervention occurring between questionnaire completion. The aim of this was to

show that there was no significant change in the responses to the tool (75, 76, 78). The timing of the repeated application was recognised as an important consideration as too soon and the respondent could remember and replicate the previous answers or too long and a change in condition could have occurred (116). Other tools were repeated over longer durations and on multiple occasions to determine whether they did change over time because of intervention (7, 77, 73).

3.4.1. Comparison of the lymphoedema specific quality of life tools using the COSMIN checklist.

Table 9. Validation of the different Lymphoedema Specific Quality of Life Tools using the COSMIN checklist criteria.

QoL tool acronym	Content Validity	Structural Validity	Internal Consistency	Cross Cultural Validity / Mmt Invariance	Reliability & Mmt Error	Criterion Validity	Responsiveness	Hypothesis Testing for Construct Validity
FACTB+4	PARTIAL	YES FACTG NO - FACTB+4	PARTIAL *	NO	PARTIAL *	NO	YES	PARTIAL *
Lymph ICF	PARTIAL	NO	PARTIAL *	NO	PARTIAL *	NO	NO	PARTIAL *
ULL-27	PARTIAL	YES	PARTIAL *	NO	PARTIAL *	NO	PARTIAL	NO
LYMQOL	YES	NO	YES	NO	PARTIAL	PARTIAL	PARTIAL	PARTIAL
FLQA-l	YES	NO	PARTIAL *	NO	PARTIAL *	PARTIAL	PARTIAL	PARTIAL
LYQLI	YES	NO	PARTIAL *	NO	PARTIAL *	PARTIAL	NO	PARTIAL
WCLS	NO. Adapted from the FLIC with lymphoedema inserted to replace cancer / illness.							

*no mention of how to handle missing items which is a requisite for the checklist criteria to be met fully.

Detailed evaluation of the seven lymphoedema specific quality of life tools was undertaken using the COSMIN checklist (table 9) (116). The WCLS did not meet any of the checklist criteria as this had been created from the FLIC tool and had had the word “lymphoedema” inserted to replace “cancer” or “illness” (115). It was then used as an outcome measure without being validated in this new form.

For assessing content validity, the COSMIN checklist identifies that the PROM should have been developed with involvement of both patients and professionals. To do this it recommends that meetings and interviews were undertaken by skilled researchers, recording and transcription of the interviews and appropriate analysis.

Three of the reviewed tools did meet these requirements fully. The two that partially met the criteria did not involve professionals when developing the tools (Lymph ICF and ULL-27) (76, 111). In addition, one researcher completed the analysis for the ULL-27 and the COSMIN checklist specifies that this is undertaken by at least 2 researchers to reduce bias. The new questions used in the FACTB+4 tool were identified as a result of discussions with patients and professionals but not through interviews and subsequent analysis of these (75).

One of the requirements for internal consistency, responsiveness, hypothesis testing for construct validity, measurement error and criterion validity is that there is description of how missing data is handled. This was not reported for several of the tools (FACTB+4, Lymph-ICF, ULL-27, FLQA-l) which meant that these tools were not able to fully meet the criteria (75,76, 111, 113).

As part of the evaluation of structural validity the COSMIN checklist specifies the type of analysis that should be undertaken to explore how the different items in the tool measure the same condition being studied. To do this factor analysis or Cronbach’s α is recommended

(116). This was completed for all the reviewed tools except LYQLI (78).

There was one section of the checklist that none of the reviewed studies met the criteria for, cross cultural validity. This part of the validation process investigates how the tool behaves when used in different populations such as age, gender, language and ethnicity. In the validation studies subgroup analysis was not undertaken to explore any similarities or differences within the studied sample. This type of analysis is likely to be undertaken in future studies once the initial validation has been confirmed and the tool applied more widely. Since the tools were reviewed in this thesis the Lymp-ICF, LYMQOL, ULL-27 have been translated and validated in additional languages increasing the application of these tools (160 – 167).

All the tools met some of the requirements relating to reliability and measurement error. This was achieved by completion of the questionnaires on at least two occasions. It is recommended that the repeated questionnaire is done at an appropriate time interval, repeated questionnaires are completed by at least 30 participants, under similar test conditions and that the patients' condition is stable (116). Only LYQLI and FLQA-l were completed on multiple occasions in over 30 patients, however, for FLQA-l this was before and after initiating lymphoedema treatment so it would be expected that the patient's condition would have changed (78, 113). Additionally, in the validation of LYQLI it was planned that patients would repeat the tool after 1-2 weeks but they acknowledged difficulty in getting participants to return the repeated questionnaires and it took up to 7 weeks to do. In the LYMQOL validation study it was acknowledged that only a small proportion of the sample were included in the reliability analysis as most patients were treated at their first appointment and were therefore excluded (7).

Criterion validity may be the most difficult part of the COSMIN checklist to achieve as is wanting to compare and test the tool in

question against the gold standard. The tools being considered all recognised that there isn't a gold standard tool for assessing quality of life in people with lymphoedema. FACTB+4 and ULL-27 were not compared to another tool (75, 111). The other QoL tools were measured against previously validated general quality of life measure.

The responsiveness of the tools was tested by repeated measurement over time to indicate longitudinal validity. It was expected that hypotheses about the predicted changes and relationships would have been made. In addition to fully meet this part of the checklist appropriate time scales between measurements were needed to ensure that change in scores before and after the intervention occurred and the sample size large enough that appropriate statistical analysis could be undertaken. FACTB+4 met all the assumptions and LYMQOL, the ULL-27 and the FLQA-l some.

The eighth part of the checklist again uses hypothesis testing, this time to study construct validity. The COSMIN checklist identifies the importance of defining the hypotheses in advance so that unbiased conclusions can be made (116). The hypotheses should define the expected relationships with the other outcome measure(s) used and the expected differences between subgroups (discriminant validity). The Lymph-ICF met all the requirements for this component of the checklist except the information about managing missing data. Different relationships were seen in the groups with and without lymphoedema. Discriminant validity was not tested in LYMQOL and the hypothesis that QoL would decrease as limb volume/severity of lymphoedema increased was not proven (7). Neither the FLQA-l ULL-27 presented and tested hypotheses about the expected relationships.

3.5. The relationship between limb volume measurement and quality of life.

The relationship between limb volume measurement, an outcome measure often used to assess the efficacy of treatment, and quality of

life scores has not been established. QoL scores have been shown to be different between those with and without lymphoedema with decreased / worse QoL recognised in people with lymphoedema. (75, 76). This relationship has been observed within the individual domains of the assessment tools and when overall QoL was considered (75, 76).

Increased limb volume was not found to be associated with a decrease in quality of life when assessed by LYMQOL (7). In contrast to this, Lymph-ICF scores were found to be comparable with subjective and objective assessments of lymphoedema (>200ml difference between the affected and unaffected arm) (76). Responses to the question in the Lymph-ICF that asked specifically about swelling was significantly higher (worse) in the group of patients with objective lymphoedema (76). Quality of life scores for the physical and social domains of the ULL-27 were significantly lower at the first assessment in those with larger limb volume differences; however, the psychological domain scores were similar and not related to the severity of lymphoedema (77). Conversely, in the validation of the Dutch version of the ULL oedema severity using the same criteria did not demonstrated significant differences in the total QoL score or the domain scores when the different groups were compared (8).

Measuring change in QoL scores to determine significant clinical change, specifically identifying the minimum clinically important difference (MCID), has not been established in any of the identified QoL tools. Only one study considered this as part of the test-retest analysis (76). Understanding more about the measurable change will help to strengthen the understanding on the impact of the condition and the treatment(s) provided.

3.6. Assessment of quality of life in patients with mid-line breast cancer related lymphoedema.

From the studies identified from the literature search the most commonly utilised quality of life tools were the SF 36 and the FACT B or FACT B+4 tools. The majority of the studies had used quality of life measures in the assessment of BCRL of the arm. Only two studies were identified that focused on breast lymphoedema the first was a prospective study looking at the incidence of breast BCRL (51). In this study FACT-B was completed by participants at each of the assessment points up to 12 months post-surgery. The second used the EORTC-QLQ-BR23 as an outcome measure looking at the incidence of breast lymphoedema at a single assessment point, which was up to 5 years after breast cancer treatment (39). Breast lymphoedema in this study was self-reported following completion of subjective symptom questionnaire (39). A higher score was associated with increased severity of breast BCRL and participants were classed as mild, moderate and severe. In this study the incidence of breast BCRL was 75.7% and the mean symptom score was 14.4. Comparisons were made between the group with and without breast lymphoedema using the EORTC-QLQ-BR23. This demonstrated that there was a significant difference, worsening, in the breast symptoms questions for the breast BCRL group ($p<0.001$). There was also a significant negative correlation associated with the presence of breast lymphoedema and body image ($p<0.001$ $r = -0.443$).

A third study used the EORTC-QLQ-BR23 as an outcome measure in a study comparing water and land-based exercise following treatment for breast cancer (79). There was a reduction (improvement) in the scores of the breast symptom questions for the group that received water-based exercise compared with those in the land based or control group, however, no objective assessment of breast symptoms

were recorded and there was no report of the group having lymphoedema of the arm.

From the literature it is apparent that there is not currently a QoL life tool that has been developed and thoroughly validated that can be used in patients with or at risk of developing mid-line BCRL. The EORTC-QLQ-BR23 is the only tool that considers breast symptoms and the responses to the questions about breast symptoms appear to differentiate between patients with and without subjective breast lymphoedema.

It feels that there is an opportunity to develop a condition specific QoL tool that will meet the quality standards such as those suggested in the COSMIN consensus checklist. This would complement the development of an objective measurement tool to fully assess the impact of this condition. If breast lymphoedema does present as a self-limiting condition, as described in the literature, then assessment of quality of life over a appropriate time period would be useful in assessing the impact of this condition and whether intervention to treat the lymphoedema should be considered.

3.7. Patient reported symptoms of lymphoedema.

The literature search also identified two patient reported symptom questionnaires that have been developed and validated. The first, the lymphoedema breast cancer questionnaire (LBCQ) is 58 item tool that asks patients questions about the signs and symptoms pertaining to the presence of BCRL (6). The questions include changes to the chest wall and breast. In the prospective validation study participants completed the LBCQ and had limb volume measurements undertaken. In the analysis 3 questions were identified as significant in discriminating between participants with and without arm

lymphoedema (defined as a 2cm mean difference between limbs), these were “swelling now”, “heaviness in the past year” and “numbness in the past year”. The swelling question asked the respondent to consider the presence of swelling to the arm, breast or chest. However, the LBCQ was not and has not been used with objective measures or a subjective assessment of mid-line BCRL.

The second symptom tool that was identified was the Lymphoedema symptoms and intensity and distress survey (LSIDS). This is a self-report tool that was developed to evaluate arm lymphoedema and its symptoms. It was developed over three phases which included an expert panel discussion to produce the initial tool and face validity testing with patients (117). The formal validation of the 36 item tool is reported as complete and the results were in press at the time of undertaking the literature review. One of the findings was the need to develop a tool that could be used in the evaluation of lymphoedema of the trunk.

Two studies included patient completed symptom questionnaires that were developed for use in that individual study but neither were formally validated (39, 51). Both questionnaires included symptoms associated with breast lymphoedema such as; swelling, heaviness, discomfort and redness / erythema. Patients were asked to rate the presence and severity of each symptom using numerical scales. Only one study combined completion of a self-reported symptom questionnaire with clinical examination and found that although more symptoms were reported in those patients with clinically determined breast lymphoedema, patients without lymphoedema reported breast oedema and erythema as present (11.6% and 13 % respectively). This finding confirms that there is a need for further assessment in addition to a self-reported tool used to confirm the presence of lymphoedema and in doing so this could reduce the amount of false positive diagnoses.

A simple self-completed lymphoedema identification tool validated alongside objective assessment techniques would be a significant development in the assessment of breast and chest wall lymphoedema. Objective assessment techniques often involve equipment that not all clinicians have access to.

3.8. Conclusions.

There are several quality of life assessment tools that have been developed and validated in patients with breast cancer and with BCRL. These include generic tools and condition specific tools. The levels of validation vary. The validation processes undertaken identified limitations in the tools available and this may account for the number and variety of tools in use.

There have not been many studies that have looked specifically at the impact of mid-line lymphoedema on quality of life. Development of a condition specific quality of life tool would benefit this patient group to assess the impact on QoL at the time of BCRL development and also if repeated after treatment for use as an outcome measure. A QoL tool used alongside a validated symptom questionnaire and validated objective measurements would be of benefit to both patients and clinicians.

Chapter 4. Aims and Objectives of the Clinical Study.

4.1. Introduction.

The aim of literature searches and subsequent reviews were to determine the extent and quality of the research that had been undertaken previously on the mid-line BCRL. This identified that there has not been much research undertaken on mid-line BCRL in particular lymphoedema affecting the chest wall. There were very few studies identified that looked at the incidence of chest wall BCRL and acknowledged the difficulty in measurement of oedema to this area. As a result, the focus of this thesis has adjusted to exclude this BCRL to the chest wall and concentrate on breast BCRL only. The review ascertained that there are objective assessment techniques available that are currently used to assess lymphoedema affecting the limbs and these have potential to be used in the assessment of breast BCRL. These tools have not been well studied or validated in this patient group.

As a result of the reviews a clinical research study was developed with an overall aim of providing evidence that could be used to improve the assessment / diagnosis of breast BCRL and the impact that it has on the individual.

4.2. Clinical Study Objectives.

The design of the clinical study enabled several objectives to be proposed with different hypotheses tested. The objectives included;

- To explore the signs and symptoms associated with mid-line / breast lymphoedema.
- To Develop and validate the Breast Lymphoedema Symptom Questionnaire (BLSQ).
- To identify the incidence of previously undiagnosed / unrecognised breast lymphoedema in the study sample.
- To consider the risk factors that have previously been associated with the development of arm and breast BCRL and to determine whether they are related to this study sample.
- To test and validate the objective measurement techniques identified from the literature reviews and determine whether they can be used in the assessment of breast lymphoedema.
- To develop and validate a Breast version of the LYMQOL tool.

Examination of the signs and symptoms pertaining to breast lymphoedema was achieved in two ways; firstly, by comparisons of the signs and symptoms present or absent in participants identified as having breast lymphoedema following clinical examination.

Secondly, the signs and symptoms reported in the reviewed studies and from those identified by specialists working in the lymphoedema service were used to develop a breast lymphoedema symptom questionnaire (the BLSQ). This patient reported signs and symptoms questionnaire was validated to determine which and how many symptoms were associated with clinically determined breast lymphoedema. Analysis considered whether there were certain questions or an overall score of the BLSQ which can be used to support the diagnosis of breast lymphoedema, referral to a lymphoedema service or to provide reassurance that breast lymphoedema is not present. It was hypothesised that participants with breast BCRL would have more symptoms present than those without.

Analysis was undertaken to identify differences between those who did and did not have breast lymphoedema. This analysis considered the risk factors associated with arm BCRL identified from the literature review to determine whether these characteristics were also relevant to the presence of breast lymphoedema. If the risk factors for the development of breast BCRL are similar to that of arm BCRL then it would be hypothesised that participants who underwent more invasive breast cancer treatment would be more likely to develop BCRL of the breast. In addition, participants with a higher BMI would be more likely to have breast BCRL.

In addition to the clinical assessment and patient report of breast lymphoedema this study also included testing the reliability and validity of some of the objective measurement techniques that were identified in the literature review. These were skin thickness measurement by ultrasound, tissue dielectric constant (TDC) and tissue tonometry. It was hypothesised that the measurements would differ significantly between those with and without breast lymphoedema. It would be expected that they would be increased in the group with breast lymphoedema.

Patients with and without breast lymphoedema were required in the study sample to enable comparisons to be made and to determine if any of the measurement techniques could correctly identify lymphoedematous breast tissue. Having patients with and without breast lymphoedema recruited also enabled the impact of breast lymphoedema on an individual's quality of life to be considered.

For the studied assessment techniques that were found to be able to distinguish between oedematous and non-oedematous breast tissue receiver operating characteristic (ROC) analysis performed. Sensitivity and specificity calculations would support the diagnostic accuracy of these tools. From this analysis diagnostic thresholds or normal ranges were proposed that could be applied in clinical practice to support

the diagnosis of breast BCRL and help evaluate the treatments provided.

As the literature review did not identify a validated quality of life tool for mid-line lymphoedema, this was developed and tested alongside the objective measurement tools. The tool was developed using the same methodology that had been applied in the arm and leg version of LYMQOL. This testing of LYMQOL-Breast included consideration of questions from the COSMIN checklist. Applying this checklist to the methodology and testing helped to demonstrate whether the tool was rigorous and fit for purpose.

All of the objectives were tested in one overall study, utilising one sample group. Women who were known to have breast lymphoedema and attended the lymphoedema service and also women who attended routine breast cancer follow up appointments without previously diagnosed breast lymphoedema were invited to take part. This enabled comparisons between the two groups to be made.

Repeated assessments in a subgroup of patients at a second study visit provided additional data regarding the reliability and repeatability of these techniques.

Chapter 5. Methods.

5.1. Introduction.

Completion of the systematic reviews helped the development and focus of the research questions and the overall study aims. It confirmed that there is a need for more research to be undertaken on mid-line BCRL as there is very little on this area compared to research focusing on BCRL of the arm. Breast lymphoedema has become more pertinent due to the increase in breast conserving surgery with or without adjuvant radiotherapy over the last 10-15 years.

From the reviews it was evident that there is no rigorously studied assessment technique to determine the presence of breast lymphoedema. In addition, they demonstrated that there is no current gold standard assessment tool for assessing the presence of breast lymphoedema and identified the advantages and disadvantages of the different assessment techniques currently available. This may be why this area of lymphology has many unanswered questions and that in current clinical practice lymphoedema affecting the mid-line is assessed subjectively by the clinician.

The literature identified that breast BCRL has been studied more frequently than chest wall BCRL. There was only one study that focused on truncal or chest wall BCRL (58) and the limitations of the technique applied in this study acknowledged. Clinically chest wall BCRL does not appear to be as common as breast BCRL. The lack of literature on this type of BCRL could be because this anatomical area is harder to study. The nature of arm and breast BCRL allow for comparisons to be made between the affected and unaffected side, which chest wall BCRL following mastectomy does not. Due to these reasons the research study undertaken in this thesis focused only on breast BCRL. If the literature review had identified more papers that

focused on the incidence and more reliable assessment techniques for chest wall BCRL then this area would have been included.

In addition to the validation of one or several objective assessment techniques, a patient completed symptom assessment validated against clinical examination, by a lymphoedema expert, would enable those clinicians without access to objective assessment tools, to confidently and accurately assess breast lymphoedema.

The second literature review focused on the quality of life tools that were available, looking specifically at how the have been validated and utilised. There were few tools that included aspects relating to mid-line lymphoedema and those that did so have not been well studied. This identified that whilst there are several QoL tools available, which ranged from generic to condition specific questionnaires, there are not any currently available tools that have been developed for or validated to assess QoL associated with breast lymphoedema. The detrimental impact on QoL in people with lymphoedema was identified and described throughout the review highlighting the need for this to be included as part of the patient assessment. The LYMQOL arm and leg versions were developed and validated in 2010 (7). Since then these tools have been used in clinical practice and research studies around the world. They have been translated and validated in several languages. Requests have been made to the study team for additional versions including a breast LYMQOL. Development and validation of this tool was felt to complement the other aims of this study and improve holistic patient assessment. The methodology used in the validation of the arm and leg versions of LYMQOL was followed to maintain continuity.

This chapter describes the research plan that was undertaken to meet the objectives that were introduced in chapter 1 and focused as a result of the reviews in Chapters 2 and 3. Justification of the sample size calculation and the rationale for participant selection is provided. An overview of the how the objective assessment techniques selected

for use in the clinical study is included. Details of the data analysis that was completed is given to demonstrate that this was appropriate and relevant for the research questions.

5.2. Research Sample.

The study required women who had undergone breast cancer treatment and had received a wide local excision (WLE) to take part. The study sample included women with and without breast lymphoedema to determine whether the assessment tools could distinguish between a lymphoedematous and non-lymphoedematous breast. Ideally the group would have been split with half having breast lymphoedema present following clinical examination and half of the group having no breast lymphoedema. Measurements were undertaken on both breasts to enable comparisons to be made between the affected and unaffected breast to determine whether they differed significantly. Analysis was undertaken to compare the differences between the two breasts in the non-lymphoedema group.

Prior to any data collection Research Ethics approval was sought from the NRES Committee North West – Haydock, reference 15/NW/0608. Local approval and study sponsorship was sought from the University of Nottingham and Derby Hospitals NHSF Trust.

5.2.1. Sample Size Calculation.

A sample size calculation using nQuery Advisor version 7.0 was undertaken. The sample size calculation used an approach designed to look at precision, enabling sensitivity and specificity to be calculated. This approach was based following consideration of the size of the

confidence interval of the effect. A second sample size calculation was also carried out to ensure that the size of the sample was sufficient to undertake analysis examining the reliability of the assessment techniques.

Applying a confidence level of 0.95, using a 2 sided interval with an expected proportion of 0.80 for sensitivity and specificity and a precision (width of confidence interval) of 0.12 a sample of 86 participants was required. This was based on 43 participants being enrolled who had clinically assessed breast oedema and 43 without.

For the reliability sample size calculation, applying a confidence of interval of 0.95, using a 2 sided interval, with an expected proportion of successes equalling 0.5, an agreement measure of 0.8 and precision of 0.15 a sample of 62 participants was required. This was the number of participants required to attend a second study visit.

5.2.2. Participation Identification and Approach.

The study recruited a convenience sample of women who attended the Breast Care Unit or the Lymphoedema clinic at the Royal Derby Hospital. Patients attending follow up appointments after breast cancer surgery with the Breast Advanced Nurse Practitioners (ANP) were given the patient information sheet. The lymphoedema clinical database was used to identify current patients receiving treatment for breast lymphoedema and these patients were approached at a follow up appointment or were sent an invitation letter. All patients were provided with a return slip and pre-paid reply envelope. The slip asked the patient to identify whether they wished to consider or decline participation in the study. Only patients who returned the slip indicating an interest in participating were contacted about the study.

5.3. Inclusion and Exclusion Criteria.

Inclusion criterion for the study was such that all patients were:

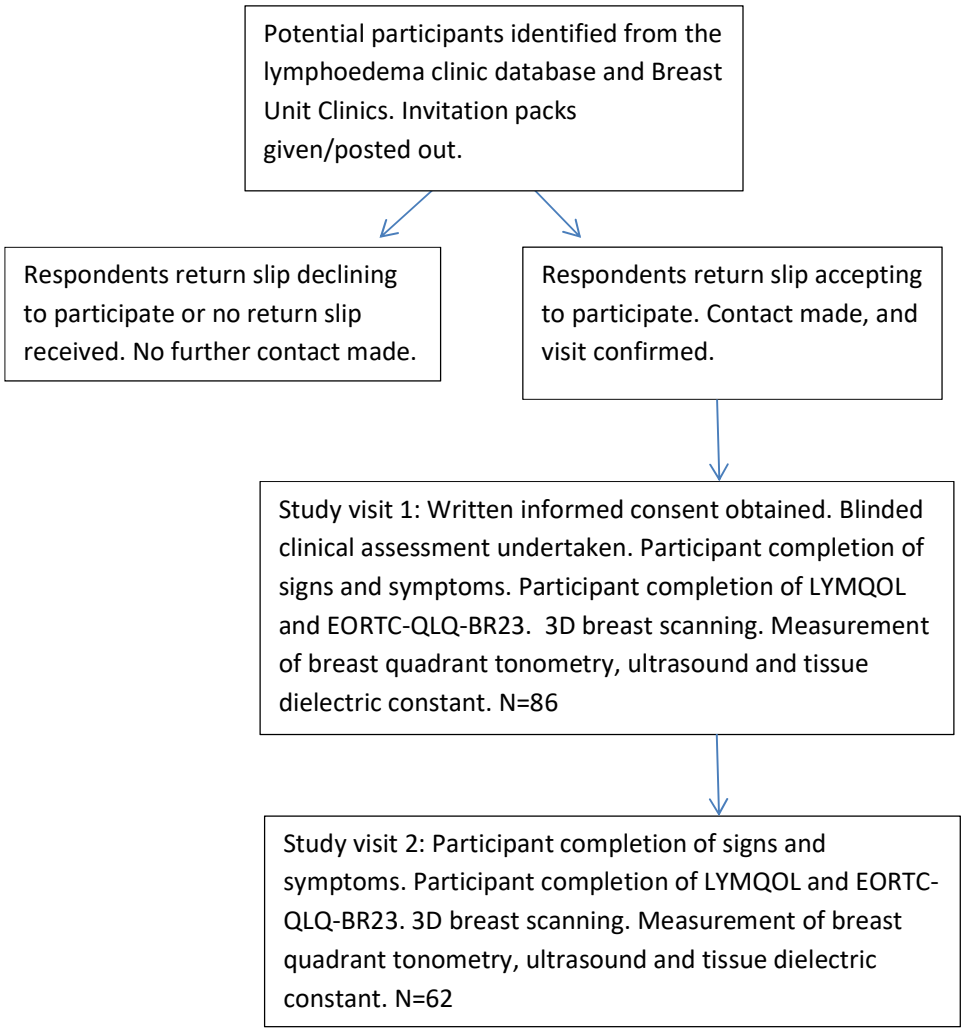
- Female – Men are less likely to be diagnosed with breast cancer, fewer than 1% of people diagnosed with breast cancer in the UK in 2015 were men (118). In addition, the differences in the male / female anatomy are likely to influence the measurements obtained.
- >18 years. Breast cancer is extremely rare in children and adolescents.
- Previous treatment for breast cancer which included wide local excision (WLE).
- Ability to provide informed consent.
- No clinical evidence of breast cancer recurrence to ensure that the presence of active disease or treatment for active disease did not influence the measurements.

5.4. Study Participation.

The information sheet included a description of the trial schema (figure 5). All eligible and willing participants were asked to attend at least one appointment at the Lymphoedema Clinic at the Royal Derby Hospital. The appointment was made, following a discussion with the patient at a mutually agreeable date and time. The information sheet explained that the visit would last between 1 – 1.5 hours and during that time written informed consent would be sought and which assessments would be completed. For each of the measurements a short description was provided in the information sheet. Additional information included details about the clinical assessment by a

Medical Doctor and that they would be asked to complete the three questionnaires, the BLSQ, LYMQOL-Breast and the EORTC-QLQ-BR23. At the end of the initial visit if the participant was willing and able to attend a second appointment within 7 days of the initial visit then a date and time for this was agreed.

Figure 5. Trial schema



5.4.1. Blinded Expert Examination.

Due to the lack of an agreed gold standard assessment technique blinded expert opinion was utilised in this study. The Lymphoedema Service is led by a Consultant Physician with over 25 years' experience in lymphology and is recognised nationally and internationally as an expert in the field. He assessed each of the participants in the study after they had undergone the objective assessments. It was not divulged to him whether the participant was known to have breast lymphoedema or the results of the measurements. This was also explained to the participant to prevent them revealing this.

All participants were examined whilst lying supine. Assessment of the breast was undertaken by examining each of the four quadrants for pitting oedema individually. The "pitting" test required the clinician to press firmly for several seconds with a thumb or finger onto the area being examined, once removed if the finger/thumb print remained then pitting oedema was deemed to be present. Pitting oedema was required to be present in at least one of the four breast quadrants for that participant to be identified as having breast lymphoedema. The other signs and symptoms that were assessed as part of the clinical examination included skin changes; recognised as thickening or a peau d'orange appearance, redness or inflammation, tenderness on palpation, an increase in temperature compared to the contralateral breast and the presence of seam marks or indentations from clothes or bra. These were all assessed as present or absent.

The signs and symptoms of breast lymphoedema were agreed following the literature review as they had been identified in previous studies as indicative of the presence of breast lymphoedema. In addition, the Lymphoedema Specialists working in the service, both Doctors and Nurses were asked for the signs and symptoms of breast lymphoedema that they would look for as part of a clinical examination.

5.4.2. Objective Assessment Techniques.

The objective measurement techniques selected for the study following the literature review were ultrasound, tissue dielectric constant (TDC) and tonometry. Although the literature review identified limitations for each technique they have all been used to determine changes in the size, tissue composition and tone of the limbs indicating the presence or absence of lymphoedema. This study explored whether they can be considered as valid and reliable techniques in the assessment of breast lymphoedema. Measurement difficulties or concerns with the accuracy of each measurement were recorded to enable the application of each method to be evaluated.

Measurements were undertaken in each of the four quadrants of the breast to enable comparisons to be made with the corresponding quadrant of the contralateral breast. With the exception of tonometry repeated measurements were obtained, 2 ultrasound measurements for each quadrant and 3 TDC measurements for each quadrant. The mean of each of the measurements was calculated. Tonometry was not repeated because the weighted probe will indent oedematous tissue and therefore cannot be repeated in the same area until fluid in the tissues has re-accumulated.

Intra rater reliability of the assessment techniques including the questionnaires was tested as repeated measurements were undertaken. Second assessments were completed on a sub set of patients within a 5-10 day period. For the techniques and questionnaires to be deemed reliable then the repeated assessments needed to yield similar results to the initial assessment as it was not expected that there had been any changes during the interval period. If a participant was identified as having breast lymphoedema at the first assessment then they were offered treatment after the second

assessment if willing to attend or in a separate clinic appointment. For those known to have breast lymphoedema the treatment did not change between the first and second assessment.

5.4.3. Questionnaire Development.

LYMQOL Breast and the Breast Lymphoedema Symptom Questionnaire (BLSQ) were developed using the same format as the limb versions of LYMQOL (7).

LYMQOL is comprised of four domains: function, appearance, symptoms and emotion. The emotion domain and the overall quality of life score are used with permission from the EORTC group. The questions in the other domains were developed from patient reports and from the literature.

The BLSQ was developed from patient reported symptoms from clinical experience and from the literature. The symptoms included breast discomfort, swelling, redness and change to breast tissue.

Opinion about the questions used in LYMQOL –Breast and the BLSQ was sought from Lymphoedema Therapists and Clinicians working within the service (n = 12). They were asked to review the questionnaires and make suggestions including any changes to the wording or additional / omitted questions. The questionnaires were then sent to patients attending the Lymphoedema Services at Queens Medical Centre and Kings Mill Hospital for breast BCRL (n=20). The purpose of this was to receive feedback and test the face validity of the questionnaire. Patients were asked; if the tools were easy to read and clear, about the length of the questions and to identify any areas that were missing, or they felt could be omitted. The patient responses confirmed that the tools were easy to complete, and no additional questions were included as a result. Following this process, the

current version of both questionnaires were produced that were used in this study.

The validity of LYMQOL Breast was tested in this study and was compared against the validated EORTC-QLQ-BR23 questionnaire. The EORTC-QLQ-BR23 tool was developed and validated to assess quality of life in patients undergoing breast cancer treatment. There are four questions in the EORTC-QLQ-BR23 which specifically ask about breast symptoms. These are pain, swelling, sensitivity and skin problems.

It was hypothesised that QoL would be lower in the breast lymphoedema cohort. For the BLSQ it was hypothesised that participants with breast lymphoedema would report more symptoms than those without.

There was no validated patient completed symptom tool for breast lymphoedema identified in the literature so the BLSQ was tested against clinical examination. Analysis was undertaken to look at the relationships of patient reported symptoms to clinically diagnosed breast lymphoedema. If necessary, following the results of the analysis modifications to the BLSQ may be undertaken remove questions which were found not to be associated with breast lymphoedema.

The questionnaires were completed by participants either in the clinic or taken home to do. For those who completed them at home a stamped addressed envelope was provided to encourage return of the questionnaires. Prior to completion an overview of the questionnaires was given including instructions on how to complete them. The questionnaires provided a date range to recall when answering the questions. The EORTC-QLQ-BR23 has in total 53 questions which ask the individual to consider how they have felt over the past week. There are 4 responses for each question ranging from “not at all” to “very much” except for the global health status and quality of life questions which have 7 responses. Some of the questions are scored

singularly and reported as items others are grouped together and scored as scales. There is further classification of the questions into functional or symptom scales. A “raw” score was calculated for each of the scales by adding together the score for the completed answers in that scale and dividing the total by 3, which is the range of possible responses (6, 18-20). The raw score undergoes a linear transformation resulting in the total score for each item or scale being between 0 and 100. For the functional scales a higher score represents a better level of functioning, however, for the symptom scales / items a higher score represents a worse level of symptoms.

The LYMQOL Breast tool followed the format of the Arm and Leg versions that were validated previously and has 23 questions split into the four domains. There are 4 responses for each question ranging from “not at all” to “a lot”. Each response is scored from 1 (not at all) to 4 (a lot). A score was calculated for each of the individual domains. This is achieved by totalling all of the answered questions in an individual domain by the total number of questions answered. If an individual missed fifty percent or more of the questions in any one domain then that domain average was not calculated. Higher domain average scores are associated with lower quality of life. The final question used a visual analogue scale asking the individual to rate their overall quality of life from 0 (poor) to 10 (excellent). Scoring of this question is the opposite of the domain averages as a higher response is associated with better quality of life.

The BLSQ is comprised of 14 questions asking the individual whether each symptom or difference compared to the contralateral breast is present or absent for two time periods, within the past week and the past year. This questionnaire is scored by totalling the number of yes’ reported and dividing by the number of questions completed (maximum of 28 if all questions answered). This is multiplied by 100 to produce the percentage of symptoms experienced. The higher the score the more symptoms present. If less than fifty percent of

questions were answered then this was recorded as missing and was not included in the analysis.

5.4.4. Study Procedures.

All potential participants were approached about the study and provided with the patient information sheet by members of the clinical team. The research team only contacted a potential participant when they returned the reply slip, using the freepost envelope provided which confirmed their interest in taking part. Telephone contact was then made with the participant to provide explanation about the study and arrange a study appointment if the individual was willing to take part.

On attending the study appointment explanation of participation was provided including further description of the assessments, the clinical examination and questionnaires. Written informed consent was obtained prior to any information being recorded and each participant was issued with a unique study number.

Patient and treatment characteristics were recorded including; breast cancer surgery specifying type, grade of cancer, number of lymph nodes removed and number of lymph nodes positive, adjuvant breast cancer treatment (chemotherapy, radiotherapy and hormone treatment), post-operative complications such as infections, wounds and seromas, BMI and bra size (cup and chest circumference). Analysis was undertaken to ascertain whether there were any differences in these characteristics between the group with and without breast lymphoedema. It was felt that this information could be used to help identify those at increased risk of developing breast lymphoedema which would enable additional education to be provided and potentially prospective surveillance or additional monitoring offered.

5.4.5. Assessment using Ultrasound, tissue dielectric constant and tonometry.

Of the three objective measurements TDC was always recorded first. The reasoning for this is that the ultrasound gel could affect the TDC probe readings as the gel is water based. The tonometer measurements were obtained last as potentially the weighted probe could indent the tissues and displace the fluid in the tissues at that individual measurement point influencing the other measurements.

5.4.5.1. Tissue Dielectric Constant Readings.

The TDC readings were obtained using a Delfin Moisture Meter D (Delfin Technologies Limited, Finland). The medium or 2.5mm probe was used for all of the measurements. The participant was laid supine with both arms down by their side. Each breast was marked using a washable marker at 5 cm from the nipple into the middle of each of the four breast quadrants. If there was a scar in any of the quadrants this was recorded on the data collection proforma. Triplicate measurements were recorded in each of the four breast quadrants for both breasts and the mean for each quadrant calculated. The TDC value is directly proportional to the water content in the tissue being assessed and therefore higher values were expected in an oedematous breast. Theoretically the value obtained can range from 1 indicating no water to 78 indicating 100% water in the area being measured.

5.4.5.2. Ultrasound Measurements.

Ultrasound measurements were obtained using the Sonosite Edge Ultrasound (FujiFilm, Sonosite, Netherlands). A high frequency 6-

15MHz probe was used. The participant was laid supine with the corresponding arm raised above the head. Participants were positioned in this way to improve sound penetration and enable good visualisation of the breast quadrants (119). A thick layer of ultrasound gel was applied, and the transducer positioned perpendicular to the skin with gentle pressure applied. This was undertaken to ensure complete contact with the breast and eliminate any air pockets which could block sound waves passing through.

Live images were produced by the ultrasound device from which individual frames were saved and measurements obtained. Due to the difficulties identified in previous studies when trying to identify and measure individual skin layers total cutaneous thickness was measured. Two measurements were obtained from different points on the same saved image frame using the measurement cursors. The area chosen to measure was always perpendicular and the measurement start /end points were from the anterior echogenic border of the epidermis to the posterior echogenic border of the dermis.

5.4.5.3. Tissue Tonometry.

Prior to use the tissue tonometer (Flinders, Australia) was calibrated using the supplied calibration plate. For the measurement to be undertaken the tonometer was required to be placed flat against the breast quadrant being measured as this enabled the weighted plunger to press against and indent the tissue, if oedema was present. It was not possible to measure all four of the breast quadrants for the whole sample as the tonometer could not be applied to the lower quadrants of some breasts, particularly for participants with large, ptotic breasts. Any measurements that could not be obtained were noted. The tonometer was held in place in place until the dial stopped moving. The dial consists of a smaller inner dial which displays the

whole unit and an outer dial which displays the hundredths of a unit. The softer the tissue being measured the further the tonometer will indent, and a higher reading obtained.

5.5. Data Analysis.

The aim of this study was to validate the measurement techniques available in the assessment of breast lymphoedema against the "gold standard" technique of clinical examination. All of the analysis was undertaken using SPSS version 22.0. The data entry and analysis were completed by the researcher.

Prior to any statistical tests being undertaken analysis was performed to determine whether the data met the assumptions of normality or not. This was achieved by reviewing histograms and Q-Q plots of the data. If the histogram shape and the curve of best fit displayed a bell shape and the Q-Q plot values were on the line then a normal distribution was assumed. The Shapiro Wilk test for normality was also performed. Depending on the results parametric tests or the non-parametric equivalent test were performed. For the normally distributed data the mean and standard deviation was reported. For the non-normally distributed data medians and inter-quartile ranges were reported.

5.5.1. Descriptive analysis of the sample characteristics.

Descriptive statistics were undertaken to explore the characteristics of the whole sample group and whether there were differences between those who did and did not have breast lymphoedema. The

Chi squared test was performed and the Odds Ratio (OR) and Relative Risks (RR) calculated.

5.5.2. Analysis of the objective measurement tools.

The data from the objective measurement tools; TDC, ultrasound and tonometry were compared and analysed using several methods. Two sample and paired t-tests, or their non-parametric equivalents were undertaken to compare the different groups. Measurements from the affected breast were compared with those from the same quadrant on the contralateral breast.

It was hypothesised that the measurements of both the individual quadrants and mean total breast measurements for TDC specifically would be different in the group with clinically diagnosed lymphoedema of the breast. It was postulated that the TDC values for the affected quadrants and the overall ratios would be higher in the lymphoedema group.

For the ultrasound measurements it was expected that total cutaneous skin thickness would be thicker in the lymphoedematous breast quadrants.

Finally, it was expected that the tonometer readings would be higher in the breast quadrants with lymphoedema.

A statistically significant difference was expected when the affected breast quadrants were compared to the corresponding unaffected quadrants. No difference was expected when the treated and untreated breast quadrants of the non lymphoedema group were compared.

Receiver Operator Characteristic (ROC) curves and the Area Under the Curve (AUC) statistics were undertaken to enable diagnostic threshold

level to be produced. From these the sensitivity and specificity calculations plus positive (PPV) and negative predictive values (NPV) and positive and negative likelihood ratios were calculated, and comparisons made of the threshold levels against the "gold standard" clinical assessment as the determinant of the presence / absence of breast lymphoedema for each of the objective measurement techniques. The PPV and NPV indicated the accuracy of a test for categorising people as correctly having or not having the condition. Likelihood ratios (LR) indicated the value of the test for increasing the certainty of a positive diagnosis and supported the diagnostic accuracy of the tests. A likelihood ratio of greater than one was indicative that the test result was associated with the disease and a value of less than one associated with the absence of the disease.

For the TDC measurement and ultrasound assessments previously identified threshold levels were compared to the data produced in this study. ROC curves, sensitivity and specificity calculations were also produced for the BLSQ to ascertain further information on the threshold levels and the ability of this tool to correctly discriminate between the presence and absence of breast oedema.

5.5.3. Intra-rater Analysis.

Intra-rater analysis of the objective measurement tools and both of the questionnaires was undertaken using the data from the participants who completed two assessments. Cohen's Kappa coefficient was calculated to produce levels of agreement for the BLSQ and LYMQOL-Breast. The one sample t-test or its non-parametric equivalent, Wilcoxon Signed Rank test, calculated to ascertain whether the measurements changed significantly from the first to second assessment.

Bland and Altman plots were produced to determine measurement error and limits of agreement between the repeated measurements. It was hypothesised that there should not be any significant change between assessments as no interventions or treatment changes were made between visits. In addition to the plots analysis was undertaken to provide further information. Initially a one sampled t-test was undertaken to ascertain whether there was a significant difference between the repeated measurements and a $p > 0.05$ was indicative that there were no significant differences. Linear regression analysis was undertaken to determine whether there was proportional bias in the measurements, supporting that there was no trend or proportional bias in the dataset. The unstandardized coefficient B produced should be low and close to 0.

5.5.4. Analysis of the symptoms associated with breast lymphoedema.

The Mann Whitney U, Chi squared test and Cramers Phi were used to compare the average number of symptoms experienced by participants with and without clinically detected lymphoedema. Cramer's Phi was chosen as it enabled greater understanding of the effect size and identification of the most significant questions.

5.5.5. Validation of the LYMQOL-Breast and Breast Lymphoedema Symptom Questionnaire.

Validation of LYMQOL-Breast and the BLSQ included:

- Face validity: this was undertaken by asking respondents to complete a questionnaire alongside the draft LYMQOL questionnaire and draft BLSQ to ascertain whether the

questions included were relevant, expected and whether the number of questions acceptable.

- Content validity: this was undertaken using the same additional questionnaire which was used to check whether the respondents felt that there were any important areas missing in the draft LYMQOL Breast or draft BLSQ or whether any questions that were included could be omitted.
- Internal validity: this was undertaken by testing the internal consistency of the tools using Cronbach's Alpha and split half testing. This identified how the questions in one domain of the LYMQOL tool related to each other. The higher the Cronbach's α statistic the more consistent the questions. An acceptable Cronbach's α level should exceed 0.7 and good scale reliability would produce a score of 0.8 – 0.9. An individual statistic was produced for each of the questions in a domain showing how each individual question adds to the domain. The α level that would be obtained if individual questions were removed from that domain produced. If the α levels were significantly raised on the temporary removal of individual question(s) then this change(s) was considered when the final versions produced.
- Reliability was examined using test-retest technique. The group of participants who attended both assessments completed the two questionnaires on both occasions. Reliability was tested using the Pearson Correlation Coefficient and a weighted Kappa test.
- Construct validity: this was tested by comparing the scores of the questionnaires against the blinded clinical assessment. The participants with clinically diagnosed breast lymphoedema should report more symptoms on the BLSQ and have reduced QoL.
- Discriminant validity: this was be tested by comparing the responses of the breast lymphoedema group to the group without lymphoedema.

Testing these properties of the tools considered the COSMIN methodology and associated checklist which identified the different components of reliability, validity and responsiveness required for a health related patient reported outcome (HR-PRO) (116). As part of the International Delphi study that developed the COSMIN checklist the panel reached consensus that there weren't gold standard instruments in existence for HR-PRO measures and therefore criterion validity is difficult to assess. In this study, however, comparison was made with the EORTC-QLQ-BR23 questionnaire as this is a commonly used tool which has been validated to measure quality of life in patients who have undergone breast cancer treatment. This was undertaken to test the hypothesis that people with breast lymphoedema had lower quality of life than those without breast lymphoedema. The COSMIN checklist describes responsiveness as the ability of a tool to detect change over time (116). For the participants who attended two visits the questionnaires were completed on both occasions. As no intervention was changed or initiated between visits it was hypothesised that there should not be significant change in the responses provided when completing the questionnaires. However, it was acknowledged that full and thorough testing of the responsiveness of the LYMQOL-Breast and the BLSQ was not undertaken in this study as participants were not followed up for a long enough period. In addition the diagnosis of breast lymphoedema would have been made at the first visit and therefore may have some influence on the responses to the questionnaires completed before and after this.

Comparisons were made between the responses of the LYMQOL-Breast questionnaire to the EORTC-QLQ-BR23. It was expected that quality of life was lower in the group with breast lymphoedema when assessed by the EORTC-QLQ-BR23 and that this pattern would also be seen in the LYMQOL-Breast responses.

5.5.5.1. Minimum detectable change of the LYMQOL-Breast Questionnaire.

The data from the repeated LYMQOL-Breast questionnaires was used to calculate whether variation in scores was due to true change or measurement error. This provides additional information about the reliability of the LYMQOL tool and what represents meaningful change in the domain scores.

This included; calculating the standard error of measurement (SEM) which is the change in a score that is not due to measurement error but indicative of a meaningful change, minimal detectable change (MDC) which compliments the SEM giving the smallest detectable change that can be considered above the measurement error and the reliable change index (RCI), a statistic which assesses the magnitude of change necessary for the measure to be considered statistically reliable.

There are three commonly used MDC depending on the level of confidence interval desired. These are calculated for a 68%, 95% or 99% confidence interval. The MDC95 (95% confidence interval) was chosen for use in this study. The MDC represents a 95% confidence interval and the value acknowledges an increase or decrease of the MDC when a real change was considered. The calculation for MDC95 = 1.96 x SEM x √2.

The reliable change index (RCI) was calculated to ascertain whether change over time of an individual score could be considered statistically significant. It is calculated from the change in score between the first and second assessments and divided by the square root of the SEM. If the result was greater than 1.96 this was considered to be a true change. The participants who attend the second assessment did so within 7 days and did not receive any new or additional treatment between visits, therefore it was hypothesised that the RCI would be less than 1.96 ie. No change.

Chapter 6. Results

6.1. Introduction.

This chapter will present the results of the data analysis. Rationale for the statistical tests applied were described in the previous chapter including why a parametric or equivalent non-parametric test was applied.

This chapter considers the sample demographics and the breast cancer treatment received with comparisons made between those with and without breast lymphoedema.

The signs and symptoms identified from the clinical examination and those reported by the participants will be analysed to identify which signs / symptoms could be used to support a clinical or measurable diagnosis of breast lymphoedema.

Analysis has been undertaken to determine the validity of the objective measurement techniques in the assessment of breast lymphoedema. Comparisons between oedematous and non-oedematous breasts have been made and where applicable ROC analysis and thresholds for intervention / assessment recommended.

6.2. Overall Sample Demographics.

Patients were approached from March 2016 to November 2017 and eighty-nine women consented to take part in the study. Participants were approached from the lymphoedema service and from the Breast Clinic. Consecutive patients attending follow up appointments with the Advanced Nurse Practitioners (ANP) were identified by the ANP as potentially eligible and provided with the patient information sheet

(PIS) and a brief introduction to the study. 14 participants were recruited from the lymphoedema service and 75 from the breast clinic.

6.2.1. Participant age.

The mean age of the sample was 61.1 years (standard deviation, sd = 9.6 years, range 29-80 years). Length of time from surgery to study participation ranged from 6 months to 12 years. Mean BMI was 29.25 (sd = 5.81, range 19.2 – 45.14). The majority of the sample was right hand dominant (92.1%).

6.2.2. Bra size and chest circumference.

Bra size by cup and band circumference was recorded for 81 participants. Fifty-two different bra sizes were worn by the sample, the most common bra size was a 36C, this was worn by 8 (10%) women. Cup size ranged from an A cup to a HH cup and band circumference from 34 inches to 50 inches (Figure 6 & 7).

Figure 6. Distribution of bra cup size

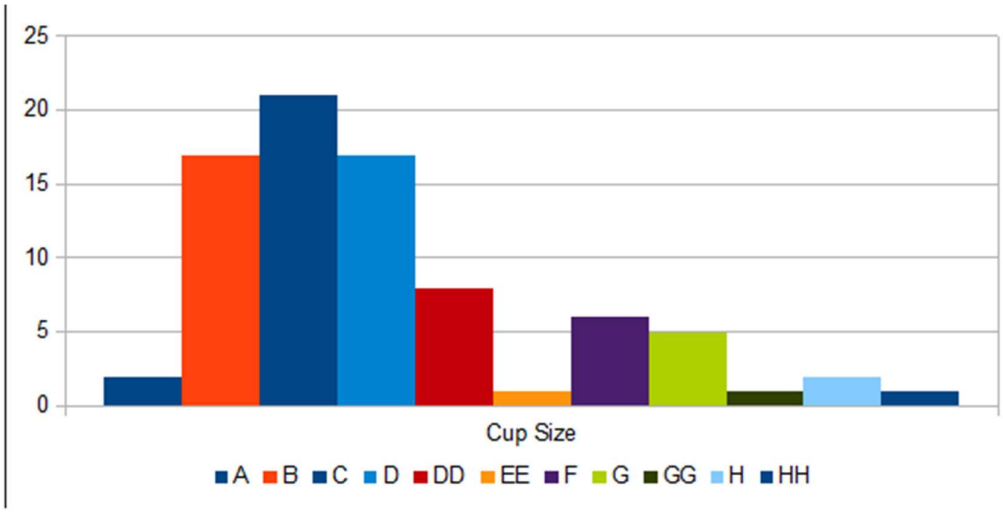
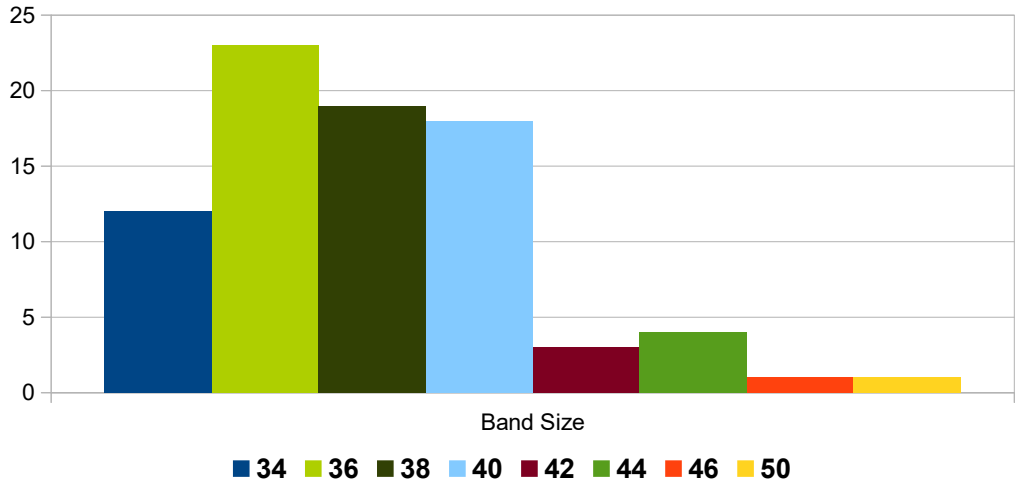


Figure 7. Distribution of bra band width / chest circumference



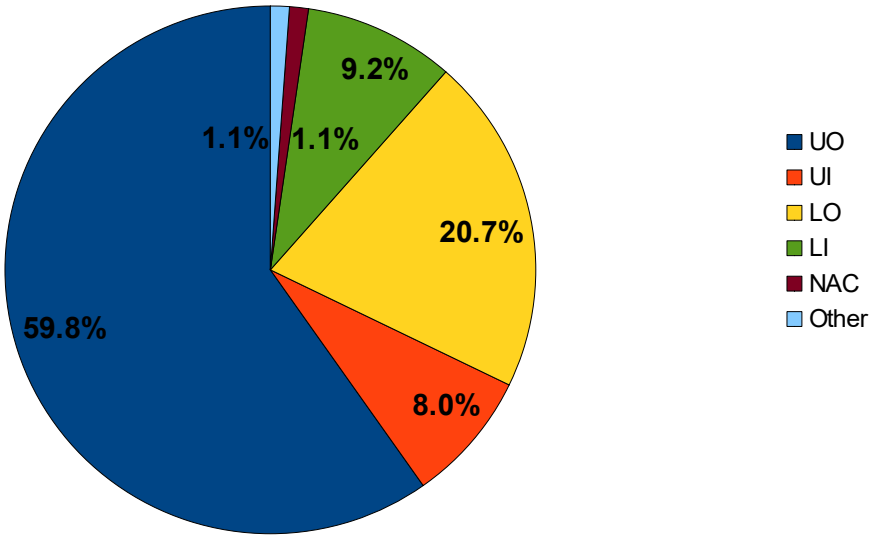
6.3. Breast Cancer Disease Characteristics.

6.3.1. Breast Cancer Surgery.

The entire sample had undergone a WLE with 67 undergoing a sentinel node biopsy (SNB) and 23 having had an axillary node clearance (ANC). Six women had undergone both procedures and five women had not undergone any axillary procedure. Fifty-five participants had undergone a WLE on their left breast and 34 on the right breast.

The most common location of breast cancer was in the upper outer (UO) quadrant being affected in 59.8% of the sample followed by the lower outer quadrant (20.7%). (Figure 8) The inner side of the breast was less commonly affected with 9.2% having surgery on the lower inner (LI) quadrant and 8% on the upper inner quadrant.

Figure 8. Location of breast cancer by breast quadrant.



6.3.2. Breast Cancer Histology.

Eighty-four participants were treated for an invasive breast cancer and five for ductal carcinoma insitu (DCIS). Sixty-three (75%) were treated for an invasive ductal carcinoma, with seven participants each treated for invasive lobular, mixed invasive carcinoma or another invasive breast cancer. Of those with an invasive breast cancer sixty (72.3%) also had DCIS or lobular carcinoma insitu (LCIS) present on histopathology of the excised tumour.

Table 10. Tumour grade (n=84)

	N	%
Grade I	14	16.7
Grade II	41	48.8
Grade III	29	34.5

Approximately half of the group had a grade II tumour and one third had a grade III tumour (Table 10). Twenty-two (26.2%) were found to have lymphatic or vascular invasion (LVI) present on histopathology. The Nottingham Prognostic Index (NPI) ranged from 2.06 to 6.8 with a mean NPI of 3.98 (sd 1.102).

For those participants who had an invasive breast cancer, histology of the tumour identified that most patients had Oestrogen receptor positive (ER+ve) (88%, 74/85) and Her2 receptor negative breast cancer (84.5%, 71/84).

6.3.3. Lymph Node Removal.

Overall the number of lymph nodes (LN) removed ranged from 0 to 38. The mean number of LN removed was 6.17 (sd 8.442) and the median number of nodes removed was 2 (inter quartile range, IQR, 1-10). The number of LN removed, and presence of metastatic deposits varied depending on the extent of the procedure(s) to the axilla.

For those who underwent a SNB only (n=61) the mean number of LN removed was 1.87 (sd 1.231, range 1-7). As would be expected, in the SNB group the number of LN removed and that were positive was lower with a mean of 0.11 (sd 0.321, range 0-1) LN removed with only 7/61 patients having a single positive LN.

For the 23 participants who underwent an ANC (with or without a SNB) the mean number of LN removed was 19.5 (sd 6.479, range 11-38). The ANC group had a mean of 5.18 (sd 8.606, range 1-36) LN positive. The standard deviation in this group is large due to one patient who had metastatic deposits in all 36 LN that were removed. The median number of positive LN is 2 (IQR 1-5).

6.3.4. Adjuvant Treatment(s).

Adjuvant treatments included chemotherapy (40/84, 44.9%), radiotherapy (88/89, 98.9%) and hormone therapy such as Tamoxifen, Anastrazole and Letrozole (65/84, 73%). The chemotherapy regimes varied depending on the length of time between cancer treatment and study participation which is reflective of the changes in the treatments used over the past 12 years. The table below displays the range of chemotherapy given, most participants (33/40) underwent 6 cycles.

Table 11. Chemotherapy Regime (n=40)

Chemotherapy Regime	N	%
FEC-T (5FU, Epirubicin, Cyclophosphamide, Docetaxel)	28	70
FEC (5FU, Epirubicin, Cyclophosphamide)	7	17.5
Epi-CMF (Epirubicin, Cyclophosphamide, Methotrexate, 5FU)	2	5
CMF (Cyclophosphamide, Methotrexate, 5FU)	1	2.5
AC (Doxorubicin, Cyclophosphamide)	2	5

Details of radiotherapy treatment was recorded for 87/88 participants who received it. The entire group received radiotherapy to the breast, the most common dose being 40 Gray (Gy) (70%). Higher doses were received by 26 participants (30%) (50Gy = 23, 60 Gy=3).

Hormone treatment was received by 65 participants currently receiving three different drugs: Tamoxifen (n=29), Anstrazole (n=35) and Letrozole (n=1).

6.3.5. Post-Operative Complications.

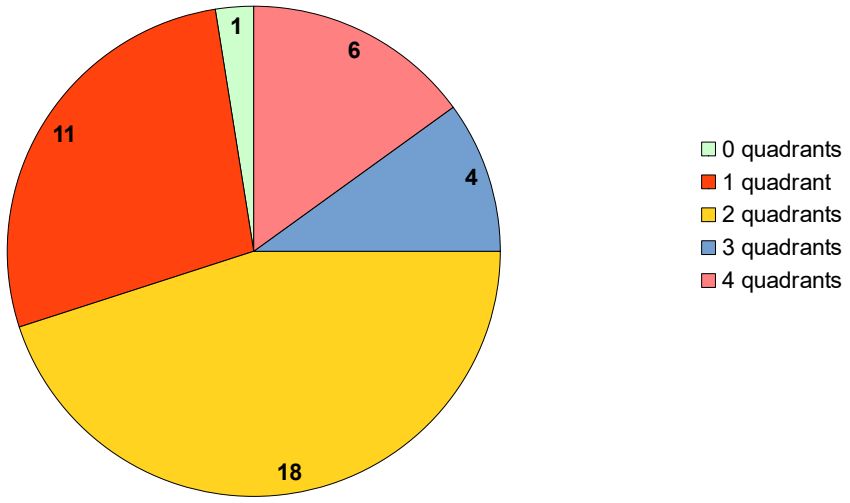
Post-operative complications were identified from the medical notes and by asking each participant directly whether they had experienced a seroma, cording, wound infection or cellulitis. A seroma which required drainage was experienced in 8 participants (9%), cording in 2 participants (2.2%), post-operative wound infection in 7 participants (7.9%) and cellulitis in a different 8 participants (9%). For the patients who experienced cellulitis 3 required hospital admissions for intravenous (IV) antibiotics and all required a course of oral antibiotics. All episodes of cellulitis were confirmed by a Doctor.

6.4. Diagnosis of Breast Lymphoedema.

Following clinical examination breast lymphoedema was confirmed in 40 women (44.9%). The main criteria for diagnosis breast lymphoedema was the presence of pitting oedema in at least one quadrant of the breast, this was confirmed in all but one of the participants with breast lymphoedema. This patient reported other symptoms /changes to the breast tissue which supported a diagnosis of breast lymphoedema. Of the 40 women with breast lymphoedema present following clinical examination this had not been formally diagnosed prior to taking part in this study in 29 cases (72.5%).

The majority of participants (29/40) had at least two quadrants of the breast that were found to have pitting oedema on clinical examination, with 6 participants having all four quadrants affected (Figure 9).

Figure 9. Breast quadrant(s) found to have pitting oedema present (number of patients n=40)



The lower half of the breast was most commonly affected when the individual breast quadrants were compared. Only one patient had pitting oedema to the upper inner quadrant only. Thirty-one participants (of 39, 79.5%) had pitting oedema in the lower outer quadrant with twenty-nine (74.4%) in the lower inner quadrant compared with twelve (30.8%) in the upper outer quadrant and eleven (28.2%) in the upper inner quadrant. This differs from the quadrant affected by the tumour as only 12/39 patients had the WLE on the lower half of the breast.

6.4.1. Signs and Symptoms of Breast Lymphoedema.

Signs and symptoms associated with breast lymphoedema were commonly reported / observed during the clinical examination but were not present in the entire sample. This is presented in table 12.

Table 12. Frequency of the signs and symptoms pertaining to breast lymphoedema identified on clinical examination

Presence of Sign / Symptom	Breast Lymphoedema (n=40)	No Breast Lymphoedema (n=49)	Chi Squared Value	P Value
	Number (%)	Number (%)		
Pitting oedema	39 (97.5)	0	85.050	<0.001
Thickening of the breast tissue	35 (87.5)	3 (6.1)	59.608	<0.001
Peau d'orange skin changes	29 (72.5)	1 (2)	48.927	<0.001
Discolouration to the breast	19 (47.5)	3 (6.1)	20.262	<0.001
Inflammation of the breast	13 (32.5)	1 (2)	15.413	<0.001
Increase in temperature of the breast	15 (37.5)	3 (6.1)	13.439	<0.001
Tenderness or pain to the breast	25 (62.5)	6 (12.2)	24.503	<0.001
Diurnal variation in the pattern of swelling	14 (35)	1 (2)	17.072	<0.001

The most commonly recorded signs associated with breast lymphoedema included thickening of the breast tissue, peau d'orange skin changes and discolouration to the breast. Other signs and symptoms were not as frequently recorded, however, the Chi Squared (X^2) test demonstrated highly significant differences between the two groups and each of these symptoms, $p<0.001$. For each sign / symptom there were more participants observed in the breast lymphoedema group than was expected if that individual sign / symptom was not associated with the presence of breast lymphoedema.

6.5. Breast Lymphoedema Risk Factors.

6.5.1. Breast Cancer Surgery.

Analysis that compared the type of axillary surgery and the presence of at least one positive lymph node was undertaken. Using the X^2 test more participants were observed than expected with breast lymphoedema who had received an ANC or who had at least one positive lymph node, this difference was statistically significant in both cases, p=0.009 and p= 0.013 respectively (see table 13).

Table 13. Chi Squared test comparing axillary surgery and the presence of positive lymph nodes. (Obs = observed, Exp = expected)

	Positive LN		**Negative LN**		**ANC**		**SNB**	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
Breast Lymphoedema	19	13.6	20	25.4	16	10.7	23	28.3
No Breast Lymphoedema	10	15.4	34	28.6	7	12.3	38	32.7
X^2 statistic	6.144				6.816			
P	**0.013**				**0.009**			
Relative Risk (95% CI)	1.769 (1.143 – 2.737)				1.845 (1.211 – 2.810)			

Exploring this relationship further calculation of the relative risk demonstrated that those patients who underwent an ANC or those who had at least one positive LN were almost twice as likely to develop breast lymphoedema as those who had a SNB or had negative lymph nodes. These groups were not mutually exclusive. Although most participants who had lymph node positive disease had undergone

an ANC there were some participants with lymph node positive breast cancer who had undergone a SNB only.

6.5.2. Adjuvant Treatment.

Adjuvant treatment included chemotherapy, radiotherapy and hormone therapy. The entire sample except one patient received radiotherapy therefore no comparisons could be made between those who had or did not have radiotherapy. Table 14 displays the number of participants who received chemotherapy and hormone therapy. The X^2 test did not demonstrate a significant relationship comparing hormone therapy and this was further supported as the 95% confidence interval crossed 1, indicating no relationship. Chemotherapy was significant with more patients that were found to have breast lymphoedema had received chemotherapy as part of their breast cancer treatment (p= 0.031, RR = 1.657).

Table 14. Chi squared test comparing receipt of chemotherapy and hormone therapy.

	Chemo		**No Chemo**		**Hormones**		**No Hormones**	
	Obs	Exp	Obs	Exp	Obs	Exp	Obs	Exp
Breast Lymphoedema	23	18	17	22	33	29.2	7	10.8
No Breast Lymphoedema	17	22	32	27	32	35.8	17	13.2
X^2 statistic	4.629				3.306			
P	**0.031**				**0.069**			
Relative Risk (95% CI)	1.657 (1.038 – 2.645)				1.741 (0.893 – 3.394)			

6.5.3. Patient Characteristics.

There was no significant difference between the age of participant and the presence or absence of breast lymphoedema (t-test, p = 0.375) (Table 15).

Other characteristics did demonstrate statistically significant differences between those with and without breast lymphoedema. The mean values for weight, BMI and NPI were higher in the lymphoedema group (p <0.001, <0.001 and 0.04 respectively) (Table 15). The confidence intervals for the weight, BMI and NPI variables further supported the data as they did not cross 1. Median bra chest size was higher in the lymphoedema group, 40 inches compared to 36 in the non lymphoedema group (p <0.001), see Figure 10.

Table 15. T-Test comparing lymphoedema and Age, weight, BMI and NPI.

Variable		n	Mean	Standard deviation	Mean difference (confidence interval)	Standard error of difference	P value
Age	Lymphoedema	40	59.98	10.58	-2.045 (-6.11 – 2.02)	2.045	0.32
	No Lymphoedema	49	62.02	8.72			
Weight	Lymphoedema	37	86.94	14.30	13.08 (6.34 – 19.81)	3.385	<0.001
	No Lymphoedema	47	73.86	16.21			
BMI	Lymphoedema	37	32.52	5.03	0.548 (3.23 – 7.73)	1.132	<0.001
	No Lymphoedema	47	27.03	5.24			
NPI	Lymphoedema	39	4.25	1.05	0.494 (0.024 – 0.96)	0.236	0.040
	No Lymphoedema	45	3.75	1.11			

Figure 10. Comparison of Chest circumference

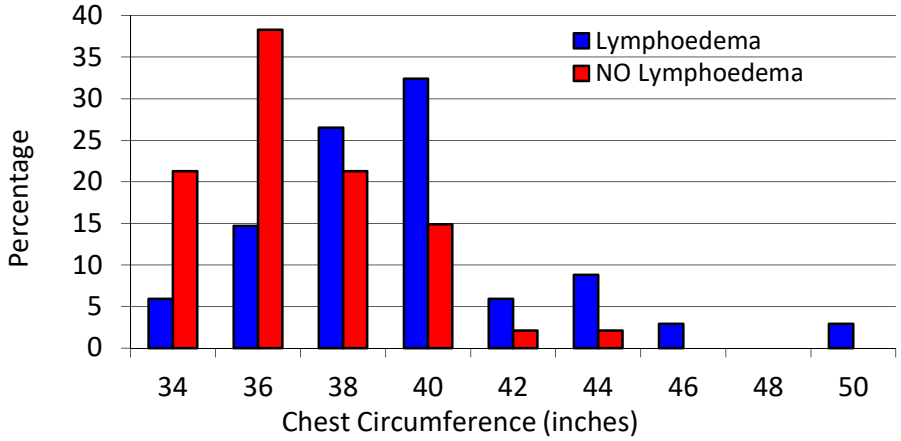


Figure 11. Comparison of Bra Cup Size.

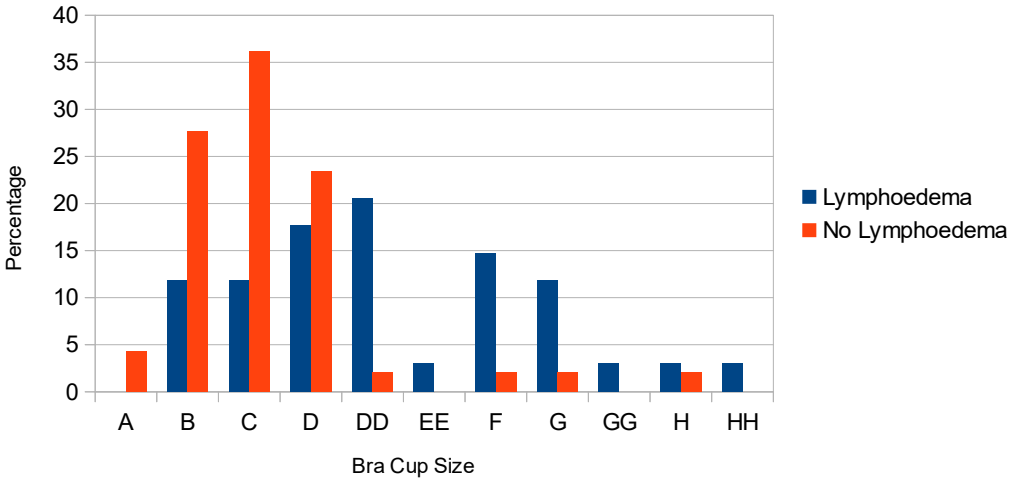


Figure 11 displays bra cup size comparing the group with breast lymphoedema to the group without. The distribution varied between the two groups, the lymphoedema group wore larger cup sized bras. The majority of the group without breast lymphoedema wore a C cup or smaller (63.8%); however, this cup size was less frequently worn in the lymphoedema group (23.5%). The most commonly worn bra cup in the lymphoedema group was a DD (20.6%). The Mann Whitney U test

confirmed a statistically significant difference between these groups ($p<0.001$).

Table 16. Mann Whitney U test comparing bra chest circumference and the presence / absence of breast lymphoedema

Variable		n	Mean	Median	IQR	Mean Rank	Mann Whitney U	P value
Bra Chest Size	Lymphoedema	34	39.47	40	38-40	52.29	415.0	<0.001
	No Lymphoedema	47	36.89	36	36-38	32.83		

6.6. Patient reported symptoms.

The Pearson Chi-square test confirmed that there were significant differences between all of the signs and symptoms reported by patients with and without breast lymphoedema. In addition to this, the effect size, reported by the Phi statistic measuring the size of the difference confirmed an effect size of >0.3 for each question. A Phi value of greater than 0.1 equates to a small effect size, 0.3 a medium effect and 0.5 large effect. The questions with the strongest association are highlighted in table 17. These were swelling to the breast in the past week, feeling of heaviness in the breast over the past week and past year, the breast being tender to touch over the past week and year, numbness/altered feeling to the breast in the past week, tightness in the breast over the past week, bra or clothes marks left in the past week and year, thickening of the skin over the past week and year, dimpling/peau d'orange skin changes over the past week and year, hardness of the breast over the past week and year and an increase in warmth on touch over the past year.

Table 17. Breast Lymphoedema Symptom Questionnaire (BLSQ)

BLSQ Question	Week or year	Lymphoedema	No Lymphoedema	Pearson Chi Square	Phi
		Yes % (n)	Yes % (n)		
1. Do you feel that your breast is swollen?	W	67.4 (23)	14.6 (6)	<0.001	0.542
	Y	75.9 (22)	39 (16)	0.003	0.407
2. Does your breast feel heavy?	W	69.7 (23)	9.8 (4)	<0.001	0.619
	Y	75.9 (22)	25 (10)	<0.001	0.530
3. Is your breast painful?	W	60.6 (20)	14.6 (6)	<0.001	0.479
	Y	75.9 (22)	42.5 (17)	0.006	0.379
4. Is your breast tender to touch?	W	81.3 (26)	17 (7)	<0.001	0.640
	Y	92.8 (26)	42.5 (16)	<0.001	0.554
5. Compared to your other breast, is the feeling (i.e. numbness) in your breast different?	W	78.8 (26)	21 (8)	<0.001	0.583
	Y	86.2 (25)	36.8 (14)	<0.001	0.493
6. Compared to your other breast, does your breast feel tight?	W	67.7 (21)	12.2 (5)	<0.001	0.526
	Y	66.7 (22)	20 (8)	<0.001	0.470

7. Do your bras or close fitting clothes leave marks on your breast or chest?	W	81.3 (26)	22.5 (9)	<0.001	0.584
	Y	85.7 (24)	35 (14)	<0.001	0.531
8. Compared to your other breast, is the shape and size of your treated breast different? If yes, please describe how it is different	W	88.2 (30)	62.2 (23)	0.026	0.318
	Y	92.8 (26)	65.7 (23)	0.028	0.330
9. Compared to your other breast, does the skin on your treated breast feel thicker?	W	82.4 (28)	16.7 (7)	<0.001	0.655
	Y	79.3 (23)	14.6 (6)	<0.001	0.664
10. Compared to your other breast, does the skin on your treated breast look dimpled or like that of orange peel?	W	61.8 (21)	2.4 (1)	<0.001	0.649
	Y	62 (18)	12.2 (5)	<0.001	0.549
11. Compared to your other breast, does the skin on your treated breast feel harder?	W	75.8 (25)	14.6 (6)	<0.001	0.647
	Y	72.4 (21)	14.6 (6)	<0.001	0.606
12. Compared to your other breast, is the skin on your treated breast reddened (i.e. inflamed)?	W	38.2 (13)	9.5 (4)	0.003	0.343
	Y	58.6 (17)	22 (9)	0.002	0.415
13. Compared to your other breast, is the skin on your treated breast warmer to the touch?	W	48.5 (16)	11.9 (5)	<0.001	0.404
	Y	64.3 (18)	17.5 (7)	<0.001	0.508
14. If you have a scar on your breast, does this feel thickened?	W	63.6 (21)	31.7 (13)	0.016	0.333
	Y	67.9 (19)	35.9 (14)	0.025	0.324

None of the questions received a 100% yes or no response identifying that there is no individual / specific question that can be asked to distinguish those with or without breast lymphoedema. Some symptoms such as pain (year), tenderness (year), numbness (year), change in size and clothes marking (year) and scar thickening were reported as present in >30% patients that did not have clinically apparent breast lymphoedema. For the majority of respondents in both groups the proportion of symptoms reported in the past week were less than when compared to the previous year. The exceptions to this were skin thickening, dimpling / peau d'orange changes, hardness of the breast and thickening of the scar which were reported as present in a comparable proportion of patients at both time points.

6.6.1. Diagnostic Accuracy of the BLSQ.

The aim of the symptom questionnaire was to help improve the diagnostic accuracy of breast lymphoedema and therefore additional analysis was undertaken. This looked at the sensitivity and specificity of the BLSQ and a Receiver Operator Characteristic (ROC) curve was produced. When the BLSQ was completed responses were marked as "yes", "no", "not applicable" and in some cases questions they were left blank. These questions were recorded as missing. A not applicable response would have been used if the BLSQ was completed within a year of undergoing breast cancer treatment, as the questions asking about the past year were not relevant. The percentage of questions answered "yes" from the overall number answered was calculated and used to compare the group with and without breast lymphoedema. The difference in mean scores and the significant independent samples t-test are ($p<0.001$) confirmed this difference, specifically that scores were higher in the breast lymphoedema group (table 18).

Table 18. Percentage of symptoms present from the BLSQ including independent samples t-test.

	N	Mean Percent score	SD	T-Test	P value
Breast LE	34	69.0	28.45	7.811	<0.0001
No Breast LE	42	23.34	20.85		

Footnote: 17 participants did not complete and / or return the BLSQ to enable inclusion in the analysis.

Figure 12. ROC Curve for the BLSQ

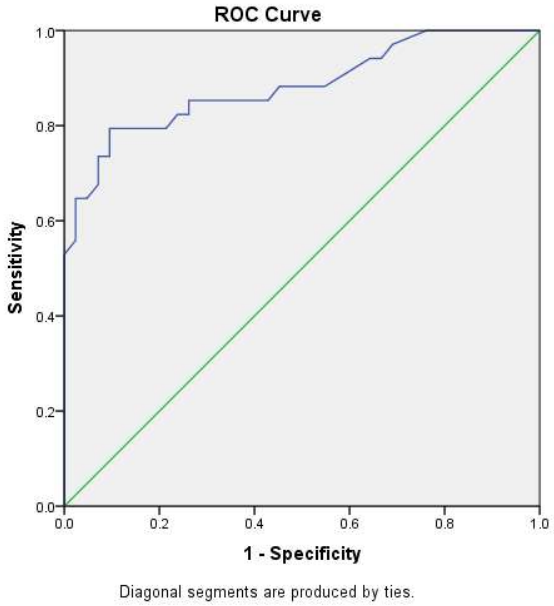


Table 19. The BLSQ AUC statistics plus proposed cut off, sensitivity and specificity

BLSQ	
AUC	**0.882**
Standard Error	0.041
P	**<0.001**
95% CI	0.802 -0.962
Proposed Cut Off (%)	**<48.2**
Sensitivity	**79.4**
Specificity	**90.5**

Table 20. Breast Lymphoedema Symptom Questionnaire Positive and Negative Predictive Values and Likelihood Ratios

	PPV	NPV	+LR	-LR
BLSQ	87.10	84.44	8.358	0.120

From the ROC curve sensitivity and specificity levels were used to identify a threshold for the BLSQ. This was supported by a high and significant AUC statistic. The AUC analysis demonstrated that if the BLSQ score was less than 48.2%, in 90.5% of cases that the participant did not have breast lymphoedema.

6.6.2. Repeatability of the Breast Lymphoedema Symptom Questionnaire.

The BLSQ was completed on two occasions in the group of participants who attended both assessments. There was no change or commencement of lymphoedema treatment and therefore it was hypothesised that responses to the BLSQ should be similar. Test-retest

analysis using the kappa coefficient demonstrated good or very good levels of agreement for 25 out of the 28 questions (kappa >0.7) (Table 21). There was one question, tightness in the past year, which didn't reach the 0.05 level required.

Table 21. BLSQ Test-retest analysis using the Kappa Coefficient.

Question	Week or Year	N	Kappa Coefficient	Level of agreement
1. Do you feel that your breast is swollen?	W	23	0.819	Very Good
	Y	21	0.811	Very Good
2. Does your breast feel heavy?	W	22	0.703	Good
	Y	21	0.710	Good
3. Is your breast painful?	W	20	1.00	Very Good
	Y	19	0.890	Very Good
4. Is your breast tender to touch?	W	22	0.727	Good
	Y	20	0.794	Good
5. Compared to your other breast, is the feeling (i.e. numbness) in your breast different?	W	22	0.818	Very Good
	Y	21	0.720	Good
Compared to your other breast, does your breast feel tight?	W	23	0.732	Good
	Y	21	0.417	
6. Do your bras or close fitting clothes leave marks on your breast or chest?	W	21	0.905	Very Good
	Y	19	0.784	Good
7. Compared to your other breast, is the shape and size of your treated breast different? If yes, please describe how it is different	W	23	0.782	Good
	Y	19	0.753	Good
8. Compared to your other breast, does the skin on your treated breast feel thicker?	W	23	0.824	Very Good
	Y	21	0.712	Good
9. Compared to your other breast, does the skin on	W	23	0.819	Very Good

your treated breast look dimpled or like that of orange peel?	Y	21	1.000	Very Good
10. Compared to your other breast, does the skin on your treated breast feel harder?	W	22	0.538	Moderate
	Y	21	0.690	Good
11. Compared to your other breast, is the skin on your treated breast reddened (i.e. inflamed)?	W	23	0.679	Good
	Y	21	0.800	Good
12. Compared to your other breast, is the skin on your treated breast warmer to the touch?	W	22	0.455	Moderate
	Y	19	0.671	Good
13. If you have a scar on your breast, does this feel thickened?	W	22	0.652	Good
	Y	20	0.900	Very Good

6.7. Validation Testing of the Objective Assessment Tools.

6.7.1. Ability to distinguish oedematous and non-oedematous breast tissue by ultrasound.

Using the paired sample t-test, the mean skin thickness ultrasound measurements were significantly higher in the affected breast qudrant than the contralateral (unaffected) breast quadrant (all $p<0.05$) for each of the four quadrants. For all four quadrants the mean skin thickness in the affected group was approximately double the measurements of the corresponding unaffected quadrant. The inner quadrants were thicker in both the affected and unaffected groups when compared to the outer quadrants. As there were fewer participants with lymphoedema in the upper quadrants the numbers in these groups are smaller.

Table 22. Paired t-test comparing skin thickness measurement by Ultrasound scanning of the individual breast quadrants

Quadrant	Lymphoedema (LE) or no lymphoedema (No LE)	n	Mean (mm)	Standard deviation	Mean difference (confidence interval)	Standard error of difference	P value
Upper outer	LE	12	3.20	0.885	1.50 (0.83 – 2.17)	0.30	<0.001
	No LE	12	1.70	0.400			
Lower outer	LE	31	3.73	1.527	2.12 (1.61 – 2.63)	0.25	<0.001
	No LE	31	1.62	0.340			
Lower inner	LE	29	4.06	1.445	2.21 (1.69 – 2.73)	0.25	<0.001
	No LE	29	1.847	0.481			
Upper inner	LE	11	4.19	0.954	2.205 (1.62 – 2.80)	0.26	<0.001
	No LE	11	1.98	0.237			

6.7.2. Ability to distinguish oedematous and non-oedematous breast quadrants using TDC.

Applying the paired samples t-test, mean TDC readings were significantly higher in all of the affected breast quadrants compared to the unaffected breast quadrants. These were comparable with the ultrasound measurements. The inner quadrants had higher TDC readings but the difference between these and the outer quadrants was by a few units only (Table 23).

Table 23. Tissue Dielectric Constant of the individual breast quadrants, comparing the oedematous to contralateral quadrants.

Quadrant	Lymphoedema (LE) or no lymphoedema (No LE)	n	Mean	Standard deviation	Mean difference (confidence interval)	Standard error of difference	P value
Upper outer	LE	12	40.21	8.776	15.173 (10.02 – 20.33)	2.34	<0.001
	No LE	12	25.04	4.516			
Lower outer	LE	31	45.09	11.425	19.743 (15.25 – 24.24)	2.20	<0.001
	No LE	31	25.34	5.817			
Lower inner	LE	29	47.37	10.517	17.699 (12.71 – 22.69)	2.44	<0.001
	No LE	29	29.67	7.055			
Upper inner	LE	11	49.51	11.310	2.426 (17.76 – 28.58)	2.42	<0.001
	No LE	11	26.34	4.718			

Table 24. Comparison of the Tissue Dielectric Constant Ratios (Affected Breast:Unaffected Breast)

	N	Mean	Standard deviation	Mean difference (confidence interval)	Standard error of difference	P value
Lymphoedema Present	40	1.624	0.306	0.450 (0.340 – 0.561)	0.055	<0.001
Lymphoedema Absent	49	1.174	0.188			

When TDC is used to assess the presence of oedema the measurements commonly the raw data is not used but comparison made between the affected and unaffected area(s). This is achieved by pairing the measurements and calculating the ratio of the affected to unaffected area. For breast oedema the 4 quadrants of each breast are added to together and the total/overall TDC value of the affected breast compared to the total TDC value of the unaffected breast. Using the Independent samples t-test, the mean ratio was significantly higher in the group with breast lymphoedema than the non-lymphoedema group ($p<0.001$).

In previous studies, if a scar was present in one or more of the breast quadrants then this quadrant(s) was excluded in the calculation of the total breast ratio. To ascertain whether there was a significant difference between the scarred and non-scarred quadrants and therefore the scarred quadrant(s) should be omitted the Wilcoxon Signed Ranks Test was undertaken.

Table 25. Tissue Dielectric Constant Ratio - excluding scarred quadrant(s)

	N	Mean	Standard deviation	Mean difference (confidence interval)	Standard error of difference	P value
TDC ratio	52	1.449	0.330	-0.0025 (-0.206 – 0.0256)	0.014	0.859
TDC ratio excluding scarred quadrant(s)	52	1.452	0.391			

The p value achieved was >0.05 demonstrating no significant difference between the groups. This result confirmed that the scarred quadrants do not need to be excluded when calculating the TDC ratio of the affected to the unaffected breast quadrants.

6.7.3. Ability to distinguish oedematous and non-oedematous breast quadrants using tonometry.

Table 26. Comparison of the Tonometer Measurements of the Individual Breast Quadrants using the Wilcoxon Signed Rank test.

Breast quadrant	Lymphoedema (LE) or no lymphoedema (No LE)	N	Median (IQR)	P value
Lower Outer	LE	29	0.91 (0.88 – 0.95)	0.443
	No LE	28	0.93 (0.90 – 0.94)	
Lower Inner	LE	26	0.925 (0.90 – 0.94)	0.074
	No LE	26	0.94 (0.92 - 0.94)	
Upper Outer	LE	11	0.92 (0.88 – 0.95)	0.575
	No LE	11	0.90 (0.88 - 0.94)	
Upper Inner	LE	11	0.95 (0.92 - 7.8)	0.398
	No LE	11	0.94 (0.94 – 0.96)	

Comparing the affected and unaffected measurements from the tonometer, p values were >0.05 for each of the four breast quadrants. This result supports that the null hypothesis is accepted and that there is no significant difference in the tonometer measurements for any of the four quadrants (Table 26). Comparison of the median values demonstrated that these are similar in both groups. The IQR for the upper inner quadrant was larger than the others obtained with the 75th percentile equal to 7.8. The other IQR are all under 1.0.

6.7.4. The unaffected breast as a comparator.

Analysis of the affected and unaffected breasts in the both the lymphoedema and non-lymphoedema group was undertaken to determine whether the unaffected breast can be used as a comparator. It was hypothesised that the measurements of the affected and unaffected breast should be similar and therefore analysis looking for differences between the two breasts non-significant.

Table 27. Paired sample t- test comparing ultrasound measurements of skin thickness of the affected and unaffected breast quadrants in the lymphoedema and non-lymphoedema group.

	N	Mean (mm)	Mean difference (95% confidence interval)	Standard Error	P value
Lymphoedema Group					
Affected UO	40	2.46	0.871	0.140	<0.001
Unaffected UO	40	1.59	(0.587 – 0.115)		
Affected LO	40	3.50	1.88	0.220	<0.001
Unaffected LO	40	1.62	(1.435 – 2.325)		
Affected LI	40	3.95	2.07	0.155	<0.001
Unaffected LI	40	1.88	(1.589 – 2.544)		
Affected UI	40	3.09	1.30	0.236	<0.001
Unaffected UI	40	1.79	(0.983 – 1.61)		
Non Lymphoedema Group					
Affected UO	49	1.66	0.171	0.057	<0.001
Unaffected UO	49	1.49	(0.0607 – 0.28)		

Affected LO	49	1.89	0.290	0.073	<0.001
Unaffected LO	49	1.60	(0.143 – 0.037)		
Affected LI	49	2.10	0.0351	0.075	<0.001
Unaffected LI	49	1.75	(0.20 – 0.502)		
Affected UI	49	1.94	0.238	0.085	<0.001
Unaffected UI	49	1.70	(0.066 – 0.409)		

For each of the breast quadrants assessed the quadrant of the affected breast demonstrated an increased mean skin thickness compared to the unaffected breast. This relationship was seen in both the group with lymphoedema and more surprisingly the group with no lymphoedema. In the non lymphoedema group the differences between the quadrants appeared to be small, however, they were statistically significant, $p<0.001$ for each quadrant. This difference has demonstrated that after breast cancer treatment despite there not being clinically apparent lymphoedema in the individual breast quadrants of the affected breast they become thickened.

Table 28. Paired t- test comparing TDC measurements of the affected and unaffected breast quadrants in the lymphoedema and the non lymphoedema group.

	N	Mean	Mean difference (95% confidence interval)	Standard Error	P value
Lymphoedema Group					
Affected UO	40	34.05	9.77	1.402	<0.001
Unaffected UO	40	24.27	(6.94 – 12.614)		
Affected LO	40	43.78	18.41	1.957	<0.001
Unaffected LO	40	25.37	(14.45 – 22.37)		
Affected LI	40	47.03	17.38	1.967	<0.001
Unaffected LI	40	29.65	(13.40 – 21.353)		
Affected UI	40	40.15	13.59	1.661	<0.001
Unaffected UI	40	26.56	(10.231 – 16.95)		
No Lymphoedema Group					
Affected UO	49	28.90	3.067	0.784	<0.001
Unaffected UO	49	25.84	(1.49 – 4.644)		
Affected LO	49	31.06	4.655	1.052	<0.001
Unaffected LO	49	26.41	(2.539 – 6.770)		
Affected LI	49	35.70	5.22	1.182	<0.001
Unaffected LI	49	30.48	(2.843 – 7.60)		
Affected UI	49	31.75	3.496	0.958	0.001
Unaffected UI	49	28.45	(1.57 – 5.421)		

A similar pattern to the ultrasound measurements was demonstrated with the TDC measurements. In the non-lymphoedema group the differences between the quadrants was smaller, the mean measurements differed by only a few units, this was a statistically significant difference. The breast quadrant in the treated breast had higher TDC readings than the breast quadrants of the untreated breast. This difference demonstrates that after breast cancer treatment there is more local tissue water at a depth of 2.5mm in all of the breast quadrants of the treated breast than the untreated breast in both those with and without breast lymphoedema.

Table 29. Wilcoxon Signed Ranks test comparing tonometry affected and unaffected breasts of the lymphoedema and non lymphoedema groups.

	N	Median	IQR	Test value	P value
Lymphoedema Group					
Affected UO	39	0.93	0.91 – 0.95	-1.513	0.130
Unaffected UO	38	0.92	0.90 – 0.94		
Affected LO	37	0.92	0.88 – 0.94	-0.957	0.338
Unaffected LO	37	0.92	0.90 – 0.93		
Affected LI	36	0.92	0.89 – 0.94	-1.637	0.102
Unaffected LI	37	0.93	0.90 – 0.94		
Affected UI	39	0.93	0.91 – 0.95	-0.179	0.858
Unaffected UI	39	0.93	0.91 – 0.94		
Non Lymphoedema Group					
Affected UO	46	0.94	0.92 – 0.94	-0.673	0.501
Unaffected UO	46	0.94	0.93 – 0.94		

Affected LO	44	0.93	0.92 – 0.94	-0.40	0.968
Unaffected LO	44	0.93	0.9175 – 0.94		
Affected LI	46	0.93	0.9175 – 0.94	-0.127	0.899
Unaffected LI	46	0.93	0.92 – 0.94		
Affected UI	46	0.93	0.92 – 0.9425	-0.502	0.615
Unaffected UI	46	0.93	0.92 – 0.94		

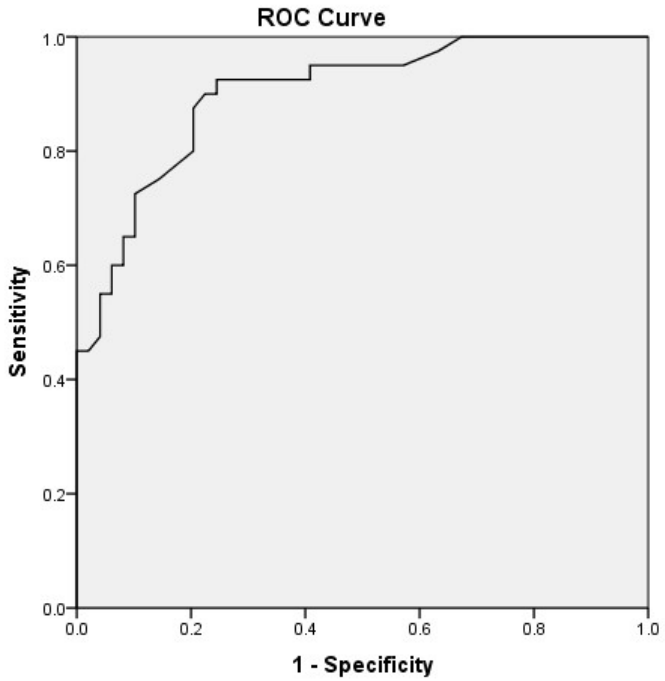
For each of the four quadrants the median and IQR values were similar and this was confirmed using the Wilcoxon signed rank test as $p>0.005$ for each test, indicating that there was no significant difference in the tonometer measurements obtained on the affected or unaffected breast.

6.8. Receiver Operating Characteristic (ROC) Curves.

To look further at the diagnostic accuracy of a test, receiver operating characteristic (ROC) curves were produced which enabled the area under the curve (AUC) to be calculated. Using the sensitivity and specificity levels a threshold level for USS skin thickness and TDC was proposed.

6.8.1. ROC Analysis for Tissue Dielectric Constant for the Whole Breast.

Figure 13. ROC curve for TDC ratio.



The AUC statistic for TDC is 0.901, standard error = 0.032 and produced a 95% confidence interval of 0.839 – 0.964 (Figure 13). An AUC of 1 demonstrates a perfect test with values between 0.8 – 0.9 reported as demonstrating a good test. The confidence interval didn't cross 1 and the p value is less than 0.001 confirming a statistically significant relationship. Analysis of the ROC curve identified a TDC threshold using ratio of 1.34 which produced a sensitivity of 87.5% and specificity of 79.6%.

Table 30. Sensitivity and specificity of TDC ratio at 1.34 threshold range.

	TDC Ratio >1.34	TDC Ratio <1.34
Breast Lymphoedema	35	5
No Breast Lymphoedema	10	39
Sensitivity (Confidence Interval)	87.5% (77.6 – 97.7%)	
Specificity	79.6% (68.3 – 90.9%)	

Table 31. TDC Ratio PPV, NPV, +LR, -LR

	PPV	NPV	+LR	-LR
TDC Ratio	77.8%	88.6%	4.29	0.157

The high PPV and NPV identified that approximately 78% and 87% of participants with or without breast lymphoedema were correctly identified using the TDC threshold of 1.34. Using the TDC threshold ratio of >1.34 the positive likelihood ratio (+LR) was >1 and the negative likelihood ratio (-LR) <1 indicating that these tests may improve the assessment of breast lymphoedema.

6.8.2. ROC Analysis for Ultrasound Measurement.

Figure 14. ROC Curve for Ultrasound of the Lower Outer quadrant

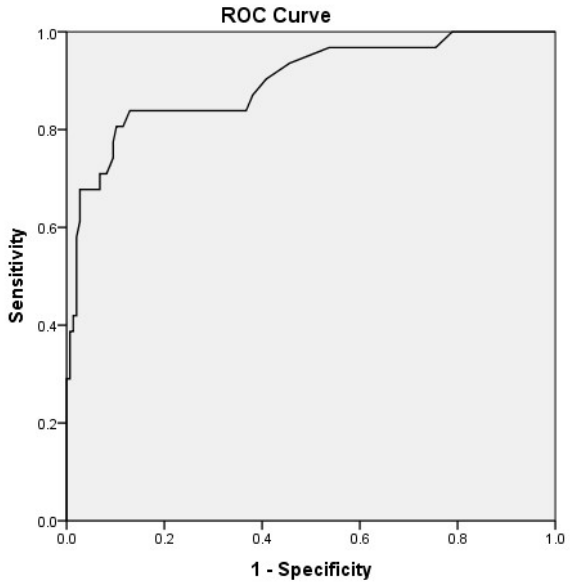


Figure 15. ROC Curve for Ultrasound of the Lower Inner Quadrant

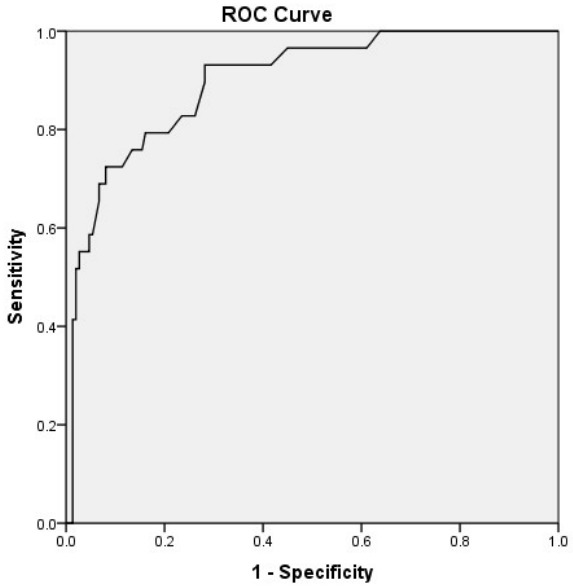


Figure 16. ROC Curve for Ultrasound of the Upper Outer Quadrant

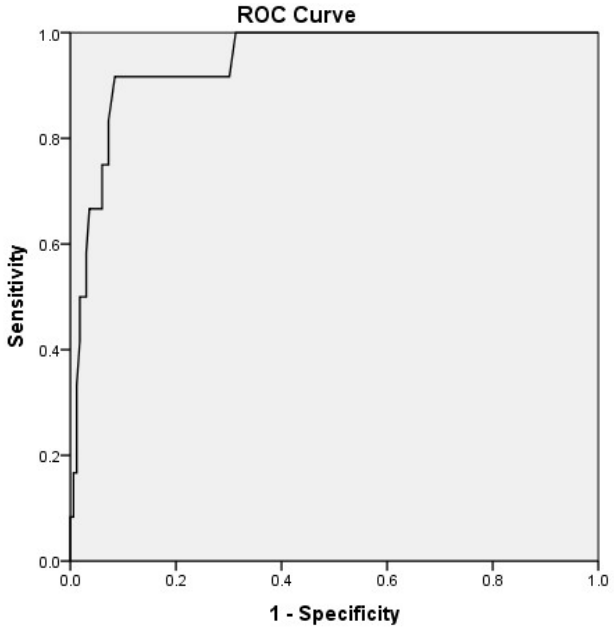


Figure 17. ROC Curve for Ultrasound of the Upper Inner Quadrant

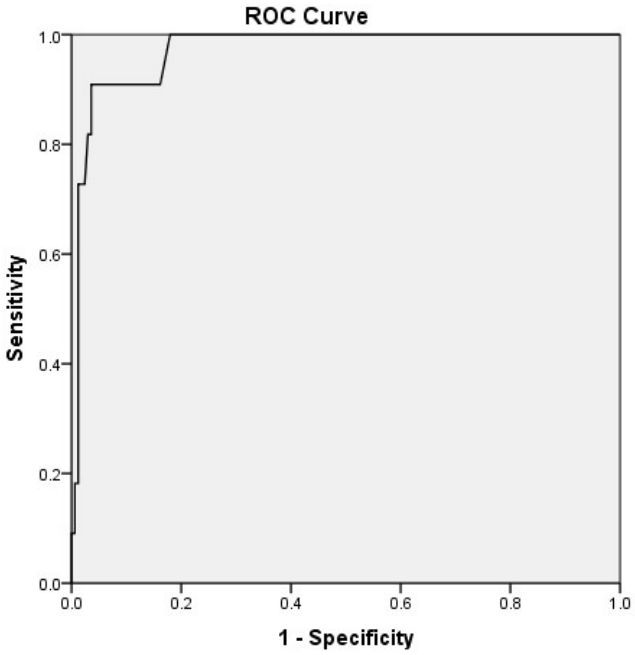


Table 32. Ultrasound AUC statistics plus proposed reference ranges, sensitivity and specificity

	AUC	Standard Error	**P**	95% CI	**Proposed Threshold (mm)**	**Sensitivity**	**Specificity**
LOQ	**0.898**	0.035	**<0.001**	0.83 – 0.966	**≥ 2.3**	**83.9%**	**87.1%**
LIQ	**0.898**	0.030	**<0.001**	0.839 – 0.958	**≥2.6**	**79.3%**	**83.9%**
UOQ	**0.946**	0.026	**<0.001**	0.896 – 0.997	**≥2.5**	**91.7%**	**91.6%**
UIQ	**0.972**	0.016	**<0.001**	0.94 – 1.00	**≥3.0**	**90.9%**	**93.4%**

Table 33. Ultrasound Positive and Negative Predictive Values and Likelihood Ratios

	PPV	NPV	+LR	-LR
LOQ	57.8%	87.1%	6.504	0.185
LIQ	48.9%	95.4%	4.925	0.247
UOQ	44.0%	99.3%	10.917	0.091
UIQ	47.6%	99.4%	13.773	0.097

The AUC, associated p values, sensitivity and specificity results support the use of skin thickness measurement of the breast quadrants by ultrasound scanning in the identification of breast lymphoedema. The PPV identified that approximately 44-58% of the sample with a positive test did have breast lymphoedema. However, the NPV values are much higher, 87-99% indicating that participants who had a “normal” ultrasound measurement did not have breast

lymphoedema. Comparable to TDC data the positive likelihood ratio (+LR) was >1 and the negative likelihood ratio (-LR) <1 for the USS thresholds again indicating that these tests add value to the assessment of breast lymphoedema.

6.8.3. Comparison with previously reported TDC reference ranges.

Previous studies have utilised a reference range for TDC ratio of 1.26 for upper limb, including the thorax and 1.40 for breast oedema. Table 34 identifies the sensitivity and specificity using both proposed threshold levels. With the 1.26 cut off the sensitivity of the test reduced from 85.7% to 73.5%, as 8 additional patients without breast lymphoedema had a positive reading, however, the specificity improved from 81.5% to 92.3% as only 3 patients with breast lymphoedema had a ratio of less than 1.26. In addition to the sensitivity and specificity the positive predictive value (PPV) and negative predictive value (NPV) provide information regarding the accuracy of the test to correctly identify either a true positive or true negative.

Table 34. Sensitivity and specificity of provided TDC ratios.

	Breast Lymphoedema	No Breast Lymphoedema	Sensitivity	Specificity	PPV	NPV
TDC Ratio >1.4	30	5	75%	89.8%	85.7%	81.5%
TDC Ratio <1.4	10	44				
TDC Ratio >1.26	37	13	92.5%	73.5%	74%	92.3%
TDC Ratio <1.26	3	36				

6.9. Repeated Measurements.

The sample size calculation identified that 62 participants were required to attend two study visits as this would enable analysis to be undertaken which would confirm that any significant findings were not due to chance. Unfortunately, due to participant and researcher availability only 25 participants underwent two study visits.

Table 35. Comparison of USS measurement at visit 1 and visit 2 (n=25)

Quadrant	Visit 1	Visit 2	Test Statistic	P value
	Median (IQR) (mm)	Median (IQR) (mm)		
Affected OU	1.8 (1.40 – 2.525)	1.55 (1.35 – 2.675)	-0.129	0.898
Affected LO	2.0 (1.525 – 4.15)	2.5 (1.475 – 4.275)	-1.321	0.187
Affected LI	2.35 (1.90 – 4.325)	2.55 (1.80 – 4.375)	-0.544	0.587
Affected UI	2.4 (1.65 – 3.35)	2.45 (1.475 – 3.625)	-0.386	0.699
Unaffected OU	1.35 (1.25 – 1.65)	1.4 (1.225 – 1.75)	-0.336	0.737
Unaffected LO	1.50 (1.25 – 1.65)	1.55 (1.25 – 1.80)	-0.868	0.385
Unaffected LI	1.65 (1.25 – 2.10)	1.65 (1.40 – 1.90)	-0.891	0.373
Unaffected UI	1.55 (1.35 – 2.075)	1.60 (1.25 – 1.875)	-0.845	0.398

Repeated ultrasound measurements of the affected and unaffected breast quadrants did not demonstrate any significant differences between the two assessments as the p values were all >0.05 and the medians and IQR similar (table 35).

Table 36. Comparison of TDC values at visit 1 and visit 2 (n=25)

Quadrant	Visit 1	Visit 2	Test Statistic	P value
	Median (IQR)	Median (IQR)		
Affected OU	30.8 (25.7 – 36.4)	29.93 (24.105 – 34.865)	-0.296	0.767
Affected LO	35.33 (29.28 – 50.915)	34.67 (26.035 – 49.55)	-1.272	0.204
Affected LI	41.53 (29.315 – 54.315)	40.93 (28.335 – 50.685)	-1.251	0.211
Affected UI	33.1 (28.45 – 46.40)	33.93 (26.15 – 45.485)	-1.372	0.17
Affected average mmt	34.98 (29.105 – 45.63)	35.83 (26.64 – 44.18)	-1.090	0.276
Unaffected OU	23.33 (22.05 – 26.5)	23.6 (22.3 – 26.37)	-0.982	0.326
Unaffected LO	24.73 (22.15 – 27.72)	25.47 (21.78 – 29.15)	-0.901	0.367
Unaffected LI	27.2 (23.75 – 29.6)	28.47 (25.605 – 30.285)	-0.886	0.376
Unaffected UI	25.5 (23.015 – 27.95)	26.57 (23.82 – 28.365)	-0.578	0.563
Unaffected average mmt	24.7 (23.975 – 27.44)	26.49 (23.365 – 28.97)	-1.332	0.183

The repeated TDC readings did not show any statistically significant differences between the median and IQR for the first and second assessments, $p>0.05$ for all quadrants (table 36).

To explore this relationship further the paired data was combined to produce 200 paired readings for the TDC and USS respectively. From this data the difference between the first and second measurements and mean values were calculated. The Bland and Altman plots demonstrated the measurement error and limits of agreement. In addition, the non-significant one sampled t-test, outputs from the linear regression analysis and unstandardized coefficient B supported the repeatability of both TDC and USS measurement. Figures 18 & 19 displays the plots and tables 36 & 37 the analysis.

Table 37. One sample t-test, 95% confidence intervals and linear regression analysis for repeated measurements of USS

	Mean	95% Confidence Interval		T-Test p value	Linear Regression	
		Lower Limit	Upper Limit		Unstandardised Coefficient B	P Value
Difference between USS mmt 1 & 2	0.008	-0.857	0.873	0.798	0.009	0.748

Figure 18. Bland and Altman plots for repeated USS.

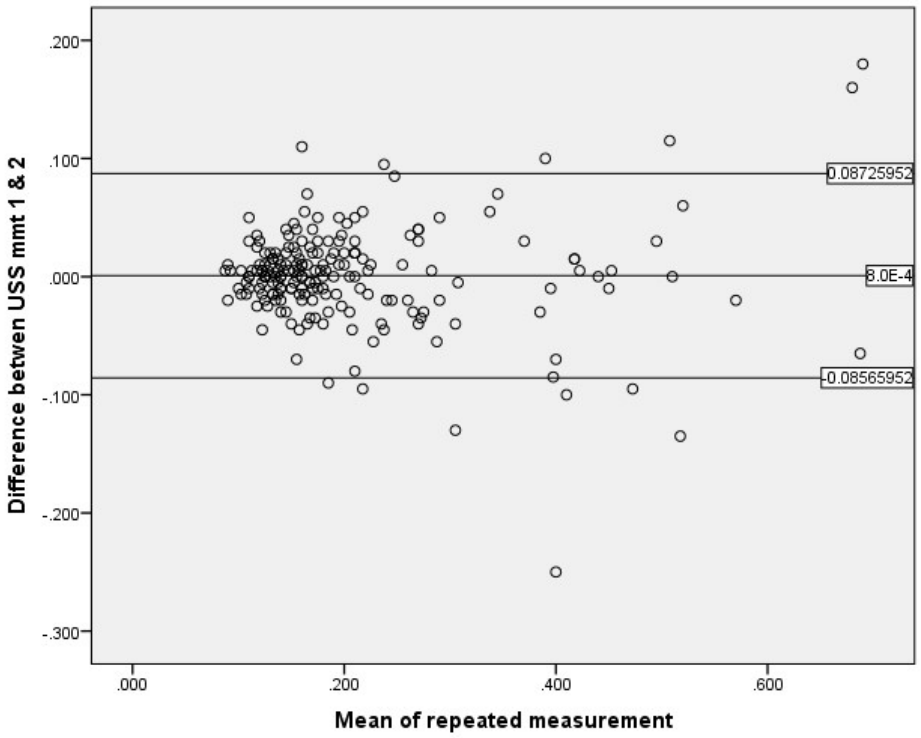
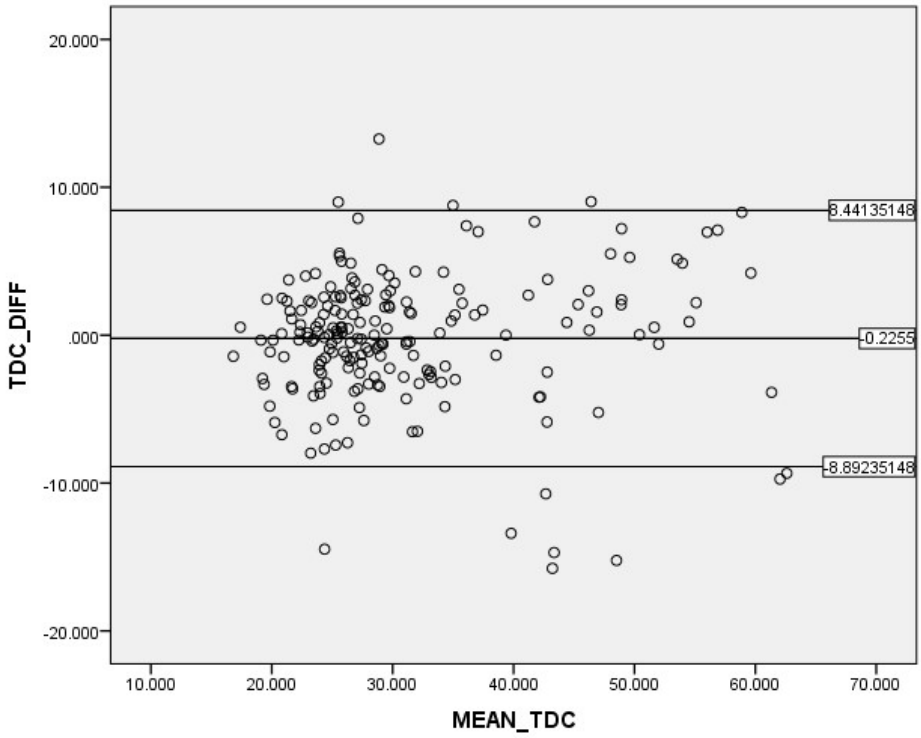


Table 38. One sample t-test, 95% confidence intervals and linear regression analysis for repeated measurements of TDC

	Mean	95% Confidence Interval		T-Test p value	Linear Regression	
		Lower Limit	Upper Limit		Unstandardised Coefficient B	P Value
Difference between TDC mmt 1 & 2	-0.2255	-8.892	8.441	0.472	0.021	0.509

Figure 19. Bland and Altman plots for repeated TDC



6.10. The Relationship between Body Mass Index and Age on Ultrasound and Tissue Dielectric Constant measurements.

There have been two recent studies published between the time that the literature review was undertaken and this study was completed. It was felt that these findings should be considered in order to identify whether these relationships were also present in this study. Previously, age was negatively correlated with skin thickness on ultrasound measurement of the unaffected breast (120). More recently arm TDC ratios were not found to be affected by BMI (121).

Table 39 details the Pearson Correlation Coefficients (2 tailed) for Age and USS and TDC measurement. This did not show any significant correlations for the ultrasound measurements but a weak negative correlation for the TDC measurements for the upper outer (UO) quadrant of both breasts. In the initial analysis of this sample age was

not significantly different between the groups further supporting this finding.

Table 39. Pearson Correlation Coefficient for Age and USS / TDC (2 tailed).

Affected Breast					
Quadrant	N	Ultrasound		TDC	
		p	r	p	r
UO	89	0.183	-0.142	0.040	-0.218
LO	89	0.104	-0.173	0.172	-0.146
LI	89	0.155	-0.152	0.419	-0.087
UI	89	0.194	-0.139	0.232	-0.131
Unaffected Breast					
UO	89	0.963	-0.005	0.029	-0.232
LO	89	0.960	0.005	0.114	-0.169
LI	89	0.739	0.036	0.500	-0.073
UI	89	0.925	-0.010	0.803	-0.027

BMI was significantly different between the two groups and higher in the breast lymphoedema group. There were weak and moderate positive correlations for ultrasound measurements of both breasts and weak positive correlations for TDC measurements of the affected breast. No correlations were found for TDC measurement of the quadrants in the unaffected breast (Table 40)

Table 40. Pearson Correlation Coefficient (2 tailed) exploring the relationship between BMI and USS / TDC.

Affected Breast					
Quadrant	N	Ultrasound		TDC	
		p	r	p	r
UO	89	<0.0001	0.397	0.033	0.233
LO	89	0.005	0.302	0.016	0.262
LI	89	0.002	0.331	0.036	0.229
UI	89	<0.001	0.463	0.003	0.323
Unaffected Breast					
UO	89	0.034	0.232	0.379	-0.097
LO	89	0.915	0.012	0.159	-0.155
LI	89	0.019	0.256	0.268	-0.122
UI	89	0.020	0.254	0.069	-0.203

6.11. Conclusions.

This study had several aims all associated with improving the diagnosis and recognition of breast lymphoedema after breast cancer.

Despite the study aiming to recruit women with and without breast lymphoedema, the results demonstrated that breast lymphoedema had not been previously recognised or treated in 72.5% of those found to have breast lymphoedema following the clinical examination undertaken in this study. This finding confirms that this is a current and unrecognised problem for patients who have undergone breast cancer treatment.

It appears that some of the risk factors associated with the development BCRL of the arm are also risk factors for the development of breast lymphoedema. In addition, the relationship

between increased breast size and the development of breast lymphoedema was established in this study.

Specific symptoms reported by patients and recognised by clinicians can be applied to aid the diagnosis of breast lymphoedema. Analysis of the BLSQ has demonstrated that this is a useful and valid tool which will enhance screening and clinical assessment. In particular the ROC analysis suggested that a BLSQ score of 48.2% for use in patient screening to determine which individuals would benefit from further assessment.

Measurement of skin thickness by ultrasound scanning and skin water measurement by tissue dielectric constant were both found to be reliable methods for assessing breast lymphoedema. ROC analysis produced threshold values that could be applied in practice to distinguish between oedematous and non-oedematous breast tissue. In this study the tissue tonometer was not found to be reliable in distinguishing between oedematous and non-oedematous breast tissue and therefore not recommended as an assessment tool for breast lymphoedema

The analysis identified that the treated breast skin was thicker by ultrasound measurement and had a higher TDC reading than the non-treated breast even in participants who did not have breast lymphoedema.

Repeated assessment confirmed the reliability of the ultrasound and TDC measurements. Repeated measurements did not differ significantly when the initial and second assessment measurements were compared.

Chapter 7. Results from the Validation of the LYMQOL Breast.

7.1. Introduction.

This chapter will present the analysis undertaken to determine whether the LYMQOL Breast questionnaire can be used as a reliable and validated tool. A detailed description of the validation process was provided in Chapter 5.

7.2. Internal Consistency.

The Cronbach's α statistic was produced for each of the four LYMQOL-Breast domains to demonstrate the level of reliability or internal consistency. In addition to the domain test the individual questions were analysed to determine whether they add to the domain or not.

For the Function domain 58 completed questionnaires were analysed. The overall Cronbach's α = 0.877 for the 6 items. The individual questions demonstrated good levels of reliability to the overall domain and the individual questions (Table 41). Deleting any of the questions did not increase Cronbach's α.

Table 41. Function domain, Cronbach's α

Question:	Cronbach's α if deleted
1) How much does your swollen breast or chest affect the following daily activities?	
a) occupation	0.876
b) housework	0.828
c) dressing	0.851
d) washing	0.869
Q2) How much does it affect your leisure activities/ social life?	0.837
Q3) How much do you have to depend on other people?	0.864

For the Appearance domain 74 questionnaires were analysed (table 42). The overall Cronbach's α = 0.882 for the 5 items in the domain. The overall level of scale reliability was high. There was one question identified (Q8) that if it was removed the overall Cronbach α value would be increased. However, the α value increase without this question was very small increasing from 0.882 to 0.887.

Table 42. Appearance Domain, Cronbach's α

Question:	Cronbach's α if deleted
(Q4) How much do you feel the swelling affects your appearance?	0.861
(Q5) How much difficulty do you have finding clothes including bras to fit?	0.863
(Q6) How much difficulty do you have finding clothes including bras you would like to wear?	0.821
(Q7) Does the swelling affect how you feel about yourself?	0.839
(Q8) Does it affect your relationships with other people?	0.887

The overall Cronbach α value for the symptom domain demonstrated good scale reliability, α = 0.870 for the 5 items in the domain (table 43). 73 completed questionnaires were analysed. Again, there was one question in this domain, Q11, which appeared to lower the overall Cronbach's α slightly from 0.883 to 0.870 (Table 43). It was not felt that removing this question would add to or improve the tool.

Table 43. Symptoms Domain, Cronbach's α

Question:	Cronbach's α if deleted
(Q9) Does your swollen breast or chest cause you pain?	0.816
(Q10) Do you have any numbness in your swollen breast or chest?	0.863
(Q11) Do you have any feelings of "pins & needles" or tingling in your swollen breast or chest?	0.883
(Q12) Do you have any feeling of tightness in your swollen breast or chest?	0.816
(Q13) Does your swollen breast feel heavy?	0.813

The Emotion domain produced the lowest Cronbach α value, 0.678 for the 6 items, with 72 questionnaires analysed (table 44). Examination of the individual questions identified that removing question 16 the overall domain Cronbach α score significantly increased to 0.852 (Table 44). Not only did removing this question increase the overall α but it now exceeded the acceptable level into the level indicative of good scale reliability.

Table 44. Cronbach α values for the Emotion domain

Question: In the past week….	Cronbach's α if deleted
(Q14) Have you had trouble sleeping?	0.595
(Q15) Have you had difficulty concentrating on things, e.g. reading?	0.632
(Q16) Have you felt tense?	0.852
(Q17) Have you felt worried?	0.591
(Q18) Have you felt irritable?	0.600
(Q19) Have you felt depressed?	0.638

Further analysis to determine internal consistency was achieved by completing split half testing. This tested the association between randomly assigned survey items. This test followed the assumption that the two halves of the tool should yield similar true scores and error variances. Comparisons were made between the first half and second half of the questions and between the odd and even numbered questions (Table 45).

Table 45. Split half testing

	First half questions	Second half questions	Odd numbered questions	Even numbered questions
Cronbach's α Value	0.943	0.745	0.922	0.714
Number of items	12	11	12	11
Spearman Brown (Unequal)	0.828		0.915	

From table 45 it can be inferred from the high level of correlations produced that the individual questions relate to each other and also to the overall theme of LYMQOL Breast.

7.3. Construct and Discriminant Validity Testing.

Construct and discriminant validity tested whether the LYMQOL scores changed depending on the presence or absence of breast lymphoedema. It was postulated that individuals with breast lymphoedema would have worse quality of life and therefore higher scores for the domain averages and a lower overall QoL rating than those without breast lymphoedema.

As one overall group the mean and median domain averages were low, indicating good quality of life. This was further supported by a high overall quality of life rating, mean = 7.44 (sd 2.055) as shown in table 46.

Table 46. Domain averages for LYMQOL Breast – Overall study sample group.

	N	Mean	Standard deviation	Median	IQR
Function Domain	77	1.318	0.466	1.00	1 – 1.55
Appearance Domain	78	1.533	0.701	1.2	1 – 2
Symptom Domain	76	1.530	0.648	1.2	1 – 2
Emotion Domain	76	1.589	0.648	1.33	1 – 2
QoL	73	7.44	2.055	8	6-9

Table 47. LYMQOL Breast domain averages Breast Lymphoedema group

	N	Mean	Standard deviation	Median	IQR
Function Domain	34	1.588	0.532	1.5	1 – 2
Appearance Domain	35	1.95	0.788	2	1.2 – 2.25
Symptom Domain	34	1.95	0.687	2	1 – 2
Emotion Domain	34	1.835	0.700	1.67	1 – 2
QoL	34	6.76	1.955	7	6 - 9

Table 48. LYMQOL Breast domain averages Non-Lymphoedema group

	N	Mean	Standard deviation	Median	IQR
Function Domain	43	1.105	0.256	1	1 – 1
Appearance Domain	43	1.193	0.367	1	1 – 1.4
Symptom Domain	42	1.191	0.330	1	1 – 1.2
Emotion Domain	42	1.390	0.531	1.085	1 – 1.703
QoL	39	8.03	1.980	9	7 - 9

Table 49. Mann Whitney U test LYMQOL Breast domain comparisons

	Lymphoedema	Mean Rank	Sum of Ranks	Z statistic	P value
Function	Yes	51.09	1737.0	-4.677	<0.001
	No	29.44	1266.0		
Appearance	Yes	52.44	1835.50	-4.845	<0.001
	No	28.97	1245.50		
Symptoms	Yes	52.60	1788.50	-5.172	<0.001
	No	27.08	1137.50		
Emotion	Yes	47.91	1629.0	-3.403	0.001
	No	30.88	1297.0		
QoL	Yes	28.37	964.5	-3.305	0.001
	No	44.55	1736.5		

Comparing the median, inter quartile ranges, mean rank and the sum of ranks for each of the four QoL domains these were all higher in the Breast Lymphoedema group. Higher individual question or domain average is associated with lower / worse QoL. The Mann Whitney U test was significant for each of the four domains and for the overall QoL rating ($p \leq 0.001$ in each case). The median QoL rating was lower in the breast lymphoedema group indicating worse QoL ($p=0.001$).

7.4. Comparison with the EORTC-QLQ-BR23.

As there isn't a validated condition specific QoL tool to compare to the LYMQOL Breast tool, comparisons were made with the validated EORTC-QLQ-C30 and the breast cancer specific BR23 module. The EORTC is scored by calculating the means for the different scale topics and transforming the average scores linearly. In the QoL scale

and functional domains a higher score represents better QoL or function. However, in the symptom scales a higher score is indicative of a higher level of that symptom / problem.

Histograms and the Shapiro-Wilk test for the EORTC functional domain; physical, role, cognitive, emotional and social when comparing the two groups demonstrated a positively skewed, non-normal distribution. The median values and IQR were higher in the non-lymphoedema group indicating a higher / healthier level. For all except the emotional domain these were significantly different when tested using the Mann Whitney U test (table 50).

Table 50. EORTC Functional Domains averages and Mann Whitney U Test

Domain	Lymphoedema?	Median	IQR	Mean Rank	P value
Physical	Yes	80	65 – 93.3	28.46	<0.001
	No	93.3	86.67 – 100	47.34	
Role	Yes	83.3	62.5 – 100	30.60	0.001
	No	100	100 -100	45.64	
Cognitive	Yes	83.3	66.67 – 100	33.54	0.044
	No	83.3	83.3 – 100	43.31	
Emotional	Yes	83.3	70.83 – 95.83	34.33	0.141
	No	91.67	75 – 100	41.70	
Social	Yes	83.3	66.67 – 100	31.04	0.002
	No	100	83.3 - 100	45.29	

The global health domain that combines overall health and QoL was significantly higher (better), p=0.015, in the non-lymphoedema group

(median 83.3, IQR = 66.67 – 91.67) than in the breast lymphoedema group (median 70.83, IQR = 58.3 – 83.3).

For the other functional and symptom scales some demonstrated statistically significant differences between the two groups and some did not (table 51). Looking at the questions asked and the timescales from diagnosis and treatment to taking part in the study it would be postulated that symptoms such as nausea and vomiting, insomnia, appetite and diarrhoea should be similar as these are often caused by adjuvant cancer therapies such as chemotherapy. However, the BR23 systemic therapy domain was statistically significantly higher in the lymphoedema group ($p=0.011$). In addition, some of the QLQ-30 symptom scales including fatigue, pain, dyspnoea and constipation were reported as more problematic in the breast lymphoedema cohort. There was no difference between the two groups for the questions on future perspectives ($p=0.068$) and body image ($p=0.177$). In addition to this sexual function was reported at a significantly higher, healthier level, for those with breast lymphoedema ($p=0.024$).

The four questions in the breast symptom scale were significantly higher in the breast lymphoedema group ($p<0.001$). The arm symptom scale was also significantly higher in the breast lymphoedema group. It was not recorded if participants had arm lymphoedema.

Table 51. EORTC QLQ30-BR23 functional domains, symptom scales and single item question averages and Mann Whitney U Test

Question	Function / Symptom	Breast LE?	Median	IQR	Mean Rank	P value
Nausea & Vomiting	Symptom	Yes	0.00	0 – 0	41.93	0.08
		No	0.00	0 – 0	36.69	
Pain Scale	Symptom	Yes	33.33	0 – 54.17	49.53	<0.001
		No	0.00	0 – 16.67	30.67	
Dyspnoea	Symptom	Yes	16.67	0 – 33.33	44.4	0.026
		No	0.00	0 – 33.3	30.67	
Appetite Loss	Symptom	Yes	0.00	0 – 0	39.53	0.727
		No	0.00	0 – 0	38.58	
Constipation	Symptom	Yes	0.00	0 – 33.33	45.5	0.002
		No	0.00	0 – 0	33.86	
Diarrhoea	Symptom	Yes	0.00	0 – 33.33	42.53	0.082
		No	0.00	0 – 0	36.21	
Financial Difficulties	Symptom	Yes	0.00	0 – 0	40.97	0.128
		No	0.00	0 – 0	36.60	
Body Image	Function	Yes	83.33	58.33 – 91.67	33.72	0.177
		No	87.50	66.67 – 100	40.38	
Sexual Function	Function	Yes	100	66.67 – 100	41.43	0.024
		No	66.67	66.67 – 100	31.05	

Systemic Therapy	Symptom	Yes	23.81	9.52 – 28.57	45.38	0.011
		No	14.29	4.76 – 23.81	32.51	
Breast Symptoms	Symptom	Yes	37.5	16.67 – 52.08	51.07	<0.001
		No	4.17	0 – 16.67	28.32	
Arm symptoms	Symptom	Yes	22.22	11.11 – 44.44	49.34	<0.001
		No	0.00	0 – 11.11	30.83	
Hair loss	Symptom	Yes	0.00	0 – 33.33	13.29	0.327
		No	33.33	0 – 50.0	16.21	

Table 52. EORTC QLQ30-BR23 functional domains, symptom scales and single item question averages and T-Test

Question	Function / Symptom	Breast LE?	Mean	SD	P value	95% CI
Fatigue	Symptom	Yes	34.97	25.24	0.001	8.26 - 28.08
		No	16.80	15.60		
Insomnia	Symptom	Yes	41.18	32.89	0.060	-0.58 – 27.12
		No	27.91	28.11		
Sexual Enjoyment	Function	Yes	48.15	24.22	0.829	-27.55 – 22.26
		No	50.80	32.69		
Future Perspectives	Function	Yes	43.75	33.27	0.068	-27.79 – 1.00
		No	47.14	26.84		

7.5. LYMQOL Test Retest Reliability.

A sample of participants returned for reassessment within 7 days of the initial visit. The protocol aimed for 62 participants to undergo a second assessment, but unfortunately a repeat visit was not always possible within the time scale needed and only 25 participants attended twice. The LYMQOL questionnaire was completed by 23 participants on two occasions.

It was hypothesised that there should not be any significant change as no intervention / treatment was offered or changed during this time.

Table 53. Test retest of LYMQOL domains using the Pearson Correlation

Question / Domain	n	Pearson correlation	P value	Degree of correlation
Function domain	23	0.886	<0.001	Good
Appearance domain	23	0.883	<0.001	Good
Symptoms domain	23	0.827	<0.001	Good
Emotion domain	23	0.872	<0.001	Good
Q21: Overall QoL rating	21	0.887	<0.001	Good

There have been different interpretations published relating to what level constitutes acceptable correlations (122). The levels of agreement for all the domains and the overall QoL rating are all >0.8 which is accepted as a good correlation and all were statistically significant (table 53).

Table 54. Weighted Kappa analysis for ordinal questions from LYMQOL

Question / Domain	n	Weighted Kappa	Degree of correlation
Q1a: occupation	18	0.217	Not significant
Q1b: housework	23	0.525	Moderate
Q1c: dressing	23	0.679	Good
Q1d: washing	23	0.348	Fair
Q2: Leisure activities	20	0.800	Good
Q3: dependency on others	20	0.200	Not significant
Q4: appearance	23	0.507	Moderate
Q5: clothes to fit	22	0.697	Good
Q6: clothes you like	23	0.512	Moderate
Q7: feel about yourself	23	0.676	Good
Q8: relationship with others	23	0.148	Not significant
Q9: Pain	23	0.708	Good
Q10: Numbness	22	0.604	Moderate
Q11: Pins and needles	22	0.427	Moderate
Q12: Tightness	23	0.313	Fair
Q13: Heavy	23	0.641	Good
Q14: Trouble sleeping	23	0.468	Moderate
Q15: Trouble concentrating	23	0.339	Fair
Q16: Tense	23	0.531	Moderate
Q17: Worried	23	0.529	Moderate
Q18: Irritable	23	0.836	Very Good
Q19: Depressed	22	0.680	Good

Different levels of agreement have been proposed for interpreting the Kappa statistic (123). All except 3 questions demonstrated a

significant relationship and at least a fair correlation, including 8 questions which demonstrated a good or very good level of agreement (table 54). The questions that were not significant were Q1 – occupation, Q3 – dependency on other people and Q8 relationships with other people. The responses at each assessment varied for 4 and 5 participants. For the occupation question the variation was between not being affected at all to being affected a little, or vice versa. This change is one category different. For the other two questions there were two participants and one participant respectively that changed their answer by 2 categories; for example, from "not at all" to "quite a bit".

7.6. Ability of LYMQOL-Breast to Detect Change.

Using data from the LYMQOL scores for the whole sample plus the repeated questionnaires additional analysis was undertaken to look into the variation and change in scores which represent true change and not due to measurement error (table 55)

The standard error of measurement (SEM) was calculated for each of the four domains using the standard deviations and Cronbach's α reliability (r). There are different methods for obtaining SEM and in this study the equation SEM = $\sqrt{1-r}$ was used. It was proposed that a change in score greater than the SEM represented meaningful variation in the measured construct and was not a result of measurement error.

Table 55. Standard Error of Measurement of LYMQOL domains – including Emotion domain with/without Q16 (tense) included.

Domain	**Standard deviation**	**r**	**SEM**
Function	0.46579	0.877	0.16336
Appearance	0.70064	0.882	0.24068
Symptoms	0.64193	0.870	0.23145
Emotion	0.64755	0.679	0.36745
Emotion (excluding Q16)	0.64755	0.852	0.24912

In addition of the SEM the minimal detectable change (MDC) (at the 95% confidence interval level) was calculated for each of the four domains (table 56).

Table 56. MDC95 for LYMQOL-Breast domains including the Emotion domain with/without Q16 (tense).

Domain	MDC95
Function	0.45281
Appearance	0.66713
Symptoms	0.64155
Emotion	1.01852
Emotion (excluding Q16)	0.69053

This demonstrated that except for the original Emotion domain an increase or decrease in the domain average that remains in the same response category, ie. A change of <1, could represent a true change in QoL.

Table 57. RCI calculations for the LYMQOL-Breast domains

Domain	RCI <1.96	RCI >1.96
Function	23/23	0/23
Appearance	23/23	0/23
Symptoms	21/23	2/23
Emotion	23/23	0/23

For all the domains the change in RCI was less than the desired 1.96 except on 2 occasions, both in the symptom domain (table 57). Both participants rated the symptoms worse (higher) at the initial visit than at visit 2. It was not recorded why these symptoms changed between visits. The participants were identified at visit 1 whether breast oedema was present of absent. There were 29 participants who had not been previously diagnosed with breast lymphoedema which was confirmed following study participation. Whether once this diagnosis had been confirmed they were more reassured about the cause of these symptoms which was reflected on repeating the questionnaire is not known.

7.7. Conclusions.

Assessment of the LYMQOL Breast identified it to be a valid and reliable tool for assessing quality of life in patients with breast lymphoedema.

All of the questions except for one, Q16, were found to add to the domain topics As a result this question has been removed from the final version of the LYMQOL breast tool.

Similar patterns were seen when LYMQOL-Breast was analysed alongside the EORTC-QLQ-BR23, both demonstrated that quality of life was lower in those with breast lymphoedema.

The addition of MDC values will enable future users to consider change in domain averages when evaluating patient outcomes.

Chapter 8. Discussion.

8.1. Introduction.

This chapter will critique the methodology and finding of this study to determine how to they support and add to the current evidence. In addition, any of the results that oppose or disagree with previous findings will be considered. The population included in the sample will be compared to those undergoing breast cancer treatments as any major differences will influence whether the recommendations should be applied in clinical practice and to the wider population. The limitations of this study will be identified and how future studies could be designed to overcome these. Finally, this chapter will identify the relevance to clinical practice, how the findings have the potential to innovate and improve the assessment of breast lymphoedema and future direction of further research.

8.2. Generalisability of the study findings to the UK Breast Cancer population.

8.2.1. Breast cancer characteristics.

Breast cancer is recognised as a heterogeneous disease which results in variety in the characteristics of not only the disease itself but also in those who are diagnosed.

From the available literature the reported incidence of breast lymphoedema is wide ranging (9.6 – 59.8%) due to the different methodologies applied. The lowest ranging study used a retrospective

review of medical notes and assessed patients at 4 weeks post radiotherapy and therefore is likely to be an underestimate of the true incidence. The studies that applied a clinical diagnosis alongside a prospective methodology are more likely to present results closer to the true incidence. In this current study participants who were known to have breast lymphoedema were approached from the lymphoedema service. In addition to this, women who were attending routine breast cancer follow up appointments were also approached as the study required women with and without breast lymphoedema to enable the objective measurement techniques to be tested. The motivation for accepting or declining the invite to participate was not known but for some women they felt that they had previously undiagnosed breast lymphoedema and taking part was one way of having this confirmed and the potential offer of treatment. However, of the 40 women that had breast lymphoedema confirmed for 29 women this was previously undiagnosed and for some this diagnosis was unexpected. A future prospective study using the measurement techniques validated in this study is recommended as this would provide an accurate incidence rate.

For the data produced in this study to be valid and generalisable to a wider population then the sample studied must be comparable to the wider population. The Office for National Statistics (ONS) breast cancer data for 2017 (124) identified that breast cancer risk increases with age. The age distribution in this study was similar to the national average (see table 58).

Table 58. Comparison of the age distribution of UK women diagnosed with breast cancer in 2017 with age of study participants.

	40-60 years	60-80 years	>80 years old
Age distribution of UK women diagnosed with Breast Cancer in 2017	36.6%	43.3%	15.5%
Proportion of sample	42.7%	55.1%	1.1%

Although it appears that there was not a comparable proportion of women aged over 80 included it this study it must be acknowledged that the ONS data includes all breast cancer diagnoses and is not specific to the treatments received. The National Audit of Breast Cancer in Older Patients (NABCOP) (125) undertaken for 2014-2016 showed that the route to breast cancer diagnosis and treatment offered is different in women over 70. This demonstrated that more women over 70 years of age were referred to the breast service by their GP (64%) in contrast to women aged 50-69 years whose breast cancer was identified through the national breast cancer screening programme. In addition, this report demonstrated that a wide local excision was the most common surgical procedure for all ages of patient but the proportion of women undergoing a mastectomy or no surgical procedure at all increased with age. A benefit of the national screening programme is that breast cancer is identified at an earlier stage and therefore the treatment offered more likely to be breast conserving surgery (35). Therefore, although the proportion of women >80 recruited into this study is lower than the national average it is felt to be reflective of those receiving WLE.

8.2.2. Axillary surgery and breast lymphoedema.

In this study of those with an invasive breast cancer 27.4% participants underwent an axillary node clearance and 72.6% sentinel lymph node biopsy as the most invasive lymph node procedure. The proportion of participants with lymph node negative disease was 63.9% which is comparable to data reported in the First All Breast Cancer Review of 62% (126); however, the review identified a limitation in that only two thirds of the patient data included lymph node status. Treatment of the axilla is changing and not all patients who have a lymph node positive disease now routinely undergo ANC or axillary radiotherapy.

The conclusions of a very recent study recommended that patients who require an ANC and / or loco regional radiotherapy have the risks of breast lymphoedema explained to ensure an informed decision is made (127). They identified limited axillary involvement as a consideration for patients to refuse additional treatment to the axilla. A recent Cochrane review of the evidence supported the consideration of alternative lymph node treatment when considering mortality and recurrence as outcomes (128). There was low quality evidence available for review when considering lymphoedema post intervention as an outcome. The reported incidence of arm lymphoedema after ANC from the Cochrane review was 13.2% which is lower than other reviews with a wide ranging incidence of lymphoedema after SNB from 2.2% to 11.5%. In clinical practice the reduced risk / lower incidence of arm lymphoedema following SNB compared to ANC is offered as reassurance to the patient. A systematic review and meta-analysis of arm lymphoedema after breast cancer treatment supports the lower end of the reported incidence after SNB, 5.6% following a review of 18 studies (17). In this current study lymph node positive disease and ANC both demonstrated an increased risk of breast lymphoedema than in lymph node negative disease or SNB. It was not surprising that these variables both demonstrated a significant relationship with similar relative risks as the participants who underwent an ANC would have done so due to having had a malignant axillary lymph node identified as part of their breast cancer diagnosis. Previously, in a large prospective study of breast oedema, ANC and adjuvant chemotherapy were identified as associated risk factors at time points up to 18 months post radiotherapy (127). This finding may also be related to the risk factors; receipt of chemotherapy and high NPI, reflecting that breast lymphoedema may develop because of more advanced breast cancer and the intensive treatment it requires.

Consideration of the lymphatic drainage pathways of the breast in which the majority of lymphatic flow from all four breast quadrants is through the axilla and internal mammary chain demonstrate that

impairment of flow can result from axillary surgery and / or radiotherapy to the breast or lymph nodes (129, 130).

Future research with a focus on confounding variables and multicollinearity would provide information as to whether these are individual risk factors or are inter-related. Lymphoedema of the arm has previously been identified as a predictor of mortality (131, 132). The identification of risk factors pertaining to breast lymphoedema enable patient specific advice to be given pre-treatment and also identify those who might benefit from monitoring post operatively. In the studies considered in the literature review there was agreement that the incidence of breast lymphoedema was increased in those who underwent ANC procedures. This relationship has persisted despite there being 35 years between the first study that proposed a relationship between ANC and breast lymphoedema and this current study. The sample size calculation used in this current study did not consider undertaking multivariate analysis and therefore it is not known whether 89 participants would give sufficient power to enable this to be achieved. Additional research is recommended which would further explore the weight or significance of these individual risk factors in a multivariate model for the development of breast lymphoedema.

8.2.3. Adjuvant treatment and breast lymphoedema.

In addition to the surgery offered the decisions for adjuvant treatment are dependent on the breast cancer characteristics. In 2013/14, 81.2% patients underwent surgical resection with 34.4% receiving chemotherapy and 63.2 receiving radiotherapy (133). For patients with stage 1 breast cancer at diagnosis chemotherapy is required in fewer patients, however, more receive radiotherapy than those with stage 2 cancer at diagnosis. Patients diagnosed with stage

3 breast cancer are more likely to receive both radiotherapy and chemotherapy in addition to surgery (133). The breast cancer grade in this study is reflective of the distribution in the wider UK breast cancer population (126). Lymph node status was also comparable to the wider population. In this study 36.1% patients had lymph node positive disease compared with 38% of UK patients treated for breast cancer in 2006 (126).

8.2.4. Obesity and breast lymphoedema.

Obesity and increased weight are well recognised to be not only a cause of lymphoedema / chronic oedema but also a risk factor for worsening oedema. It is associated with both negative outcomes for patients and increased difficulty in controlling the swelling (134). Previously, a BMI>30 at time of breast cancer diagnosis was found to be an independent predictor of arm lymphoedema development (135). Furthermore, a meta-analysis of over 8000 patients demonstrated an increased odds ratio for the development of lymphoedema of the arm after breast cancer treatment as BMI increased (136). Obesity is a national and international problem with BMI increasing year on year (137). This relationship has also been observed in women undergoing mammograms for breast cancer screening (138). A positive correlation was found in breast skin thickness measured on mammography demonstrating an increase of approximately 1cm from 1993 -2004 despite there being no changes in the equipment or scanning technique that could account for this change. They concluded that the increase was due to rising BMI and obesity in the patients who underwent mammographic screening. In 2017, average BMI of women in the UK was 27.8 Kg/m^2 which is an increase of over two units from 1995. The World Health Organisation (WHO) data for 2016 identified

that 28.6% of UK women were obese, in that their BMI was greater than 30Kg/m^2 (139).

In this study mean BMI was higher than the national average with 42.9% of the sample having a BMI of >30Kg/m^2 and included 1 participant with class III obesity (BMI>40Kg/m^2). The sample did however also include 20 (23.8%) participants with a healthy BMI (<25Kg/m^2) and only 1 participant in this group had breast lymphoedema. In the literature review the relationship between BMI and breast lymphoedema was considered in one study (52). Of the 240 cases reviewed in the study, mean BMI was reported as 29.26Kg/m^2 and included 36.7% patients with a BMI of >30Kg/m^2, highest BMI equalled 62Kg/m^2. Surprisingly BMI was not associated with the development of arm lymphoedema but was associated with lymphoedema affecting the breast. There was a statistically significant result when comparing the groups using the t-test (p=0.0432) and this relationship was further supported as BMI was significant in univariate and multivariate regression analysis (52). Mean BMI of the study sample was reported in one other study, but this was not considered in any of the analyses (51). In the study, of the 124 patients followed prospectively mean BMI at baseline was 29.1Kg/m^2 and ranged from 17.3 – 47.1Kg/m^2. Although the incidence of breast lymphoedema varies in this and the studies reported in the literature, due to different methodologies utilised, the BMI distribution is similar. In addition, obesity in breast cancer patients has also been associated with overall poorer prognosis with increased risk of recurrent disease and death so is an important factor to consider in this patient group (140).

8.2.5. Breast size and breast lymphoedema.

Bra or bust size has been recognised to be increasing as the body size of the population increases (141). It was reported that the average UK bra size has increased from a 34B in 2008 to a 36DD in 2019 (141). The bra size recorded in this current study was dependent on the accuracy of the participant report and not by a formal measurement. However, the range of bra sizes in both cup and chest circumference obtained appear to follow the wider picture for UK women, as reported in the Size UK study which included 4710 female participants (142).

In this study larger chest circumference and larger bra cup size were associated with the presence of breast lymphoedema. In the reviewed papers only three considered bra / chest size and the individual results were conflicting. In addition to the consideration of the relationship with bra size, tumour site and location of the oedema should also be considered. Over two thirds of participants received surgery to remove a tumour from the upper breast quadrants; however, one participant had oedema present in the upper quadrant only. For those who had oedema in one or two of the four breast quadrants it was in the lower quadrants. This raises the question of whether it is the breast cancer treatment, including surgery and radiotherapy, which impairs the lymphatic drainage from the lower half of the breast which causes the oedema? A similar presentation of lymphoedema is observed when hand and forearm swelling develop after breast cancer treatment, which is focused away from the operated area of breast and axilla. Questions regarding the lymphatic drainage pathways of the arm and breast following axillary surgery have recently been raised; specifically, whether in some cases they are able to regenerate themselves, the surgical breaks filled and the drainage pathways repaired (143). In a recent study, imaging of the arm and breast lymphatics using indocyanine green (ICG) fluorescence lymphography after ANC treatment for breast cancer demonstrated

several different variations in lymphatic flow. In addition to regenerated lymphatic pathways seen, lymphatic drainage appeared to cross the midline and drain into the contralateral axilla (143). An alternative consideration is whether increased breast size creates a venous hypertension effect on the breast resulting in more fluid for the lymph system to drain. This may be contributed to by the gravitational effect of larger, ptotic breasts. Such a phenomenon is recognised in lymphoedema associated with significant obesity that affects the abdominal apron or other areas and the development of massive localised lymphoedema (144). In such cases there is increased capillary filtration with overloaded regional lymphatics resulting in oedema development (145). In support of this theory two of the questions from the BLSQ which were significant in the differentiation between those with and without breast oedema were the presence of inflammation and warmth. These symptoms are also associated with the presence of chronic oedema of the legs due to venous hypertension.

8.3. Patient reported symptoms and the Breast Lymphoedema Symptom Questionnaire.

In this study the increased number of self-reported symptoms in the BLSQ was associated with the presence of breast lymphoedema. In addition, for each of the individual symptoms more participants with breast lymphoedema reported that symptom as present than those without breast lymphoedema. In the current study the symptoms which demonstrated the largest effect size were; skin thickening, skin dimpling / peau d'orange changes, hardness of the breast, breast tenderness, breast heaviness and clothes leaving marks. However, there was at least one participant without breast lymphoedema who experienced at least one symptom, therefore an occurrence of any

single self-reported symptom cannot be used to confirm breast lymphoedema alone. This finding is supported from the results of an earlier study which applied an 11 point numerical rating of 5 symptoms identifying that a higher total number of symptoms was associated with the clinical diagnosis of breast lymphoedema than the scoring of individual symptoms (51). In the current study self-reported changes were more commonly reported in the last year than the last week for the non lymphoedema group particularly swelling, pain, tenderness, numbness, clothes marking and scar thickening. The proposed threshold score of 48.2% provides acceptable levels of sensitivity, specificity, PPV, NPV, positive and negative likelihood ratios for this to be used in the clinical setting as a screening tool for identifying those requiring further, more detailed assessment. Further research using this tool with a group of patients undergoing treatment for breast lymphoedema is required to understand whether these symptoms reduce following lymphoedema treatment and if or when breast lymphoedema does resolve. In an earlier study the presence of a single symptom categorised the participant as having mild lymphoedema this definition would overestimate the incidence of breast lymphoedema (39). Unsurprisingly in that study the majority, 75.5% of patients were identified as having mild breast lymphoedema (39).

Repeated assessment demonstrated the BLSQ to have predominantly good or very good levels of agreement when repeated without intervention or change in treatment. Due to a reduced number of patients completing the tool on two occasions than was recommended from sample size calculation further research is warranted to ensure that these findings were not obtained by chance.

There isn't currently a similar tool that has been validated and is widely available and the BLSQ has the potential to be used as a screening tool to identify patients who would benefit from more detailed clinical assessment. The only other validated and available

tool which includes questions pertaining to breast symptoms is the LBCQ but this has only been validated in studies which focus on the development of BCRL of the arm (6). Further research using the BLSQ in a prospective study would determine additional clinical benefit in the understanding of the cause of patient reported changes and breast symptoms following breast cancer treatment. Changes to the breast after surgery and in particular after radiotherapy are often similar to the symptoms of breast lymphoedema and difficult to distinguish between breast lymphoedema or post treatment changes. Completion of the BLSQ in this group of patients may help differentiate the cause of breast changes and support decisions for appropriate referral and treatment. Additional research is needed to validate this tool further. Research into repeated completion of the tool over time after treatment for breast lymphoedema would further determine whether it has a use as an outcome measure or should be used only in screening for breast lymphoedema.

8.4. Consideration of the Objective Assessment Techniques.

8.4.1. Tissue Tonometry.

In this study the tissue tonometer was not able to distinguish oedematous and non oedematous tissue, the median readings obtained were similar and analysis did not reach significant levels. The defining characteristic for determining oedema in any breast quadrant was the presence of pitting oedema during the clinical assessment. This mimics the technique of the tonometer as the assessor presses firmly using their thumb onto the area of consideration and on removal if a thumb mark remains this confirms the presence of pitting oedema. It was therefore surprising that the

tonometer did not record higher readings in the oedematous breast quadrants.

In addition to this, readings could not be obtained for all of the study participants as the tonometer could not be positioned correctly to enable the measurement to be undertaken, this was more common when measuring the lower breast quadrants. To produce an accurate measurement the tonometer is held vertically with the weighted plunger placed flat on the breast quadrant being assessed.

The tonometer is not used commonly as an assessment tool for lymphoedema and this was identified in the literature review. The previous study that included this technique did so to explore the reproducibility of repeated measurements in a group of patients at risk of but without breast lymphoedema (61). The tonometer has been further developed by the team who produced it to overcome some of the limitations identified. The two devices have been compared and although the new device, the indurometer, has some improvements it was not shown to produce reliable measurements when repeated measurements were obtained (69, 146). The authors concluded that further modifications were required.

In a recent systematic review of the measurement of lymphoedema the tonometer was considered, however, the studies reviewed had used this technique for assessing oedema of the limbs and not the breast (147). There were few studies identified which used the tonometer to assess lymphoedema, it is less commonly used than limb volume measurement, bioimpedance and TDC. This review identified a study in which the tonometer had been used to assess lower limb lymphoedema in patients with lymphoedema as a result of lymphatic filariasis and healthy controls (148). In that study the patients were identified as having International Lymphology Society (ISL) Stage II or Stage III lymphoedema. An increased stage of lymphoedema is associated with chronic tissue and skin changes which result in thickening and oedema becoming non pitting. The tonometer

produced lower readings indicating firmer tissue which has less compressibility in the limb with lymphoedema compared to the unaffected limb or both legs in the healthy controls. Therefore, the tonometer may have a place in the assessment of non-pitting advanced lymphoedema of the limbs but at present from the results of this study is not recommended for assessing breast lymphoedema.

8.4.2. Ultrasound.

Measurement of dermal thickness by high frequency ultrasound scanning demonstrated this technique to be valid and reliable in the assessment of breast lymphoedema. This study has shown that ultrasound measurements can be used to distinguish oedematous and non-oedematous breast tissue and reproducible measurements were obtained at repeated assessments. The procedure was well tolerated and measurements were able to be performed on all of the participants in this study.

Similar to other studies the measurements obtained in this study differed depending on the quadrant or part of the breast being measured. The measurement points and number of measurements obtained in this study vary from the some of the studies identified in the literature review and from a more recent study (120). The medial (inner) aspect(s) of the breast in all of the studies, including the current study were thicker than the lateral (outer) aspect(s). This relationship was consistent for the affected and unaffected breast.

In two studies, the four quadrants of the breast were measured, however, the description of the measurement points was not given in one study and therefore it is not known whether these are consistent with the measurement points used in this study. In this current study the highest measurement for the oedematous breast was in the upper inner quadrant (UIQ) and this varied from the literature which

identified the lower breast quadrants as the thickest. The upper outer quadrant (UOQ) was the thinnest in this study and also in all of the studies reported in the literature for both the affected and unaffected breasts. In addition, the TDC readings were lowest in this quadrant. This was an unexpected result as if the lymphatic drainage of the breast is through the axillary lymph nodes, it would be postulated that there would be more fluid draining through this quadrant resulting in higher USS and TDC measurements. Additional research using live imaging techniques to assess lymphatic flow such as lymphoscintigraphy or ICG lymphography would be useful to study this finding further. In this study there were only 11 participants who had oedema in the upper inner breast quadrant and therefore any outliers in this group would potentially have increased the mean of the measurements obtained. The confidence interval and standard deviation produced in this sub group are similar to those produced for the other sub groups. The addition of the ROC analysis, the predictive values and likelihood ratios that were reported in this study provide more information about the use of these measurement thresholds in the diagnosis of breast lymphoedema. ROC curves and thresholds were also produced in a recent study that was published after the review (120). In this current study however, the proposed thresholds are higher for each of the four quadrants. This difference may result from the measurement points not being identical in the two studies. In this study the measurements were obtained in the middle of the breast quadrants and on the boundary between quadrants in the other study. For example, in this study if the shape of the breast is likened to a clock face measurements were obtained at 2 o'clock and 5'clock but in the other study measurements were obtained at 12 and 3 o'clock. From the data produced in this study interpretation of the predictive values of the ultrasound measurements enabled the differences between the two studies to be further understood. The high negative predictive values from the current study demonstrated that using these measurements as a threshold for diagnosis would result in few

false negative classifications and therefore the clinicians would be able to provide reassurance or confidence in the diagnosis of breast lymphoedema. This current study included participants with and without breast lymphoedema whereas the other only included patients with known and treated breast lymphoedema. In that study all of the sample was known to have breast lymphoedema but it was not reported whether oedema was present in all of the four breast quadrants, however, the measurements from all four were used when the thresholds were determined (120). It was identified that 28 of the 38 participants ultrasound measurements exceeded all four of the thresholds and for 9 patients this was achieved in 3 or fewer breast quadrants. As the mean measurement included non oedematous measurements then this may have lowered the mean values and the thresholds reported. Previously, when clinical examination and ultrasound measurements were both obtained the proportion of patients with lymphoedema identified following clinical examination was lower than when compared to lymphoedema determined by ultrasound assessment (59). However, the timing of these assessments were at approximately 12 months post-surgery and for the patients who had also undergone adjuvant chemotherapy and radiotherapy this was undertaken only a few months after treatment was completed. Therefore, some of the subcutaneous oedema reported and skin thickness measurements obtained could have been due to radiotherapy effects and not lymphoedema. Repeated assessments at a later timepoint would have provided additional information. It has been shown that following radiotherapy skin thickness increases in the months after radiotherapy and returns to baseline level at around 12 months after radiotherapy is completed (60). In addition, analysis in this current study of the group without clinically confirmed lymphoedema demonstrated that all quadrants of the breast were thicker than the unaffected breast after breast cancer treatment despite oedema not being present following clinical examination. It is not known why this finding occurred. The increase in dermal

thickening could be as a result of the radiotherapy undertaken, however, it could represent a subclinical stage of lymphoedema before pitting oedema can be identified. Further exploration of this relationship using ultrasound measurements recorded at time points before, during and after treatment would add to the evidence base and help in the understanding of the time course of breast lymphoedema and whether it is a self-limiting condition.

The mean measurements of the quadrants in the group without lymphoedema were close to or exceeded the threshold for lymphoedema as proposed in the other study (120). Although the sensitivity and specificity in that study were high it was identified that in 11% of the sample had measurements from the unaffected breast which exceeded the diagnostic threshold. Normal breast skin thickness varies between 1-2 mm, with the mean reported as 1.7mm (149). The thresholds suggested in this study all exceed 2 mm. Previously, mean skin thickness in the group least likely to develop breast oedema; those with no nodal surgery, no infections post operatively and who did not receive radiotherapy, was 1.92mm (60). Additionally, mean skin thickness for patients who had undergone ANC, including those with and without clinical signs of lymphoedema, was 2.5 mm or higher in three out of the four breast quadrants (59). Furthermore, following GEE analysis (Generalised Estimating Equation) a significant relationship was found when ANC, lymph node irradiation and post-operative infections were considered both singularly and when combined. This resulted in increased skin thickness to measurements of over 2mm at all time points for the ANC group which increased to over 3mm from 4 weeks and up to 12 months post radiotherapy (60). Therefore, to reduce over diagnosis and false positives a higher diagnostic threshold than that previously suggested, such as that proposed in this current study might be preferred.

8.4.3. Tissue Dielectric Constant.

The TDC measurements produced comparable results to the ultrasound measurements and were found to distinguish between oedematous and non-oedematous breast tissue. Similar to the ultrasound results the inner quadrants of both breasts had higher readings that the outer quadrants. The mean upper inner quadrant in the lymphoedema group had the highest TDC measurement. There were only 11 participants who were found to have lymphoedema affecting this breast quadrant and therefore the data is likely to be affected by outlying cases, however, the standard deviations are similar in this quadrant to the standard deviations for the two lower quadrants, which had approximately 30 participants in each.

The ratio of all four breast quadrants (affected: unaffected) was significantly higher when comparing the two groups despite this including the measurements for the non oedematous quadrants in the affected breast. A previous study proposed that the scarred quadrant(s) should be excluded from the overall ratios, but the mean values, standard deviation and mean difference data reported in this study are all very similar and produced a high, non significant p value opposing this recommendation (67). Scar formation was previously surmised as more relevant in the development of breast lymphoedema than axilla procedure (67). It was reported that participants with scar formation in the outer upper quadrant produced the highest TDC ratios. This result is not confirmed in this current study. In this study 53 participants were left with a scar in one or more quadrants following their surgery, however, 22 (41.5%) were found to have breast lymphoedema (X^2 p = 0.437). Looking at this further for the participants who underwent surgery to the outer upper quadrant and were left with a residual scar to that quadrant (n=29) 12 were found to have breast lymphoedema on clinical examination and 17 were not (X^2 p = 0.351). Furthermore, axillary node clearance was identified in

the current study as having a significant relationship to the development of breast lymphoedema. In the previous study although mean TDC ratios were higher in the group who had undergone ANC at all assessment time points compared to SNB this difference was not significant (67).

The TDC ratio threshold proposed in this study is in the midpoint between the two previously proposed ratios, 1.4 for breast oedema and the initial TDC threshold of 1.26 for determining the presence of forearm lymphoedema (67, 71). Using either the 1.4 or 1.34 ratio threshold increases the specificity and PPV but reduces the sensitivity and NPV. None of the proposed thresholds correctly diagnosed the entire sample, which was to be expected. If an assessment technique is used to screen patients and identify those who may have the condition in question for further assessment or to reassure those at risk of that the condition that they do not have it then a threshold may be selected due to the desired sensitivity, specificity, PPV or NPV. The price, portability and simple training that is required to use the moisture meter, compared to obtaining ultrasound images would identify this as a technique which could be used in the screening and preliminary assessment of breast lymphoedema. Therefore a lower threshold, such as the 1.34 proposed in this study is proposed as the threshold for breast lymphoedema screening and when referral to a lymphoedema service recommended for a more detailed assessment to be undertaken.

When comparing the breasts of the group who had undergone treatment for breast cancer but did not have lymphoedema a similar relationship to the ultrasound data was observed. The measurements were higher in all four of the breast quadrants of the affected breast, indicating a higher level of fluid in the tissues despite no clinical signs of lymphoedema being found and this relationship was highly significant ($p<0.001$). This relationship has not been reported previously as there are few studies which focus on TDC measurements

of the breast. It is therefore not known whether these higher TDC values are indicative of sub-clinical lymphoedema or a reflection of the changes to the breast tissue as a result of breast cancer treatment. However, none of the participants have contacted the research team or been referred to the lymphoedema service with concerns that they have developed breast lymphoedema since taking part in the study and for some women this was over 2 years ago. Comparisons of TDC measurements of the arms of healthy controls and women who had been diagnosed with breast cancer, but had not yet undergone surgery have been undertaken and the measurements were found to be similar (150). Pre-treatment TDC measurements of both breasts and the similarities or differences have not been studied. Women with and without BCRL of the arm, determined by circumferential difference in the arm being studied, were compared the TDC values of the both arms in those without BCRL were similar and produced a ratio of 1.01(forearm) and 1.02 (bicep) (151). In that study TDC measurements were also obtained from the lateral thorax and although both the raw data and ratios were higher than the arm data they were similar, p=0.896. Breast lymphoedema was not reported in these studies and some of the sample had undergone a mastectomy which makes comparisons between these studies more difficult particularly as it is common to see patients who have lymphoedema of the arm or the breast only. In addition, breast cancer treatment is directly affecting the breast tissue whether this is the surgical excision or the radiotherapy received and as a result the composition of the breast may be different, e.g have increased scar tissue than the untreated breast. This relationship is different to that of the affected and unaffected arm and may account for why the treated but non lymphoedematous breast had higher TDC and USS measurements.

As TDC is not currently a common measurement tool used in the assessment of breast lymphoedema there is potential for future research on breast lymphoedema to be undertaken using TDC as an

objective measurement tool. As raised earlier in this chapter the unknown natural history and suggestion that in some cases breast lymphoedema is a self-limiting condition then a prospective study following patients before, during and after their breast cancer treatment measuring TDC at the different timepoints would provide information on this.

Repeated measurement at a one week interval demonstrated that there were no significant differences in the measurements produced of the individual quadrants and the whole breast averages for the affected and unaffected breast. In addition to this the mean difference of the repeated measurements, the one sample T-test, regression analysis and Bland and Altman plots all confirmed the repeatability of this measurement technique. However, it must be recognised that the sample size required for the second assessment was not reached which is a limitation of this study.

8.5. The effect of age and BMI on measurements of breast tissue.

Previous studies have postulated the relationship of age and weight / body fat on skin thickness and tissue composition of the breasts (138, 152). This relationship was considered in four recent lymphoedema studies that applied ultrasound and or TDC measurements (120, 150 & 121, 153). In one study a moderate negative correlation with age in the ultrasound thickness of the unaffected breast was found (120). In the present study this relationship was not confirmed as there were no significant correlations produced from the ultrasound data. However, there was a weakly negative correlation between the TDC measurements and age for the upper outer quadrant (UOQ) for both breasts (r= -0.218 affected breast, r= -0.232 unaffected breast). It was previously hypothesised that TDC values would increase with age due to the changes in bound water within the skin (150) They did not

include measurement of breast TDC in their study and found significantly higher forearm TDC readings using the smaller probes but no significant differences with the 2.5mm probe, which was used in this current study. In an earlier study the 2.5mm probe did not demonstrate any relationship with increasing age in a sample of healthy female volunteers (154). A further report on mammographic skin thickness identified that skin thickness decreased with age ($p<0.05$) however overall breast size increased linearly ($p<0.05$) as a consequence of ptosis following the changes in the mammary parenchyma after the menopause rather than overall enlargement (152).

Increased BMI was found to be associated with the presence of breast lymphoedema in this study and has been recognised not only as a risk factor for BCRL of the arm but for breast cancer itself (155). BMI and obesity have not been considered in previous studies of breast lymphoedema. The ultrasound measurements of both the breasts demonstrated a positive correlation with increasing BMI. There was a moderate positive correlation for all quadrants in the affected breast and a positive but weak correlation for three out of the four quadrants in the unaffected breast (lower outer breast non significant). A similar relationship was found when assessing changes to the skin layers in the abdomen and thigh of an obese sample using ultrasound (156). In that study dermal thickness was significantly positively correlated with BMI ($r= 0.448$ abdomen and $r = 0.681$).

TDC values were found to have a weak positive correlation for the affected breast but no correlation was found for the unaffected breast. Two recent publications and one earlier study have considered the relationship of TDC in the obese population (121, 153, 154). Due to the dependency on the water content of the tissues being measured by TDC tissues comprising of increased fat content would result in lower TDC values. In this study there was a weak positive correlation in the affected breast and no correlation in the unaffected

breast. This finding conflicts with the hypothesised relationship between TDC and increased weight / BMI. However, a negative correlation was not found in two recent studies, with one specifically sampling patients in a weight loss program with a high BMI (mean 31.8 Kg/M^2) (153). Interestingly in that study total body water (TBW) and total body fat (TBF) measured by bioimpedance spectroscopy did both demonstrate significant differences when values in people with a BMI above and below 30 were considered. TBW was lower in the obese group and TBF higher. The largest or deepest measuring probe used in the current study and the previous studies on BCRL was the 2.5mm probe. It therefore could be questioned whether the largest/deepest probe (5.0mm) is required for incorporating changes in the subcutaneous tissues as part of TDC values? When the current study was designed exploration of these relationships was not considered in the sample size calculation and methodology.

8.6. Assessment of Quality of Life.

8.6.1. Validation of the LYMQOL-Breast.

Quality of life was recorded using the validated EORTC-QLC-BR23 a quality of life tool specific to breast cancer treatment and also the newly developed LYMQOL-Breast. The aim of utilising the LYMQOL-Breast questionnaire in this study was to undertake validation testing to determine whether it could be used clinically in addition to the previously validated arm and leg versions (7). These original LYMQOL versions were validated and published in 2010 and are widely used in both the clinical and research setting around the world. They have been translated and validated in to several languages. Requests have

been made to the author for additional versions such as a breast and head and neck LYMQOL.

LYMQOL-Breast was devised following input from clinical specialists, Doctors and Therapists, working in the field of lymphology and patients attending one of the three clinics supported by the team. Opinion was sought on the suggested questions to ensure that they were applicable to the topic and to determine whether any additional questions were recommended. The patients were also asked about the readability and language of the questions, making sure that they were understandable from a patient's perspective.

The methodology for validating the new version of LYMQOL mirrored the approach used for the arm and leg versions (7) and followed the COSMIN recommendations. In this current study LYMQOL-Breast was tested for and demonstrated internal consistency, reliability, content validity, face validity, criterion validity and some aspects of construct validity. Responsiveness was not fully tested and further assessment in a sample of patients undergoing lymphoedema treatment who completed the LYMQOL-Breast at repeated intervals pre and post treatment would explore this further. The sample of participants who attended two assessments in this study had similar responses on both occasions. As part of the checklist looking at the internal consistency questions are asked about the sample size calculation. When the sample size calculation was performed the LYMQOL validation was not considered in this. However, it is felt that the number of participants who completed the LYMQOL questionnaire at least once (n=78) was sufficient.

The individual questions when assembled into the domains for function, appearance and symptoms each produced good levels of correlation supporting that they were measuring the same overall concept. However, the questions for the emotion domain produced a lower Cronbach's α of 0.678. This improved to 0.852 when the question "In the past week have you felt tense" removed.

High levels of correlation were produced when split half testing was undertaken, reinforcing that the individual questions relate to each other and the overall concept of quality of life.

It was hypothesised that participants with breast lymphoedema would have lower or reduced quality of life compared to those without lymphoedema and this relationship was proved in the testing of discriminant validity. The overall quality of life rating was 7.44 (out of 10) and the domain averages were low which both suggest a good level of quality of life for the whole group. When comparisons were made between the two groups there were statistically significant results indicating poorer / reduced quality of life in the group with breast lymphoedema. The four LYMQOL domains demonstrated comparable relationships to the corresponding domains of the EORTC-QLQ-BR23 and similar patterns were observed when comparisons were made between the group with and without breast lymphoedema. The EORTC-QLQ-BR23 is a breast cancer specific tool and therefore covers a wider breadth of questions relating to breast cancer treatment than the LYMQOL-Breast and some of the significant differences between the two groups were harder to explain or understand. Therefore, it is felt that there is added value in using a condition specific quality of life tool, such as LYMQOL, for patients with breast lymphoedema. The breast lymphoedema group reported worse quality of life for fatigue and pain. Lymphoedema generally is recognised not to cause pain, however, breast lymphoedema is one area where it is anticipated that the patient may report pain and discomfort. This is felt to be due to the limited space between the tissue layers and therefore a small amount of additional fluid in the breast tissue could be uncomfortable. If a patient has pain it could be associated with altered sleep patterns, specifically difficulty sleeping and therefore the individual might be more fatigued. The breast lymphoedema cohort also reported worse levels of quality of life associated with systemic therapy, constipation and dyspnoea. The systemic therapy scale is made up of 7 questions which include a dry mouth, altered

taste, hairloss, painful eyes, feeling ill, experiencing hot flushes and headaches. These are commonly reported side effects of chemotherapy and hormone therapy and therefore the difference may be associated with the poorer prognosis breast cancer and more adjuvant treatment received in the breast lymphoedema group. Reassuringly and surprisingly there was no difference between the groups when body image and future perspectives were considered. The EORTC group has produced reference data mainly from cancer clinical trials worldwide for the EORTC-QLQ-C30 tool (157). In addition to the overall group data specific reference data for individual cancer types including breast cancer was incorporated. Comparing the data from this study to the breast cancer cohort the medians are similar or the same for several of the functional domains. Global health status / quality of life was lowest in the EORTC cohort and highest in the whole sample in this study, with the breast cohort between the two (66.7, 83.3 and 70.83 respectively). Physical functioning was lower in the breast lymphoedema group than the other two groups (80 compared to 86.7). Emotional functioning was lower in the EORTC group (75 compared to 83.3 for both other groups). Fatigue, pain and dyspnoea were worse in the breast lymphoedema group than the EORTC group. The reference data used information that was collected at baseline assessment and therefore may explain why overall quality of life in the EORTC cohort and symptoms were perceived as more of a problem following breast cancer treatment. It is reassuring that apart from physical functioning the domain medians are similar or better than the EORTC group.

8.6.2. Comparison of the EORTC-QLQ-BR23 data with other studies.

The EORTC-QLQ-BR23 has been used in two studies looking at breast lymphoedema (39, 127). Comparable relationships were produced in all three studies with QoL and physical functioning reported as lower

in the breast lymphoedema group. The relationship with increased pain was also reported in the breast lymphoedema group in one of the studies and this was a relationship that persisted throughout the duration of the study which was 24 months (127). Similarly, a weak but significant positive correlation was found for the systemic therapy domain and those with breast lymphoedema (39). Conversely, in this current study there was no difference between the lymphoedema and non lymphoedema groups for body image and future perspectives. A significant negative correlation was found for both questions in one study and reduced body image in the breast lymphoedema group at the time points prior to radiotherapy commencing and at 6 months post radiotherapy in the other, more recent, prospective study (127, 39). Some or the entire sample included in these other studies would have completed the EORTC-QLQ-BR23 at earlier time points during their breast cancer treatment. This would have included completion during and having just finished adjuvant chemotherapy with regimes known to have alopecia as a side effect of the treatment. It must also be acknowledged that in both of these earlier studies the presence of breast lymphoedema was not determined by a clinical assessment or objective measurement but on questionnaire completion. Supplementary exploration of the EORTC-QLQ-BR23 is warranted to understand this relationship further. In addition, in both of the reported studies there was no difference in sexual functioning and in the current study sexual functioning was significantly higher (better) in the breast lymphoedema group.

The EORTC-QLQ-BR23 breast symptom scale was higher in the group with lymphoedema. Questions included the reporting of breast pain, swelling, oversensitivity and skin problems which are some of the symptoms associated with breast lymphoedema. This builds on the results of the LYMQOL analysis and supports its validation, particularly the differences between the two groups when comparing responses for the symptom domain.

8.6.3. Repeatability of LYMQOL-Breast.

The test retest analysis produced good levels of correlation for the repeated LYMQOL questionnaires for all four of the domains and overall QoL. Looking at the individual questions the weighted kappa analysis identified 3 of the 23 questions as not significant, however 20 produced at least fair levels of agreement with 8 questions demonstrating good or very good agreement. It is not known why the answers at the second time of completion differed. Effect on occupation changed by one response level from “not at all” to “a little” or vice versa. Dependency on others and effect on relationships both included changing by two response levels, again some participants reported an improvement and some a deterioration. These three questions are considered to have clinical value. A previous study looking at the prevalence and impact of lymphoedema reported that 80% of the sample questioned had required time off work with 9% having changed jobs or given up work completely due to their lymphoedema (158). Understanding of the relationships that patients have with their friends and family is deemed clinically important. If a patient is reliant on others to enable them to attend appointments this may influence the treatment offered or the patient’s adherence to the recommended treatment. Lymphoedema changes the way that the affected area looks and is perceived. In addition, some of the treatments, such as compression garments, highlight the presence of the condition to the patient and to others which can have an impact on body image. Having an awareness of this is useful clinically as can help in understanding why a patient may not want or use the recommended treatment. Consideration of the responses to these questions can also be used to help identify when a patient might benefit from additional support and referral to other teams such as Occupational Therapy or Clinical Psychology.

Since the development and validation of the original LYMQOL tools, further information regarding the minimal detectable change (MDC) in domain score has been recognised as important for patient reported outcome measures. There are several methods for calculating MDC and the distribution-based approach was used for this study. This analysis indicated that for each of the domains a response did not need to increase or decrease by a full response level to be deemed a significant change. For the emotion domain MDC95 was calculated twice to include and then exclude question 16 (feeling tense). When this question was included the MDC was much higher. It is proposed that the final version of the LYMQOL-Breast questionnaire does not include this question. In addition to the MDC, the reliable change index (RCI) was less than 1.96 for the entire repeated LYMQOL domains except in 2 cases, both for the symptom domain. This is associated with there being no true change between questionnaire completions. As the questionnaire was repeated without any intervention it was hypothesised that the responses should not change. It is not known why the domain scores, in the symptom domain, changed between assessments as no intervention was provided. For both of these participants the symptom domain was lower at the repeated assessment. Participants were identified at visit 1 whether breast lymphoedema was present of absent. Overall, there were 29 participants who had not been previously diagnosed with breast lymphoedema. Whether once this diagnosis had been confirmed they were more aware of their breast symptoms and were reassured that the symptoms they were experiencing were due to breast lymphoedema and therefore reported this as lower in the repeated questionnaire is not known?

The LYMQOL tools were designed to be completed by patients attending lymphoedema services for initial diagnosis and subsequent treatment. Therefore, it would be expected that these patients experience some or all of the concerns addressed in the questionnaire. In the current study the sample included participants

who didn't have breast lymphoedema and therefore a ceiling effect was observed in some cases. However, when the domain scores were considered there were patients who had and did not have breast lymphoedema across the range of average scores. More participants reported "none" or "little problem" for the functional domain than the other three domains which is reassuring that women after breast cancer treatment can complete activities of daily living without too much difficulty.

8.7. Study limitations.

The main limitation of this study is that the number of participants who underwent both assessments was lower than the 62 that was specified in the sample size calculation. Due to the window given for the second assessment it was difficult to agree a second appointment that was suitable for the participant and the researcher. Although the analysis from the repeated assessments supported the use of the objective assessment techniques, the BLSQ and LYMQOL-Breast as reliable further research to confirm this is needed. The aim of the second assessment was to provide evidence and understanding of the reliability of the objective assessment tools and questionnaires. The analysis undertaken did support these to demonstrate reliability, but further research is required to confirm this. Additional research on the reliability to meet the COSMIN checklist criteria is required as the follow up period undertaken in this study was not sufficient to fully meet achieve this.

The clinical assessment was undertaken by a single clinician. It had been hoped that an additional physician would also be present to complete a second assessment which would have enabled inter rater reliability to be examined. On reflection we could have obtained photographs of the participants breasts which could have been

reviewed by other clinicians in the team. Although reviewing photographs would not enable full assessment of the participants breasts skin changes, inflammation and even pitting can be identified from photographs allowing some level of inter rater reliability to be measured. In addition the temperature of the breasts could have been recorded which would have provided a physical measurement and strengthened the assessment. The identification of raised breast temperature was a subjective assessment following palpation of each breast.

The diagnosis or confirmation of breast lymphoedema was made following the clinical assessment. For a participant to have breast lymphoedema confirmed pitting oedema to one or more breast quadrants was required. However, one patient was identified as having breast lymphoedema without there being any pitting oedema to the breast at the time of clinical assessment. The other signs and symptoms present were indicative of breast lymphoedema and the confirmation made. On reflection, this participant should have been excluded from the analysis as she didn't meet the agreed criteria. The pitting test itself is a subjective measure of oedema and is open to interpretation. If a clinician does not press firmly or for long enough pitting oedema may be missed. Assessment by a second clinician would have strengthened the confirmation of breast lymphoedema using the pitting test and enabled levels of agreement to have been calculated. However, a single experienced clinician undertook all the assessments and used the same examination technique on all of the participants promoting a consistent approach.

The original overarching theme of this thesis was to improve the understanding and recognition of mid-line lymphoedema which included the chest wall. After reviewing the literature and consideration of the objective assessment techniques available it was not felt that chest wall BCRL could be included in the formal clinical study, which is a limitation. Although it was felt that this type of BCRL

is not as prevalent, it does occur, and future research is warranted to enhance assessment and diagnosis.

When the study design was being established it was hoped that 3D scanning and comparison of breast volume would be included in the assessments. However, funding could not be sought to cover the equipment and specialist time for inferring the images and calculating the breast volumes. It appears that this is an area that is still developing and although there are some initial publications that use 3D scanning to produce limb volumes for assessing arm lymphoedema, there have not been any many publications using this technique.

This study was not designed to determine the incidence of breast BCRL. Several of the patients approached from the breast clinic wanted to take part as they were concerned that they had breast lymphoedema and wanted the clinical assessment. This does however highlight that breast lymphoedema was not well recognised and education of the signs and risk factors is required for health care professionals. This self-selected study cohort implies selection bias in the sample (159). However, the patient group sampled was representative to the wider UK breast cancer population. A further prospective study in which patient participation commences following initial breast cancer diagnosis pre-surgery and followed up for an appropriate period of time would help overcome this limitation. It would also provide additional and accurate information about the true incidence and the time course for breast BCRL developing. Ideally this methodology would include seeking consent from women who were undergoing breast cancer treatment consecutively and having undertaken a sample size calculation designed for a prevalence study. The analysis identified that some patients appear more likely to develop breast lymphoedema due to individual characteristics, breast cancer treatment and cancer histology. This study was not powered to undertake multivariate analysis and further research with a larger sample is needed. This information would enable clinicians to discuss

individual risk and identify which patients might benefit from additional monitoring.

There is no agreed consensus on the diagnosis and measurement of lymphoedema and specific to this there is no recognised gold standard technique available for assessing breast lymphoedema. This is a limitation of all lymphoedema studies. Attempts were made to mitigate this by using blinded clinical examination. One experienced clinician undertook all the assessments and followed the same assessment criteria.

8.8. Innovation, relevance to clinical practice and future direction.

This study provides a rigorous and thorough methodology which has produced data that can be applied clinically to improve the assessment and recognition of breast lymphoedema. The results add to the existing knowledge base and have a strong clinical application that can be applied to improve practice. One of the strengths of this study include the confirmation of the presence of breast BCRL by a clinician with over 30 years' experience using predefined criteria opposed to patient report, retrospective notes review or response to a questionnaire.

The results of this study have the potential to significantly increase awareness of breast lymphoedema and improve its assessment. New information includes identification and confirmation of some of the risk factors pertaining to breast lymphoedema development. This information is crucial to provide information to patients prior to breast cancer treatment to educate them on the signs and symptoms of breast lymphoedema and potentially to be used to provide reassurance to those deemed at lower risk. In addition, this

information could be used to determine which patients would benefit from additional, prospective follow up. A further prospective study is needed to provide more accurate information on the incidence of breast BCRL and to further test the assessment techniques and questionnaires. Some of the identified risk factors seem interlinked and related to more advanced disease, specifically; ANC, positive lymph nodes, higher NPI and the receipt of chemotherapy. A prospective, powered study would be required to study these relationships further with the aim of producing a risk score. From the results of this study advice should be provided to all patients prior to undergoing breast conserving surgery on the risks of breast lymphoedema developing and any risk reduction behaviours that could be applied. Importance must be given to ensuring that women, especially those with larger breasts, have a good fitting bra which is worn daily. This may help to prevent or lessen lymphoedema developing in the lower quadrants of the breast.

From the results of this study it is proposed that the BLSQ and TDC measurements are recommended as screening tools that could be used in breast clinics or at the initial lymphoedema assessment. These have been proven as valid and reliable tools in the assessment of breast lymphoedema. The proposed thresholds appear sufficient to identify patients who would benefit from further, more detailed assessments. The BLSQ is simple and quick to complete and the overall score can be used to distinguish between women with and without breast lymphoedema. This is a novel tool that has the potential to provide a significant improvement in the recognition of breast lymphoedema. There isn't a similar, validated self-report tool for this type of lymphoedema. From clinical experience breast lymphoedema isn't currently well recognised and this could be completed by patients attending follow up appointments after breast cancer treatment. Not only would it help to identify those who would benefit from formal lymphoedema assessment it may help identify specific patient concerns. This study has shown that TDC ratios are valid and reliable

in determining the presence of breast lymphoedema. Currently, TDC isn't widely used in the assessment of breast lymphoedema and the results from this study support a change in practice to include this. In addition to the results the Moisture Meter is a relatively cheap instrument, is portable and is simple to use, which may enhance its popularity in the clinical setting. Measurement of skin thickness by ultrasound has also been shown to be a valid and reliable technique for assessing breast lymphoedema, however, ultrasound scanning requires more in depth training in addition to the device being more expensive, tens of thousands of pounds compared to a few thousand pounds. Therefore, it would be recommended for use in lymphoedema centres who will see sufficient numbers of patients to maintain the skills required.

The addition of a condition specific quality of life tool will enhance clinical assessment and provide important information relating to individual patient needs that could be used to determine the treatment(s) offered and enable the clinician to understand the impact of these. Additional research to test further responsiveness to change of the LYMQOL-Breast tool in a prospective study is warranted for the tool to be fully validated.

Further to the diagnosis of breast lymphoedema the findings from this study may aid the evaluation of the treatments provided. For many patients currently, breast lymphoedema is assessed subjectively using patient or clinician report at each appointment or by pre/post treatment photography. The assessment of TDC and ultrasound measurement alongside patient reported symptoms and quality of life will provide considerable information about the effectiveness of treatments being provided. This is such an understudied area of lymphology that having validated assessment techniques will increase understanding of the condition. Future research using these techniques as outcome measures is needed to help understand not

only the time course of breast lymphoedema but to test the value of current and new treatments.

8.9. Conclusions.

This chapter has reviewed the findings from this study and compared them to other studies on this topic.

The sample is comparable to the UK breast cancer population which supports the findings being applied to clinical practice. Breast lymphoedema has not been well studied but is a growing topic. The results of this study will help to raise awareness and improve recognition of this condition.

Several risk factors pertaining to the development of breast lymphoedema were identified. This is valuable information which will support the education of patients of patients undergoing breast cancer treatment.

This study adds to the findings from previous studies that focused on the objective assessment for screening and diagnosis of breast lymphoedema. The production of thresholds to identify patients who would benefit from further assessment or that can be used to support diagnosis are significant results of this study.

Development and validation of a patient completed symptom tool is a novel initiative in this field and should be applied clinically to help identify patients who would benefit from assessment by a lymphoedema specialist. In addition, a low BLSQ score could be helpful in ruling out breast lymphoedema and providing reassurance to patients.

During recent years the assessment of quality of life has grown in importance and is well recognised as an essential patient reported

outcome. The addition of LYMQOL-Breast adds to the holistic assessment of patients. This study has demonstrated that patients with breast lymphoedema report poorer quality of life than those without.

Overall this study provides a comprehensive review of breast lymphoedema and has identified assessments that can be used clinically to improve the assessment and diagnosis of breast lymphoedema.

Chapter 9. Thesis Conclusions.

This thesis was developed and undertaken with the overarching aim of generating information that could be applied in clinical practice to improve the assessment of mid-line BCRL. The initial stage saw the completion of two literature searches and reviews to determine the current level of evidence for the assessment of mid-line BCRL and QoL.

At the time of the literature searches, 2014, there was little research that had been undertaken and significant variety in the methodologies observed making it difficult to determine the true incidence. There were only a few papers that had utilised objective measurement tools to quantify the level of oedema and no technique that had been formally validated and used in clinical practice. It became apparent that assessing chest wall lymphoedema had been studied less frequently than breast lymphoedema from the number of papers identified in the search. Reasons for this included the difficulty in reliably measuring this area and the lack of an anatomical comparator. As a result, the focus of the thesis narrowed to only include breast BCRL as a result.

The second literature review considered the assessment of QoL. There were more papers identified from this search including 24 different QoL tools that had been developed. Some of the tools included questions that were associated with mid-line BCRL but hadn't been tested / asked in this group of patients. The focus of the validation studies and studies that included QoL as an outcome measure were for BCRL affecting the arm. For the studies that did include patients with mid-line BCRL QoL was shown to be reduced when compare to those without lymphoedema. The results of this search confirmed that developing and validating a QoL tool would benefit the understanding and holistic assessment of patients presenting with mid-line BCRL.

Breast cancer and therefore lymphoedema that develops as a result is an international problem. The lymphoedema services that exist vary significantly in the skill mix and experience of clinicians and the assessment tools that can be accessed in the clinic. Tape measures are often the only objective measurement tool that clinicians have access to. This was considered when the aim and objectives of this thesis were being determined. There was a desire that the results would include some way of improving the assessment of breast lymphoedema and confidence in diagnosis for those without access to objective assessment tools. This led to the development of the BLSQ and the consistent approach used for the clinical assessment. It was hoped that the analysis would demonstrate which questions need to be asked or which symptoms should be considered to provide a consistent and accurate diagnosis of breast lymphoedema.

Since the time that the initial themes of this thesis and study questions were developed, the awareness of breast lymphoedema that arises after breast cancer treatment has grown. This is demonstrated not only in the papers that have been published since the time of the initial searches but from discussions with peers and other researchers at international conferences. I have been contacted by colleagues in the UK and from other countries and asked about the findings of my thesis specifically how should breast lymphoedema be assessed. I have also been invited to present some of my findings at lymphoedema and breast cancer conferences. Clinicians want to provide evidence-based care to their patients and service commissioners ask for evidence that demonstrates the effectiveness of the services being funded. The range of conservative treatments available for breast lymphoedema is expanding and new products that include compression garments, massaging pads and kinesio tape are being introduced and used in the clinical setting alongside MLD and SLD. Acknowledgment that this condition is being seen and treated in clinics without effective means

of assessing the impact and outcomes of the treatments provided confirms the need for research in this area of lymphology and the potential impact that the results of this study can make.

Further evaluation of the use of the tools acknowledged in this study as valid in the assessment of breast lymphoedema is recommended to determine whether they can measure changes and therefore should be used routinely as outcome measures. This includes completion of the LYMQOL-Breast and possibly the BLSQ, to determine which symptoms improve, alongside the objective measurements of oedematous breast tissue to enable the overall impact of breast lymphoedema on the patient to be considered.

The requirement for research into breast lymphoedema at this current time is emphasised by the evolving management of the axilla in patients with SNB positive breast cancer. The recent paper which recommended that patients should be informed about the potential risk of breast lymphoedema for this to be considered and enable informed decisions to be made (127). Although this current study was not designed or powered to identify and quantify the risk factors these were considered and significant differences between the groups were identified which appear similar to those which have been associated with arm BCRL. Cancer treatment decisions are made after consideration of the potential risks and benefits. Improved understanding of which patients are at increased risk of developing lymphoedema after breast cancer treatment is needed to encourage risk reduction behaviours and potentially increased surveillance / monitoring.

The literature identified that there are different diagnostic thresholds currently used in research and clinical practice to determine the presence or absence of lymphoedema. This results in multifarious

study methodologies which makes synthesis of the results difficult. Such variety adds to the complexity of assessing lymphoedema and determining a gold standard tool. This lack of consensus and the acknowledged limitations in the individual objective assessment tools prevents consistency and therefore progression in the understanding of lymphoedema. This is further confounded due to the heterogeneity of the patients seen in clinical practice and that lymphoedema can vary in its presentation.

The results of the clinical study identified that measurement using TDC values and ultrasound skin thickness can be used to identify oedematous breast tissue. The sensitivity and specificity levels produced were acceptable and at the level required by the sample size calculation, however, not all participants were correctly identified. The proposed thresholds differ from those produced in other recent studies. For TDC although the threshold proposed in this study differed from the other for identifying breast oedema, the sensitivities and specificities produced were similar. The findings from this current study propose that TDC is used as a screening tool which would identify patients who would benefit from more detailed, specialist lymphoedema assessment to confirm diagnosis. Therefore, the slightly lower threshold proposed in this study might be preferred.

The thresholds for ultrasound measurement were different when this study and the other recent ultrasound study were compared (120). This may be due to fact that different measurement points were used in this current study compared to other (120). It is felt that due to the cost and the training requirements that ultrasound scanning is used in services with individuals that have the skills to undertake this and see enough patients to maintain the competency.

Breast lymphoedema is commonly recognised to affect the lower quadrants of the breasts and in this study fewer patients had clinically

determined oedema in the upper quadrants. Therefore, further research using these techniques and the proposed thresholds is warranted. Application of these thresholds and measurement of breast lymphoedema in clinical practice and future research will add to the evidence base.

The review of the literature and the results of the clinical study both identified that the presence of lymphoedema has a detrimental effect on quality of life. For each of the domains and overall QoL rating this was worse in the breast lymphoedema group and statistically significant differences were demonstrated. The testing undertaken of the LYMQOL-Breast confirmed this to be a valid tool that has the potential to enhance patient assessment. Reassuringly, as an overall group the domain averages and overall QoL score reflected good levels of quality of life. In addition, questions in the EORTC-QLQ-BR23 on body image and future perspectives did not show any differences between the groups and for the question on sexual function this was better in the group with breast lymphoedema. These findings differed from some of the previous literature and the perception of the relationship between breast lymphoedema and body image.

Understanding the impact of illness and conditions on an individual's QoL is recognised as an important part of patient assessment. Measuring change in QoL is considered a useful outcome measure alongside objective oedema assessment (3, 4). This is even more relevant as the relationship between QoL and lymphoedema severity is not linear (7). There are few available tools that have been designed to assess QoL in women with breast lymphoedema and none prior to this study that had been validated alongside clinical assessment and objective measurement.

Application of LYMQOL-Breast used repeatedly over time will add to and complete the validation process, to determine whether the tool

can measure change. This would include a focus on completion of the LYMQOL-Breast pre and post lymphoedema treatment.

The limitations of the clinical study were presented in Chapter 8. The main limitation identified was the reduced number of participants who completed both assessments as this has impacted on the strength of the findings from this part of the analysis. Although the data supported the objective assessment tools and both questionnaires further research is required to confirm this. When potential participants were approached about the study they were asked to attend one appointment and consider attending a second within a 5-10 day window. To overcome this a future study could request that all potential participants confirm attendance for two appointments when considering study participation or agreeing both visit dates/times at this initial time.

The other significant limitation is that chest wall BCRL was not included in the clinical study as this appears to be an area of breast cancer related lymphoedema that is significantly understudied.

This thesis has produced a lot of information on breast lymphoedema that hopefully will be considered when future studies are developed. The findings are felt provide evidence that can be used to inform and improve current practice.

In addition to the objective assessment techniques applied, the methodology included a consistent approach for undertaking clinical examination. Although the examination was undertaken by a single, experienced clinician the assessment process utilised was developed with involvement of the wider specialist lymphoedema team. This could be shared with others for use in clinical practice or future

research studies. This would enable comprehensive comparisons to be made between the findings from this study and future studies.

It is hoped that the findings and recommendations from this study will be used to develop a future longitudinal study. This would include pre-treatment baseline assessments and sufficient follow up including assessments after surgery, during and after adjuvant treatments. This would enable an accurate incidence of breast lymphoedema to be determined, a greater understanding of the risk factors and determine the true time course. Increased understanding about who is at risk and the timescales of lymphoedema development and potential resolution would improve practice and individualise patient care. There is the potential to develop a risk tool or score which would enable reassurance to be provided to those deemed at low risk and highlight patients who would benefit from closer monitoring or repeated assessments.

The ideas and theme of mid-line BCRL arose from working clinically with women at risk of developing lymphoedema after undergoing breast cancer treatment. At that time, we provided a lot of information and offered monitoring for arm lymphoedema but breast or chest wall BCRL was not included in this. At patient follow up appointments when asked about concerns regarding lymphoedema developing patients often responded that there were no concerns with their arms, but did they have swelling or lymphoedema to the breast. During the time of this thesis, we have changed our practice to ensure that all patients and the breast care team are more aware of breast lymphoedema and encouraged to seek referral to the lymphoedema team if symptoms develop. The findings from this thesis will be disseminated to the clinical team locally and hopefully at a national and international level. Individual teams can then decide whether to use the BLSQ, LYMQOL-Breast, the clinical assessment proforma, TDC and ultrasound in their clinical practice.

It is hoped that the findings from this work will be used to develop and improve clinical practice and considered in future research on this area. There are limitations in the work that was undertaken and the tools utilised. However, the papers reviewed within this thesis recognise that this is common in lymphology and that there is no gold standard, perfect tool currently available. Therefore, it is felt that despite the limitations recognised there are many strengths in this work that should be implemented.

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Table of Tables

Table of Figures

Appendix 1: Abbreviations

3D	3 Dimensional
ALND	Axillary Lymph Node Dissection
ANC	Axillary Node Clearance
ANP	Advanced Nurse Practitioner
AUC	Area Under the Curve
BCRL	Breast Cancer Related Lymphoedema
BCS	Breast Conserving Surgery
BCT	Breast Cancer Treatment
BIS	Bioimpedance Spectroscopy
BLSQ	Breast Lymphoedema Symptom Questionnaire
BMI	Body Mass Index
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
DBC	Delayed Breast Cellulitis
DCIS	Ductal Carcinoma InSitu
ECF	Extra Cellular Fluid
ER +ve	Oestrogen Receptor Positive
FACT-B	Functional Assessment of Cancer Therapy - Breast
FLIC	Functional Living Index - Cancer
FLQA-l	Freiburg Life Quality Assessment - Lymphoedema
GCI	Global Clinical Impression
GEE	Generalised Estimating Equation
GP	General Practitioner
GSI	Global Symptom Index
HR PRO	Health Related Patient Reported Outcome
ICC	Intra Class Correlation
ICG	Indacyanine Greeen
IQR	Inter Quartile Range
ISL	International Society of Lymphology
IV	Intra Venous
LBCQ	Lymphoedema Breast Cancer Questionnaire
LCIS	Lobular Carcinoma Insitu
LE	Lymphoedema
LI	Lower Inner
LN	Lymph Node
LO	Lower Outer
LR	Likelihood Ratio
LSIDS	Lymphoedema Symptom Intensity and Distress Survey

Lymph-ICF	Lymphoedema International Classification of Functioning, disability and health
LYQLI	Lymphoedema Quality of Life Inventory
MCID	Minimum Clinically Important Difference
MLD	Manual Lymphatic Drainage
mm	Millimetre
MMT	Measurement
NABCOP	National Audit of Breast Cancer in Older Patients
NAC	Nipple Areola Complex
NHP	Nottingham Health Profile
NPI	Nottingham Prognostic Index
NPV	Negative Predictive Value
ONS	Office for National Statistics
OR	Odds Ratio
PPV	Positive Predictive Value
QoL	Quality of Life
RCI	Reliable Change Index
RCT	Randomised Controlled Trial
ROC	Receivpr Operator Characteristic
RR	Risk Ratio
RT	Radiotherapy
SD	Standard Deviation
SEM	Standard Error of Measurement
SLD	Simple Lymphatic Drainage
SNB	Sentinel Node Biopsy
SPSS	Statistical Package for the Social Sciences
TBF	Total Body Fat
TBW	Total Body Water
TDC	Tissue Dielectric Constant
UI	Upper Inner
UK	United Kingdom
ULL-27	Upper Limb Lymphoedema -27
UO	Upper Outer
USS	Ultrasound Scan
VAS	Visual Analogue Scale
WCLS	Wesley Clinic Lymphoedema Scale
WHO	World Health Organisation
WLE	Wide Local Excision

Appendix 2: Final Version of LYMQOL Breast

LYMQOL MIDLINE

Lymphoedema Quality of Life Tool

This questionnaire has been designed for patients with chronic oedema/ lymphoedema of the breast or chest to measure quality of life.

Please tick the box that best describes how you feel about each of the questions. **If any of the items are not applicable to you, please write N/A in the relevant answer box(es).**

Name: …….. **Hospital Number:**……

Date: ……

(Q1) How much does your swollen breast or chest affect the following daily activities?	**Not at all**	**A little**	**Quite a bit**	**A lot**
a) occupation				
b) housework				
d) dressing				
g) washing				

(Q2) How much does it affect your leisure activities/ social life?			

Please give examples of this ……

……

(Q3) How much do you have to depend on other people?				

	Not at all	**A little**	**Quite a bit**	**A lot**
(Q4) How much do you feel the swelling affects your appearance?				
(Q5) How much difficulty do you have finding clothes including bras to fit?				
(Q6) How much difficulty do you have finding clothes including bras you would like to wear?				
(Q7) Does the swelling affect how you feel about yourself?				
(Q8) Does it affect your relationships with other people?				

(Q9) Does your swollen breast or chest cause you pain?				
(Q10) Do you have any numbness in your swollen breast or chest?				
(Q11) Do you have any feelings of "pins & needles" or tingling in your swollen breast or chest?				
(Q12) Do you have any feeling of tightness in your swollen breast or chest?				
(Q13) Does your swollen breast feel heavy?				

In the past week….	**Not at all**	**A little**	**Quite a bit**	**A lot**
(Q15) Have you had trouble sleeping?				
(Q16) Have you felt tense?				
(Q17) Have you felt worried?				
(Q18) Have you felt irritable?				
(Q19) Have you felt depressed?				

(Q20) Overall, how would you rate your quality of life at present?

Please mark your score on the following scale:

0 1 2 3 4 5 6 7 8 9 10

poor **excellent**

Thank you for completing this form.

If you have any comments or queries about it, please discuss these with ……

Dr V L Keeley, Consultant

Questions 15 to 19 have been reproduced with permission from the EORTC.

These questions are only a part of the QLQ-C30 Questionnaire.