Breast Cancer Related Lymphoedema – information for doctors on patients with lymphoedema

Breast cancer related lymphoedema (BCRL) occurs in up to 28% of patients following breast surgery for cancer where there has been axillary lymph node dissection. *This may not develop until a year or more following surgery and the precise cause is not fully understood at present*. This condition is very disabling for the patient and may be present for the rest of their lives. There is no doubt that there is a disturbance in fluid balance within the affected limb and that there is a reduced immunological response associated with this. Chronic lymphoedema has fibrotic complications that affect the venous and lymphatic systems although whether arterial changes occur is less clear. Infection as a risk factor for the development of BCRL has been identified in a number of studies. Burns or puncture wounds (including venepuncture) have been identified as precipitating factors for the development of BCRL. Infection in a limb already affected by lymphoedema is a serious complication and does appear to be related to breaches in the effectiveness of the skin barrier.

There are, often firmly held, opinions about the risk of various medical interventions causing or worsening lymphoedema in an at-risk limb. However, the evidence base is either completely lacking or contradictory. Many of the recommendations, which are repeated on public access patient information sites, simply repeat these opinions without further comment or justification.

It is important to remember that the old truism is correct; that whilst there is a lack of evidence of causation this is not the same as evidence of a lack of causation! There may be little clear clinical evidence that using the affected or at-risk limb for venous access and other medical procedures makes any difference but equally avoiding using that limb is commonsense unless there are overriding clinical reasons, such as the need for resuscitation or control of severe blood loss.

Good practice

Every patient who has had surgery that involved the axillary lymph nodes, especially those with breast cancer must be assumed to be at risk from developing lymphoedema and the precautions below should be followed unless there are overriding clinical reasons. If these are present they should be recorded at the time in the case records or anaesthetic records.

Patient groups aim to provide as comprehensive and accurate information as possible to their members. In many situations this advice helps all involved in providing care to avoid problems, especially where the condition is rare. It is important not to dismiss patient's concerns but to discuss with them what is being planned and how procedures such as recording blood pressure or achieving venous access will be performed and how the arm will be protected during anaesthesia.

If there is a change in supervising medical staff, the use of identification bracelets identifying which limb is at risk from, or has, lymphoedema is a useful precaution.

Finally, as the evidence is so sparse, ideally every patient with lymphoedema or who has had breast cancer surgery in the past should be followed up to identify if there has been a complication following anaesthesia.

The major areas of concern related to medical practice are listed below with a brief commentary on their evidence base. There are two groups of patients:

Patients at risk of developing Lymphoedema

PROCEDURE	***RECOMMENDATION***	***EVIDENCE***
Venepuncture	This *is* a potential source of infection so used an alternative site where possible.	There is no clear evidence *for this.*
Blood Pressure Recording	Use another limb	There is no clear evidence that this has any effect.
IV Access	Avoid the 'at-risk' arm	There is a risk of infection but good clinical care reduces the risk
Fluid or Drug Therapy	The at-risk arm should be avoided unless absolutely necessary.	
Use of a Tourniquet *e.g. during carpal tunnel surgery*	This has been used for short procedures < 10 minutes without problems	

Patients with established lymphoedema

PROCEDURE	***RECOMMENDATION***	***EVIDENCE***
Venepuncture	Use an alternative site wherever possible. This is a potential source of infection	
Blood pressure recording	Use another limb. Blood pressure recording may be inaccurate due to the volume change in the arm.	There is no clear evidence that this affects lymphoedema
IV Access	Avoid the lymphoedematous arm	IV cannulae themselves are potential sources of infection. The risk of infection increases with the length of the placement. Good clinical care reduces the risk.
Fluid or drug therapy	Avoid the *lymphoedematous* arm unless it is absolutely necessary to use it	Both drug and fluid absorption may be unpredictable and therefore unsafe.
Use of a tourniquet	Carpal tunnel syndrome is common in patients with lymphoedema.	Tourniquets have been used for short procedures <10 minutes without problems. There may be a short-term increase in lymphoedema in some patients.

For more information see appendix 1

Frequently Asked Questions - related to hospital admission:

1. What can make me get lymphoedema?
2. If I have lymphoedema what will make it worse?
3. Will they take my blood pressure on my affected arm?
4. Will they take blood from my affected or at-risk arm?
5. What if they want to put a drip in my affected arm?
6. What about injecting drugs into that arm?

1. **What can make me get lymphoedema?**
   We do not know why up to a third of patients get lymphoedema after surgery affecting their axillary lymph nodes, nor why it can take a year or more to develop. There are many suggestions of ways to avoid triggering lymphoedema. However there is a lack of evidence to back some of these suggestions

2. **If I have lymphoedema what will make it worse?**
   Once lymphoedema develops there are several possible methods of trying to avoid worsening of the condition. The risks of any medical procedure on the affected arm making it worse are small, but where possible, avoiding using the affected or at-risk arm is sensible. Some procedures such as using a tourniquet during surgery on that arm may make it worse for a while, but not permanently.

3. **Will they take my blood pressure on my affected arm?**
   There is no evidence that having your blood pressure measured on that arm will have any effect. It is unlikely to cause the onset of lymphoedema and it will not make established lymphoedema worse. It may be less accurate if lymphoedema is present and may be more uncomfortable. It is for these reasons that using an alternative limb is sensible.

4. **Will they take blood from my affected or at-risk arm?**
   This is one procedure that may increase the risk of triggering lymphoedema or of making it worse where present. This is because of the very small risk of infection. Skilled operators are less likely to cause problems but if there is a choice of sites commonsense suggests avoiding an 'at risk' arm.

5. **What if they want to put a drip in my affected arm?**
   The insertion of a cannula (plastic tube) through the skin into a vein remains a potential source of infection until it is removed. Very careful management of this is necessary to reduce the risk of cannula-based infection.
   However, where it is necessary to give fluids or blood because of major injury or blood loss, rapid access and transfusion is life saving. This takes precedence over any other consideration, including the small risk of triggering or exacerbating lymphoedema.

6. **What about injecting drugs into an affected or at-risk arm?**

   The absorption of drugs from the 'at risk' arm is less predictable than if given through other veins in alternative limbs. If there is a need to give drugs regularly, such as for chemotherapy, a more permanent IV catheter may be inserted into a deeper vein which will make it more convenient and safer for you.

   We would advise against injecting into the 'at risk' arm or arm with lymphoedema but with the same comment as above – <u>if there is a life-saving need for an injection and that is the most accessible route this must take precedence over all other considerations.</u>

Breast Cancer Related Lymphoedema – information for patients

This information is primarily to help with the concerns you may have when being admitted to hospital, for instance for an operation. The anaesthetists and other doctors who will be looking after you may not have had particular experience in dealing with patients with lymphoedema or in understanding what they need to do to reduce as much as possible the chance of making lymphoedema worse before, during and after your operation. We have produced a version of this information sheet for doctors and *you may wish to* take a copy with you.

It is still unclear why some people develop lymphoedema after breast surgery and others don't. Similarly, it is not entirely clear what might make it worse. This means that effective advice on how to prevent it getting worse will be the exception rather than the rule. The advice offered in many of the publications and web-sites is practical and common sense, but all too often has little scientific evidence behind it. It is far easier to repeat advice than to check if it actually makes a difference.

We are concerned that whilst the number of places where advice can be sought is growing (a good thing) there is too much variation in their advice. This leads to confusion and anxiety instead of the confidence they are supposed to build.

The following are real life examples that patients have reported:

> "I was given a booklet on arm care and prevention of lymphoedema from my hospital. Taking blood pressure and having injections in the at-risk arm are listed among the possible triggers of lymphoedema and therefore to be avoided."
>
> "My breast care nurse said that the arm on the affected side has to be protected for life."
>
> "I have had some doctors trying to convince me that it isn't a problem to take blood from my at-risk arm but have been told by others not to allow anyone to do anything to that arm for any reason, except in an emergency."
>
> "Don't be ridiculous – it's been four years since your op – there will be no risk of lymphoedema now."

We have looked in detail at the evidence behind many of the recommendations and this review is available as an appendix if you wish to read it. There are several areas where we support the widely published suggestions, but still others where there is either no evidence or that there is conflicting advice on the same topic.

The greatest risk is of infection developing in the arm, and the skin is the most effective defence against this occurring. Extreme care of the skin is essential. There are some procedures that may increase the risk.

The key procedures on the arm with lymphoedema that cause concern are:

- Being given drugs intravenously
- Having an Intravenous drip inserted
- Having a tourniquet applied
- Having your blood pressure measured
- Having blood taken

Intravenous therapy – inserting a 'drip' into a vein and giving fluids or drugs – does increase the potential risk of introducing infection, but has not been clearly shown to increase the risk. The presence of lymphoedema means that there are problems with fluid draining from that limb, for whatever reason, and increasing the amount of fluid or drugs that the limb has to remove can't seem sensible. If there are alternative sites available these should be used.

It is very important to be aware that there are occasions where the ability to give fluids rapidly – where there is life-threatening blood loss for instance – overrides any such concerns.

Drugs may need to be given through a vein. Chemotherapy is a common example, and as these drugs may harm the veins there is a risk of 'using up' the ones in the other arm or feet. Commonsense suggests that if the administration of life-saving drugs is necessary, they should be given by any route possible, but if there is a need for repeated treatment a more long-term IV access is used. This is usually a plastic catheter (tube) inserted through the skin into a deeper vein, usually in the neck, that can be kept in place for weeks.

Surgery for compression of nerves at the wrist (carpal tunnel syndrome) is common in lymphoedema and a tourniquet is routinely used in this form of hand surgery in the upper limbs to enable the delicate surgery to be performed. There is no evidence that using a tourniquet for up to 10 minutes has any long term effect although there may be a temporary increase in lymphoedema.

Having blood taken (venepuncture) from a vein by a skilled practitioner is very unlikely to introduce infection into the limb. However, where there are alternative sites it is commonsense to use them instead, even if this means 'unusual' sites such as the feet.

Measuring blood pressure involves a simple cuff on the arm which is inflated above the pressure in the arteries, and then rapidly deflated to record the blood pressure. There is no evidence that this makes any difference at all to the risk of developing lymphoedema. However, the changes in the volume of the arm may affect the accuracy of the recording and for this reason using another limb if possible is sensible.

In summary:

We all need to work together to ensure that we take as many sensible precautions to prevent lymphoedema getting worse, even though we do not know why it does in some people and not others.

There are no absolute rules on avoiding procedures, but it is obvious that avoiding such risks where possible is the best practice, whilst recognising that there will be occasions where this is not safe. Even then the risk is very small.

Appendix 1[80]

UNDERSTANDING BREAST CANCER-RELATED LYMPHOEDEMA

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ABSTRACT

Breast cancer-related lymphoedema (BCRL) is a chronic swelling of the upper limb following surgery to axillary lymph nodes. This clinical review of the literature considers the risk factors that have been identified for the development of BCRL: the extent of surgery to the breast and the axilla, radiotherapy, nodal status, infection and patient characteristics such as body mass index (BMI) and patient age. The management of BCRL is primarily conservative, but the evidence for pharmacological and surgical approaches is also considered.

INTRODUCTION

Breast cancer-related lymphoedema (BCRL) is a chronic swelling of the upper limb following surgery to the axillary lymph nodes, which was originally described by Handley in 1908[1]. In 1921, Halsted coined the phrase "elephantiasis chirurgica"[2]. Whilst dramatic swelling on the scale of "elephantiasis chirurgica" is now uncommon, BCRL in varying degrees of severity remains a debilitating and often incurable complication of breast cancer treatment. A hundred years since this condition was first described, the pathophysiology of BCRL remains poorly understood, so that treatment of this condition remains difficult, and prediction and prevention are still not possible [3].

Surgical clearance of axillary lymph nodes as part of the management of invasive breast cancer is the most important aetiological factor in the development of BCRL and the primary initiating event, but it is one of the key puzzles concerning this condition that the majority of patients who undergo this surgical intervention are spared the problem. Therefore, whilst BCRL may be initiated by removal of lymph nodes, the development of BCRL must depend on other additional factors[4].

Published rates of the prevalence of BCRL in patients undergoing axillary lymph node dissection (ALND) for breast cancer range from 16-28 %[5-9]. BCRL develops at a variable rate in individuals. Whilst 75% of women who develop BCRL will have it by 1 year post-operatively, and 90% by 3 years[7], another puzzling feature of BCRL is that there is often a significant delay in many cases between the initial insult (i.e. surgery), and the development of swelling[4].

RISK FACTORS FOR BCRL

The traditional model of causation of BCRL at first seems self-evident: that insult to the axillary lymphatic system caused by surgery and/or radiotherapy leads to obstruction of lymphatic vessels[10]. However, most women who have their axillary nodes removed do not develop swelling, so additional factors beyond surgical intervention are also likely to play a role. Many studies have examined cohorts of patients for the development of BCRL, and correlated this with patient-related factors, disease, and treatment, so as to identify risk factors for BCRL[11-21].

Extent of surgery to the breast

The extent of surgery to the breast has been shown to influence rates of BCRL. Schenumann and Willich found that following Halsted's radical mastectomy BCRL rates were 32%[5]. When a modified radical mastectomy is undertaken, this rate dropped to 19%, and in patients that received breast conserving surgery, they report rates of only 7%. Mastectomy rather than breast conserving surgery was identified as a risk factor for the development of BCRL in another recent study[19].

Other surgical considerations that have also been reported to increase arm swelling are post-operative wound infections[22], seromas[23], and reconstructive skin flaps[24].

Management of the axilla

Management of the axilla has become less invasive, and surgical options include ALND, 4 node axillary sampling (4NAS), or sentinel lymph node biopsy (SLNB). Assessment of the axilla is required in all cases of invasive breast cancer, to stage the cancer, guide further adjuvant treatment, and to remove metastatic disease from the lymph nodes, to which it commonly spreads. A correlation between the number of lymph nodes removed at surgery and the development of BCRL has been shown in numerous studies[12 15-17], but there are also many studies that have not shown this relationship[13 14 18-20].

4NAS is the process of taking 4 palpably enlarged lymph nodes in the axilla, and examining them for metastases. As long as the nodes are negative for tumour, 4NAS has been shown to produce lower rates of BCRL than ALND[11 12 15]. However, if nodes are positive, patients require completion ALND or radiotherapy, and this has its own associated risks of BCRL.

SLNB is the technique of identifying and then removing the first draining lymph nodes of the breast[25]. Randomised controlled trials have shown that SLNB results in significant reductions in post-operative complications including arm mobility, sensation, and arm swelling, when compared with ALND [26-28]. The ALMANAC study also compared 4NAS and SLNB and found decreased post-operative morbidity in the SLNB group[28]. However, the advent of SLNB will not remove the

problem of BCRL, as a group of patients still require ALND as a primary surgical procedure[25], and approximately 50% of patients undergoing SLNB will proceed to ALND[29]. BCRL still occurs following SLNB alone, but at much lower rates[30 31].

Radiotherapy

Adjuvant radiotherapy to the axilla has been correlated with the development of BCRL in many studies[5 11 12 14 16 32].

The pathophysiology of radiation-induced BCRL is related to fibrosis indirectly causing constriction of lymphatic channels[15 33-36] and directly to lymph nodes which have decreased filter and immune functions as a result[37]. Radiation also delays growth of new lymphatics into tissues healing after surgery and inhibits the normal lymphatic response to inflammatory stimuli[34].

Radiotherapy to the breast or chest wall has also been found to increase the incidence of BCRL in some studies[5 38]. Axillary radiotherapy is becoming less common, and is now reserved for inadequate surgery, residual disease, or extracapsular nodal extension[39 40].

Nodal Status

A number of retrospective studies have suggested that lymph node positivity correlates with the development of BCRL[11-14] , but other studies have failed to demonstrate this association[15-19]. A confounding factor contributing to the contradictory reports has been the administration of axillary radiotherapy to lymph node positive patients in all of these studies.

The results of two prospective studies where radiotherapy to the axilla following surgery was not administered were recently combined, and nodal positive disease was found to be a protective factor against the development of BCRL[41]. It is suggested that the presence of tumour within lymph nodes may encourage the early development of collateral lymphatic drainage within the axilla.

Infection

Infection as a risk factor for the development of BCRL has been identified in a number of studies[21 22 42 43]. The timing and frequency of infection varies, as does the subsequent onset of swelling[44]. Burns or puncture wounds (including venepuncture) have been identified as precipitating factors for the development of BCRL[19 45].

It has been suggested that the operated limb is at increased risk of developing infection due to decreased immune function with the removal of axillary lymph nodes that would otherwise trap foreign tissue, and also an impaired lymphatic

proliferation response[46]. Fibrosis of tissue leading to stasis of lymph in constricted vessels may also encourage the development of infection. Once inflammation due to infection occurs, there is further tissue fibrosis, and therefore worsening of lymphoedema[22].

Patient Characteristics

Several studies have found body mass index (BMI) to be related to the development of BCRL[14 18 19 21]. but others have not [13 17 47]. The role of patient age as a risk factor for BCRL is also unclear[45 48 49].

Many other characteristics have been recorded in studies as being independent risk factors, which include menopausal status[14], tumour stage[11], tumour size[16 17], tumour on the dominant side[13], level of hand use[21] and grade of surgeon[13].

MANAGEMENT OF BCRL

There are a wide range of treatments available for BCRL, reflecting the lack of proven efficacy of any one particular approach.

Following ALND, patients are advised to be meticulous with skin care and hygiene, and avoid cuts and injections whenever possible on the operated arm. They are also advised to avoid rigorous exercise using this limb, and not to lift heavy weights. There is little evidence base for these precautions, other than the aforementioned studies that have identified infection as a possible risk factor: they are primarily based on anecdotal reports by patients about what precipitated their swelling.

Once arm swelling has occurred, treatment can be classified into three types: conservative, pharmacological and surgical[3].

Conservative

Conservative approaches include the use of compression bandaging, which attempts to increase the elastic properties of tissue, and provides a counterforce to muscular contractions[50]. Compression banding has been shown to decrease arm swelling by over 25%, although long-term results are not so impressive and swelling often returns[51].

Manual lymphatic drainage [52] involves gentle skin massage of the trunk to empty the lymphatic channels away from the lymphoedematous limb, with gradual progression towards the affected part. A randomised trial of standard therapy (skin

care, information about lymphoedema, exercises and compression garment), versus standard therapy plus manual lymphatic drainage, at twelve-month follow-up showed that manual lymphatic drainage did not provide any additional reduction in swelling[53]. Other treatments are described in the literature, such as pneumatic compression pumps, ultrasound therapy, and multilayer bandaging[50 54-56], which are reported to have success, but with little comparative or collaborating evidence. Simple elevation has been shown to be of no benefit[57].

The role of exercise in the treatment of BCRL is controversial. Anecdotal self-reporting from patients suggests that bouts of exercise can initiate swelling. Only one small trial of 14 patients has been reported with no affect on swelling[58].

Pharmacological

Pharmacological approaches have centred on the use of benzopyrones. They encourage the breakdown of protein by inducing macrophages and stimulating them to initiate proteolysis. The theory is that proteins deposited in the lymphoedematous arm are lysed and removed, with a subsequent decrease in fluid due to reduction in interstitial osmotic potential. A randomised controlled trial of benzopyrones versus placebo showed a significant decrease in arm swelling after treatment of several months, although with no long-term follow up[59 60]. Another study found no effect of coumarin (a benzopyrone) on lymphoedema[61], and the authors reported concerns over hepatoxicity with prolonged use[62]. Benzopyrones are not licensed for use in BCRL in the UK.

A randomised controlled trial of vitamin E and pentoxifyline for treatment of chronic BCRL (the rationale being a postulated anti-fibrotic action of these drugs related to their antioxidant properties) also showed no benefit of these drugs at 6 and 12 months follow up[63].

Diuretics are not suitable for BCRL, as they only serve to increase protein concentrations in the interstitium and encourage an increase in swelling, inflammation and fibrosis[3].

Recently, the role of hyperbaric oxygen therapy for treatment of long-term lymphoedema has been investigated. As hyperbaric oxygen therapy promotes healing in bone rendered ischaemic by radiotherapy, it may also be of benefit to soft tissues. Initial investigations without a control group suggest that there is sufficient evidence to justify a randomised controlled trial[64].

Surgical

Surgical treatment for BCRL is rarely performed, and is limited to severe and refractory cases. The surgical approach may either be to debulk tissue, or divert lymphatic drainage.

The debulking procedures remove subcutaneous and epifascial tissue, whilst maintaining the epithelial cover. This was originally termed the Charles procedure, after the surgeon Sir Havelock Charles, who performed this operation on the lower limb in the early 20th century, but cosmetic results were poor, and swelling often returned[65 66]. More recently, liposuction using stab incisions at a variety of sites has been reported, with varying degrees of success[67-71].

Plastic surgical techniques using myocutanoeus flaps carrying viable lymphatic channels[72], or buried dermal flaps that divert flow to the deep lymphatics[73], have also been attempted. With the development of microsurgical techniques, anastomoses between the lymphatic system and the venous system have also been described[74-78] Relief of swelling in up to 75% of patients is described[78], although long-term results when available are not so favourable[79]. Whether as a result of cost, technical difficulty, or concerns over long-term efficacy, none of these surgical techniques for BCRL have become widely adopted.

SUMMARY

BCRL is a common complication following surgery for breast cancer. Established risk factors include extent of axillary surgery, axillary radiotherapy and infection. The introduction of sentinel lymph node biopsy has decreased the prevalence of BCRL. Treatment of BCRL is primarily conservative, with only a limited role for surgery.

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LYMPHOEDEMA WEB RESOURCES

Living with Lymphoedema after breast cancer
http://www.breastcancercare.org.uk/server/show/nav.490

Reducing the risk of Lymphoedema
http://www.breastcancercare.org.uk/server/show/nav.489

Management of cellulitis in lymphoedema. (February 2007)
Coping with lymphoedema following a mastectomy or a lumpectomy. (March 2006)
What is cellulitis? (January 2006)
www.lymphoedema.org/lsn

Prevention of upper limb lymphoedema. (February 2007)
www.lymphoedema.org/lsn

Lymphoedema. Advice on self-management and treatment. (2007)
www.beaconsfield-publishers.co.uk

Reducing the risk of lymphoedema. (November 2006)
www.breastcancercare.org.uk

Lymphoedema awareness: reducing your risk. (2006)
Living with lymphoedema after breast cancer. (July 2006)
www.breastcancerhaven.org.uk

Understanding lymphoedema. (2006)
www.be.macmillan.org.uk/orders

Lymphoedema. A guide for cancer patients. (2007)
www.royalmarsden.nhs.uk

Risk of cellulitis
www.thebls.com/concensus.php