

Breast cancer-related lymphoedema and venepuncture: a review and evidence-based recommendations

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Abstract Lymphoedema is a recognised complication of axillary surgery in women with early breast cancer. Such women are widely advised to avoid venepuncture on the ipsilateral side lest this cause complications including lymphoedema. This can lead to multiple failed venepuncture attempts causing distress to both patient and healthcare professional. We reviewed current guidelines and critically appraised the evidence relating the development of lymphoedema to venepuncture to educate healthcare professionals and develop evidence-based guidelines. A systematic search of bibliographic databases was performed and an Internet search undertaken to identify patient information leaflets from societies and support groups. Seven published articles were identified together with 15 published patient information leaflets. Only one small prospective study was identified (level of evidence 2), the remainder being case–control studies (level 3) or retrospective reviews (level 4). There is no good evidence that venepuncture can precipitate lymphoedema. New, patient-centred, evidence-based recommendations for venepuncture in women with breast cancer are proposed. Whenever possible, venepuncture should be performed on the contralateral arm. If this is not readily achieved, in the

absence of lymphoedema it is preferable to consider venepuncture in the ipsilateral arm or insertion of a central venous device than to make further attempts in the contralateral arm or resort to sites such as veins in the foot. In the absence of lymphoedema, venesection in the ipsilateral arm carries little, if any, risk of additional complications. We offer evidence-based, patient-centred guidelines for venepuncture in patients with breast cancer following an axillary intervention.

Keywords Lymphoedema · Venepuncture · Breast cancer · Sentinel node biopsy · Axillary lymph node clearance

Introduction

The loco-regional treatment of early breast cancer has evolved over the last 25 years from most women undergoing mastectomy and axillary clearance to the current widespread use of conservative surgery (or mastectomy and reconstruction) and sentinel node biopsy. Lymphoedema, defined as the subcutaneous collection of protein-rich fluid due to dysfunctional lymphatic drainage secondary to lymph node disruption or injury, was historically a frequent post-operative problem, most likely due to the invasive nature of axillary treatment. Women were routinely told that invasive procedures should be avoided in the ipsilateral arm as this may precipitate lymphoedema.

In the current era, patients in whom venous access in the contralateral arm is poor may still be subjected to multiple venepuncture attempts in that arm despite there being good access in the ipsilateral arm with no lymphoedema; in addition, central venous devices are widely available.

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Breast cancer-related lymphoedema

Breast cancer-related lymphoedema most often occurs after axillary lymph node clearance, but may also be seen in women who have undergone sentinel node biopsy, radiotherapy to the axilla or with tumour invasion [1, 2]. Factors such as local inflammation, infection or skin puncture such as venepuncture have been reported to provoke lymph accumulation [1, 3, 4], and obesity has also been identified as an individual risk factor [3, 4]. The onset of lymphoedema is usually subtle and may occur days or years after the initial insult, with patients developing chronic swelling of the upper limb and digits and experience symptoms such as heaviness, tightness and restricted function as well as being aesthetically undesirable and causing psychological distress [5]. Initially, there is pitting oedema but chronically fibrosis results in the development of non-pitting oedema [6, 7].

Lymphoedema is a clinical diagnosis, but circumferential measurements using specific anatomical landmarks and/or water displacement can also be used to give a more objective diagnosis; lymphoedema can be staged [8] from stage 0 (subclinical) to stage 3 (severe). A recent systematic review and meta-analysis stated that more than one in five patients will develop lymphoedema after breast cancer treatment [4], and a 2003 study reported that patients with acute infections associated with their lymphoedema spent an average of 12 days in hospital, with an estimated cost of £2300 per patient [9]. Of the 218 patients with lymphoedema who were interviewed, 64 (29 %) experienced at least one acute infection; 17 (8 %) required admission for intravenous antibiotics.

The incidence of lymphoedema varies considerably depending on the surgical intervention. In a recent national, population-based study of 3253 patients, the incidence of self-reported lymphoedema, defined as swelling/heaviness of the arm, was lowest following breast conservation and radiotherapy with sentinel lymph node biopsy alone (13 % of women) [10]. Relative to these women (odds ratio [OR] 1), the risk of lymphoedema was substantially higher in those also undergoing axillary lymph node dissection (OR 6.75, 95 % confidence interval [CI] 5.10–8.94) or extended-field radiotherapy (OR 7.24, CI 5.74–9.14) and those undergoing mastectomy and axillary lymph node dissection (OR 5.55, CI 3.82–8.04) or axillary lymph node dissection and extended-field radiotherapy (OR 10.9, CI 8.01–14.9) ($P \leq 0.0001$). Mastectomy and sentinel node biopsy without radiotherapy was, however, not associated with an increase in lymphoedema risk (OR 1.45, CI 0.96–2.27). Similar incidences of breast cancer-related lymphoedema after mastectomy (49.1 %) and mastectomy

with axillary radiation (38.8 %) were reported in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial [11]. The subsequent NSABP B-32 phase 3 randomised control trial explored the morbidity of axillary surgery in nearly four thousand women. Three years post-treatment, arm volume differences ≥ 10 % were observed in nearly twice as many women undergoing axillary lymph node dissection (14 %) as those undergoing sentinel node biopsy (8 %) [12, 13].

Following surgery, women with breast cancer are typically advised to avoid injury to the ipsilateral side from venepuncture, cannulation and blood pressure measurements. In theory, venepuncture carries a small risk of infection through recurrent or prolonged cellulitis further damaging lymphatics that are already compromised [14]. The evidence base supporting this advice is, however, unclear.

The aim of this study was to evaluate the existing advice and underlying evidence that venepuncture in the ipsilateral arm in women who have undergone surgery for early breast cancer is associated with an increased risk of lymphoedema to educate healthcare professionals and develop evidence-based guidelines.

Methods

A systematic search of bibliographic and grey literature concerning venepuncture-related lymphoedema in women treated for breast cancer and with subsequent lymph node surgery was conducted. The electronic databases utilised were MEDLINE (OVID 1946 to June 2015), EMBASE (1974 to June 2015) and the Cochrane Library. The literature search combined demographic-specific terms and the relevant disease: Wom*n AND breast (cancer OR carcinoma OR neoplas*OR malignan*) AND (ven*puncture OR phlebotomy OR needle OR blood [taking OR sampl* OR draw*]) AND (lymphodema OR lymphoedema). Lymph node surgery was defined as any surgery to the lymphatic system of the axilla, including axillary lymph node clearance and sentinel node biopsy. Studies reported as abstracts only were included, but those in patients who had not undergone axillary surgery or had pre-existing lymphoedema were excluded. Studies on male patients only and those not written in English were also excluded. Bibliographies of articles identified were reviewed to identify further studies.

An Internet search was undertaken to ensure that relevant patient advice articles from societies and patient support groups, not catalogued within bibliographic databases, were included.

Results

The Internet search identified 15 patient information leaflets.

Lymphoedema information for patients

Numerous English language guidelines from several countries (Table 1), along with patient information leaflets, ‘expert opinion’ and websites advise how to prevent or minimise the risk of lymphoedema after breast cancer. Most report helpful practical advice; invariably, they advise against venepuncture in the ipsilateral limb, but there is considerable variation as to whether the caveat of ‘if possible’ is used.

English language guidelines for breast cancer-related lymphoedema have been produced in several countries (Table 1). For example, in the UK the Royal College of Anaesthetists guidelines [15] state that there is no clear evidence to suggest an association between lymphoedema and venepuncture. However, as a perceived potential source of infection, an alternative venepuncture site is recommended where possible, including the feet. This guideline is cited by the Royal College of Nursing, Macmillan Cancer Support, Breast Cancer Care UK, the British Lymphoedema Society, the Lymphoedema Support Network and the Lymphoedema Network of Northern Ireland. Cancer Research UK advises against venepuncture in the ipsilateral arm, but comments that this is based on anecdotal evidence and, if done properly under clean

Table 1 Patient support societies and informative documentation recommendations

The Royal College of Anaesthetists	UK	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
The Royal College of Nursing	UK	Unless there is a medical emergency, avoid taking blood pressure measurements, injections or blood samples from the ‘at-risk’ limb as this may lead to infection and/or the onset of lymphoedema. For women who have had bi-lateral surgery or radiotherapy, blood samples may be obtained from other areas of the body, such as the feet or legs
Macmillan Cancer Support	UK	If possible, avoid having needles put into your affected hand/arm or foot/leg when you have blood taken, injections, a drip (infusion) or acupuncture. Although there is no strong medical evidence to support this, most lymphoedema experts think it is a wise precaution to take to reduce the risk of infection
Breast Cancer Care UK	UK	Avoid having your blood pressure or blood samples taken from your ‘at-risk’ arm. If both your arms are affected, then it may be possible to take your blood pressure measurements or blood samples from your legs or feet
The Lymphoedema Support Network	UK	Patients should be advised to avoid having injections and blood pressure recordings taken in the affected side
British Lymphoedema Society	UK	Avoiding injections/needles, blood tests and blood pressure readings on the affected limb, whenever possible
Lymphoedema Network of Northern Ireland	UK	If possible, never allow injections, blood taking or blood pressure cuffs on the operated arm
Cancer Research UK	UK	It is not clear whether having blood taken in the arm on the same side as your surgery, or having injections, can increase the risk of lymphoedema. So it is advisable to avoid these
The American Cancer Society	USA	Have your blood drawn from your unaffected arm if you can
The American Society of Clinical Oncology	USA	If possible, avoid medical procedures such as blood draws in your affected arm
National Lymphoedema Network	USA	If required to have venipuncture, inform the phlebotomist of your lymphoedema and use a non-lymphoedema limb, if possible. If not possible, inform the phlebotomist of your lymphoedema condition and ask for the most experienced phlebotomist. Do not allow multiple or traumatic searches for veins, which can increase tissue oedema. If a traumatic venipuncture occurs on a lymphoedema extremity, immediately wash the area, apply a cold pack, then elevate until oedema subsides
The Mayo Clinic	USA	If possible, avoid medical procedures, such as blood draws and vaccinations, in your affected limb
The Cancer Society of New Zealand	New Zealand	Always use the unaffected limb for any blood sampling or needles of any kind
National Breast and Ovarian Cancer Centre	Australia	Avoid vaccinations, injections, blood drawing, blood pressure readings and intravenous treatment administration to the treated side
The Canadian Cancer Society	Canada	If possible, avoid having needle sticks of any type in the affected limb

conditions, will not increase the risk of lymphoedema. The Cancer Research UK guidelines also acknowledge that with every venepuncture attempt, it becomes increasingly difficult to find a suitable vein.

Similarly, guidelines from the USA, Australia and Canada all advise against venepuncture in the ipsilateral arm. The National Lymphoedema Network advises requesting the most experienced phlebotomist in cases where it is not possible to avoid the ipsilateral arm and not to allow multiple or traumatic attempts at venepuncture.

Lymphoedema and venepuncture

We identified seven published articles that met the inclusion criteria. Only one was prospective; the remaining six retrospective studies are reviewed in chronological order to reflect evolving the management of early breast cancer (Table 2).

Retrospective studies

In 1955, Villasor et al. [16] reported risk factors, including venepuncture, which may lead to lymphoedema in women who underwent radical mastectomy, 51 with and 28 without arm swelling (level 3 evidence [17]). One patient developed moderate lymphoedema immediately following venepuncture and 3 further patients reported that their lymphoedema had been aggravated by venepuncture. Of the 51 women with arm swelling, infection was said to account for the development of lymphoedema in 8 (16 %) patients; no information was given, however, as to whether this was associated with venepuncture. The authors conclude that venepuncture should be avoided, but no mechanism as to why or how the lymphoedema developed after venepuncture was identified.

A retrospective review of 114 patients with moderate/severe lymphoedema (>2 cm greater circumference than the contralateral arm) after radical mastectomy was performed between 1958 and 1962 to identify the relationship between various factors and the onset of lymphoedema (level 4 evidence). After analysis of the 94 patients without evidence of local cancer post-operatively, more than half (53 %) of the patients reported recurrent cellulitis following either an insect bite, cat scratch, needle or thorn prick preceding their lymphoedema; the source of infection was, however, unclear and relationship specifically to venepuncture not described [18]. The authors conclude that avoidance of risk factors contributing to infection or delayed wound healing will reduce post-operative lymphoedema, but acknowledge that the extent of surgical removal of lymphatics is the most important causal factor. The study is, however, heavily confounded by recall bias as the results were based on patient recollection.

Ten breast cancer patients were referred to a large, regional lymphoedema centre between 1994 and 1996 with lymphoedema following venepuncture; all had undergone axillary dissection, with 3 also receiving radiotherapy to the axilla [19] (level 4 evidence). They represented, however, only 1.5 % of referrals to the centre over this period, and no justification was offered for the claim that “...venepuncture appears to have played a significant part in the history of lymphoedema”, whilst acknowledging that there is “...only minimal circumstantial evidence...” on which to base their advice to avoid venepuncture in the ipsilateral arm.

In 2006, a review that started with the statement that “lymphoedema may be triggered by any type of injection” included a small retrospective audit of 14 patients (of whom 9 had breast cancer) with previous axillary node surgery and a history of non-accidental skin puncture [20] (level 4 evidence). Interestingly, no patient reported swelling of the ipsilateral limb within the subsequent 2 months. The audit was small, but the review concludes with the recommendation that, where appropriate, the use of the ipsilateral arm for venepuncture if cannulation of the contralateral arm is problematic and placement of a central venous access device are not appropriate.

More recently, a case-control study compared 101 patients with breast cancer who had undergone axillary dissection and developed lymphoedema with the same number without lymphoedema matched by time from axillary surgery, axillary radiotherapy (or not) and stage [21] (level 3 evidence). Questionnaires were used to collect information regarding risk factors, while arm circumference measurements were used to quantify the degree of lymphoedema. Drawing blood and blood pressure measurements were combined as “medical procedures”. In total, there were 52 patients with a history of a medical procedure on the ipsilateral arm (31 controls and 21 with lymphoedema). The odds ratio for developing lymphoedema in patients who underwent medical procedures was 0.59 (CI 0.31–1.12; $P = 0.11$). The authors conclude that there was no evidence that these medical procedures were associated with an increased risk of lymphoedema. By contrast, the risk of developing moderate/severe lymphoedema was significantly associated with previous infection/inflammation in the ipsilateral arm or chest, axillary dissection on the side of the dominant hand, high body mass index and more advanced age.

Winge et al. [22] also used self-reported questionnaires regarding previous venepuncture in 348 patients who underwent axillary lymph node clearance (level 3 evidence). Of the 311 respondents, 88 (28 %) reported having intravenous procedures on the ipsilateral side but only 4 developed swelling, and the relationship to venepuncture was unclear. Given the recall bias inherent to the study

Table 2 Literature review of lymphoedema after venepuncture

Authors	Study design	Population studied	Number of patients	Axillary intervention	Findings	Conclusion and recommendations
Villasor et al. [16]	Retrospective observational study Level 3	Women with breast cancer who received a radical mastectomy	79	Radical mastectomy	1/79 (2 %) patient developed lymphoedema immediately following venepuncture	Avoid venepuncture
Britton et al. [18]	Retrospective observational study Level 4	Women with breast cancer and moderate-to-severe lymphoedema after radical mastectomy	114 (94 with no evidence of local cancer post-operatively)	Radical mastectomy	50/94 (53 %) had a history of recurrent cellulitis following either an insect bite, cat scratch, needle or thorn prick with a marked increase in swelling or pain in their arm	Avoid venepuncture
Smith et al. [19]	Retrospective observational study Level 4	Women with breast cancer who received axillary lymph node dissection (3 patients also receiving radiotherapy to the axilla)	691	Axillary node dissection	10 (1.5 %) breast cancer patients were referred with lymphoedema following venepuncture	Avoid venepuncture
Cole et al. [20]	Retrospective observational study Level 4	Women with previous axillary lymph node surgery (9 out of 14 had breast cancer)	14	Axillary lymph node surgery	No cases of lymphoedema development within a 2-month follow-up period	Low risk
Mak et al. [21]	Retrospective matched case-control study Level 3	Women with breast cancer who received axillary lymph node dissection	202 (101 cases)	Axillary lymph node dissection	52 patients (31 controls and 21 with lymphoedema) had a history of a “medical procedure” The odds ratio for the development of lymphoedema was 0.59, 95 % confidence interval 0.31–1.12 $P = 0.11$	No significant risk
Winge et al. [22]	Retrospective observational study Level 3	Women with breast cancer who received axillary lymph node clearance	348	Axillary lymph node clearance	88 reported a history of intravenous procedures on the ipsilateral side but only 4 developed swelling	Low risk
Clark et al. [1]	Prospective observational study Level 2	Women with breast cancer who received sampling, excision or biopsy of the ipsilateral axillary lymph nodes	188 18 with needle stick injury	Sampling, excision or biopsy of the ipsilateral axillary lymph nodes	8/18 (44 %) patients who had any needle stick developed lymphoedema as compared with 31/170 (18 %) patients who did not have venepuncture (no time frame) The relative risk of developing lymphoedema after venepuncture in hospital was 2.44 (CI 1.33–4.47)	Avoid venepuncture

design, the authors concluded that, if performed correctly, there is little risk of complications from venepuncture in the ipsilateral arm.

Prospective studies

The only prospective study evaluating the relationship between lymphoedema and venepuncture [1] assessed objectively the degree of lymphoedema using prospective

circumferential limb measurements pre-operatively, then at 6 months and 3 years post-operatively in women who undergone either sampling, excision or biopsy of the ipsilateral axillary lymph nodes (level 2 evidence). Patients were asked to recall any skin puncture including venepuncture, cannulation and capillary blood glucose monitoring on the ipsilateral arms. Over a three-year period, 39 of the 188 patients developed lymphoedema. Of the 170 women who did not recall ipsilateral skin puncture, 31

(18.2 %) developed lymphoedema; by contrast, of the 18 women who did recall ipsilateral skin puncture, 8 (44 %) subsequently developed lymphoedema. The relative risk of developing lymphoedema after venepuncture in hospital was 2.44 (CI 1.33–4.47); the authors conclude that puncturing the skin of the ipsilateral arm by healthcare professionals should be avoided.

This study is unique given its prospective nature and the objective measurements used to confirm the development of lymphoedema. Unfortunately, 25 % of the women recruited to the study were lost to follow up; the authors judge this attrition rate “acceptable”, but acknowledge the challenge of generalising the findings from a single-centre study of limited size to a wider population. More importantly, the single most important finding (i.e. that patients who recalled ipsilateral skin puncture) was based solely on patient recall and subject, therefore, to considerable bias. In addition, there was no indication as to how long after venepuncture the lymphoedema developed, nor why the ipsilateral arm had been used for venepuncture or whether there was any lymphoedema in that arm prior to venepuncture. Disappointingly, no larger, better designed confirmatory study has been published in the subsequent 10 years.

Discussion

As breast cancer-related mortality falls, there are growing numbers of women living with the effects of breast cancer and its treatment, including lymphoedema. There is a wealth of advice available to these patients regarding how to reduce the risk of developing lymphoedema, in particular avoidance of venepuncture in the ipsilateral arm; the most frequent source of this advice appears to be nurses [23]. The importance attributed to avoiding venepuncture in the ipsilateral arm is illustrated by a quality improvement project [24] within which 26.9 % of staff surveyed reported seeing procedures performed on an arm at risk of lymphoedema in the non-emergency setting. To better identify these patients, warning signs at the bedside and ‘At-Risk Arm’ alerts on the computerised records system were implemented; the general practitioner was also informed on discharge and a second staff survey was conducted.

The current systematic review has, however, demonstrated the paucity of evidence to support such recommendations. We have appraised the existing literature surrounding venepuncture as a risk factor for developing lymphoedema in the ‘at-risk’ arm. Although, theoretically, the risk of infection may predispose those with dysfunc-

tional lymphatic flow to the development of lymphoedema, no convincing evidence exists to support the avoidance of venepuncture following axillary surgery.

In addition, the management of women with breast cancer has changed substantially over recent years, with surgery increasingly carried out by designated breast surgeons. Likewise, many fewer patients undergo axillary clearance and those who have undergone sentinel node biopsy will have lesser degrees of disruption to the lymphatic architecture and be at lower risk of lymphoedema [25]. There is also now access to a wide range of central venous delivery devices including less-invasive devices such as peripherally inserted central catheter (PICC) lines for patients requiring long-term venous access.

In the absence of robust data to show that use of an ipsilateral arm unaffected by lymphoedema increases the risk of lymphoedema, it is not, therefore, acceptable that women be exposed to multiple attempts at venepuncture in the contralateral arm or feet with all the attendant unnecessary distress this may cause. Rather, a pragmatic, evidence-based, patient-focussed approach should be adopted when seeking venous access in patients with a history of breast cancer with the patient fully informed and involved in the decision-making process. Using the contralateral arm is the most appropriate first choice, but multiple failed attempts will lead to frustration and agitation in both patient and healthcare professional. Cannulating other areas of the body, such as veins in the foot, may be painful or inconvenient and is a procedure with which most healthcare professionals will be less familiar. After reassuring the patient that, in the absence of pre-existing lymphoedema, use of the ipsilateral arm carries little or no risk of lymphoedema. An alternative, especially for medium- or long-term access, is placement of a central venous access device.

Conclusion

After patients with breast cancer have undergone axillary procedures, where possible venepuncture should be performed on the contralateral arm. When venous access is essential, however, the evidence does not support a blanket restriction on using the ipsilateral arm provided that there is no existing lymphoedema and venous access appears good. Venepuncture in the ipsilateral arm carries a small risk of infection, but there is no robust evidence to support this increasing the risk of subsequent lymphoedema and patients should be reassured accordingly. We propose evidence-based, patient-focussed guidelines for venepunc-

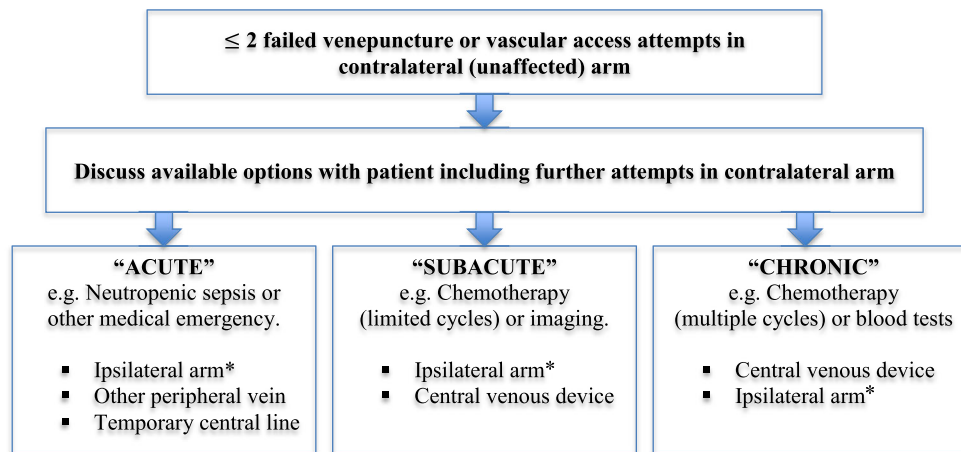


Fig. 1 Flowchart describing the different options for venesection and vascular access in patients with an arm at risk of lymphoedema. *Provided no lymphoedema and accessible vein

ture in women with breast cancer who have undergone an axillary intervention (Fig. 1).

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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