This item is the archived peer-reviewed author-version of:

The incidence and time path of lymphedema in sentinel negative breast cancer patients: a systematic review

Reference:
Gebruers Nick, Verbelen Hanne, De Vrieze Tessa, Coeck Dorith, Tjalma Wiebren. - The incidence and time path of lymphedema in sentinel negative breast cancer patients: a systematic review
Archives of physical medicine and rehabilitation - ISSN 0003-9993 - (2015), p. 1-26
DOI: http://dx.doi.org/doi:10.1016/j.apmr.2015.01.014
The incidence and time path of lymphedema in sentinel negative breast cancer patients: a systematic review

Nick Gebruers, Ph.D., PT, Hanne Verbelen, PT, Tessa De Vrieze, PT, Dorith Coeck, PT, Wiebren Tjalma, Ph.D., M.D

PII: S0003-9993(15)00090-8
DOI: 10.1016/j.apmr.2015.01.014
Reference: YAPMR 56091

To appear in: ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION

Received Date: 11 September 2014
Revised Date: 14 January 2015
Accepted Date: 16 January 2015


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Running head: Lymphedema in SLNB negative patients

Title: The incidence and time path of lymphedema in sentinel negative breast cancer patients: a systematic review

Nick Gebruers, Ph.D., PT\textsuperscript{a}; Hanne Verbelen, PT\textsuperscript{a}; Tessa De Vrieze, PT\textsuperscript{a}; Dorith Coeck, PT\textsuperscript{a}; Wiebren Tjalma, Ph.D., M.D\textsuperscript{b,c}

- Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium (e-mail: hanne.verbelen@uantwerpen.be, nick.gebruers@uantwerpen.be, tessadevrieze@hotmail.com, dorith.c@hotmail.com)
- Multidisciplinary Breast Clinic, Antwerp University Hospital (UZA), Wilrijkstraat 10, 2650 Edegem, Belgium (e-mail: wiebren.tjalma@uza.be)
- Department of Medicine, Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, 2610 Antwerp, Belgium (e-mail: wiebren.tjalma@uantwerpen.be)

Corresponding author:
Prof. dr. Nick Gebruers
Department of Rehabilitation Sciences and Physiotherapy
Faculty of Medicine and Health Sciences
University of Antwerp
Universiteitsplein 1
2610 Antwerp
Belgium
nick.gebruers@uantwerpen.be
Fax: +32 32652501
Financial disclosure:

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated AND, if applicable, we certify that all financial and material support for this research (eg, NIH or NHS grants) and work are clearly identified in the title page of the manuscript.

Funding

A grant was received from the Flemish Government (Academic fund G817-g091).

Conflict of interest

The authors have no conflict of interest to declare.
Abstract

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

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

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

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

Data synthesis: 28 articles were included, representing 9,588 SLNB negative patients. The overall incidence of lymphedema in sentinel node negative breast cancer patients ranged from 0% to 63.4%. The studies that have assessed lymphedema at predefined time points, instead of a mean follow-up time, demonstrated an incidence range at ≤3, 6, 12, 18 or > 18 months post-surgery of 3.2-5%, 2-10%, 3-63.4%, 6.6-7% and 6.9-8.2% respectively.
Conclusion: In SLNB-patients there is still a problem of lymphedema, if so it mostly occurs 6 to 12 months after surgery. Due to different assessments and criteria there is a wide range in incidence. Clear definitions of lymphedema are absolutely necessary to tailor therapy.

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

Abbreviations

ALND Axillary Lymph Node Dissection
MeSH Medical Subject Heading
QoL Quality of Life
SLNB Sentinel Lymph Node Biopsy
WoS Web of Science
ARM Axillary Reverse Mapping

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

Methodology

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

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

Please insert figure 1

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

Quality assessment

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

**Results**

Initially the search yielded 635 citations. After the first screening and removal of duplicates, 96 full text articles were retrieved. After the final screening based upon the full-texts, 28 studies were found eligible and included in this review. The results of this systematic review are based on 21 cohort studies, 3 RCT’s, and 4 cross-sectional studies. Four studies reported from the same sample of patients, these data were extracted only once. Consequently, the selected studies represent a total of 9,588 SLNB negative patients. The literature search and study selection process are shown in Figure 1.

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

In the above described results, no distinction was made based upon the different follow-up times or measuring intervals. Next, the incidence at specific time-points will be described (see table 1). These results were extracted from the studies that specifically reported the incidence at pre-defined time points. Most commonly, lymphedema assessment was done at 3, 6, 12, 18 or >18 months post-surgery. The longest follow-up time was 9.4 years in the study of Wernicke et al.\textsuperscript{32} The studies that have assessed the lymphedema at predefined time points, instead of a mean follow-up time, demonstrated an incidence range at ≤3, 6, 12, 18 or > 18 months post-surgery of 3.2-5%, 2-10%, 3-63.4%, 6.6-7% and 6.9-8.2% respectively\textsuperscript{6, 12, 15, 21, 23, 33, 35}.

Combining the information about the diagnostic criteria and the defined time points, an informative overview can be presented (see table 2). Table 2 clearly presents that the incidences’ change with regard to the chosen definition; and that lymphedema is most common between 6 and 12 months of follow-up. Also, the long term incidence is not negligible. Incidences are within narrow ranges when compared to the range presented among all studies (table 1).

Discussion

The results of our systematic review clearly demonstrate that lymphedema is a non-negligible complication in SLNB negative breast cancer patients. The overall range of the lymphedema incidence is very broad, namely 0 to 63.4%. Two studies are mainly responsible for this broad range\textsuperscript{11, 15}. Both studies have clear limitations, their results should be appraised critically with regard to the incidences found. Armer et al, reported from a very low number (n=9) of SLNB patients, of which two (22%) were diagnosed with edema\textsuperscript{11}. Francis et al have used a very liberal definition, namely 5% volume
difference between preoperative and postoperative arm volumes. Additionally, weight alterations were
only corrected when patients’ weight changed with 10 pounds or more. Therefore this approach is
totally different and incomparable with the other studies. If both studies (Armer et al. and Francis et
al.) were to be discarded from the results, the incidence range would be 0-15.8%. The aforementioned
incidence rate is less in comparison with lymphedema after ALND with a reported range of 13.5% to
28.2%. The response to our first research question is that lymphedema is less incident in SLNB than
ALND. However, clinicians and/or therapists should still be aware of the possibility of lymphedema
formation in SLNB. Mostly, the lymphedema in SLNB negative patients has a mild character.
Untreated, this lymphedema will progress to a more severe lymphedema. The results of our review
reveal that severe lymphedema (≥ 10% diff. or >5cm diff.) was encountered significantly less in
SLNB than in ALND. However, severe lymphedema was diagnosed in 0.2-9% of the SLNB patients
with lymphedema.

Several limitations among the selected studies need to be discussed. Not surprisingly, a wide variation
of assessments and accompanying measuring protocols were used by the different research groups.
Four studies relied totally on subjective assessments as for example a questionnaires or an interview
(incidence of lymphedema 0-7%). Since lymphedema is a complex morbidity; it is doubtful
that a patient is able to correctly answer questions regarding the presence or absence of lymphedema.
Therefore, objective assessment methods like the water displacement or circumference measures are
recommended. However, we also found that the objective assessments used in the selected studies had
a number of limitations. In case of the circumference measurements and water displacement method, a
wide variety of definitions is used (e.g. >1cm difference, 2cm difference, >2cm difference, 5%
difference, >10% difference). It is clear that when a higher difference is needed to diagnose edema, the
incidence will decrease. On the contrary, a limited difference in circumference (e.g. >1 or 2cm
difference) can also be found in perfectly healthy subjects. The latter is very well demonstrated in two
studies that compared the incidence based upon common lymphedema definitions. In the same
sample of breast cancer patients, the incidences varied between 21% and 70% or 41% and 94%
based upon the chosen definition to diagnose lymphedema. It is essential that international consensus
among clinicians/therapists is established concerning the definition of lymphedema. In 2007 we have proposed to use prediction formulas based upon water displacement to diagnose edema/lymphedema. Another apparent limitation, none of the selected studies have mentioned to take into account the patient’s arm dominance when defining the lymphedema volume. In case of unilateral edema, most researchers use the contralateral limb for comparison, stating that both limbs have the same volume. Unfortunately, both arms are not identical. It was demonstrated that the dominant arm of a healthy person is 3.3% (sd 3%) larger than the non-dominant arm. Based upon these findings, prediction formulas for the upper limbs were presented to cope with dominance in unilateral edema. We suggest taking into account these volume difference when assessing the edema volume in patients. Since none of the studies corrected for dominance, it is plausible that the lymphedema incidences presented in this review might still be underestimated.

Concerning the second research question regarding the time path of lymphedema after SLNB, diverging results were found (see table 1). Again, if we omit the studies of Armer et al. and Francis et al. a more focused result can be displayed and discussed. Until three months post-surgery, lymphedema after SLNB is relatively low (range 3.2% to 5%). At 6 months post-surgery an increase in lymphedema incidence is demonstrated (range 2% to 10%). The most common follow-up period to assess lymphedema in SLNB was 12 months post-surgery with incidences between 3% and 12%. Follow-up periods of 18 months and longer resulted in incidences between 6.9% to 8.2%. A follow-up of 5 years or longer was only seen in five studies of which four reported from the same cohort. Long term (≥ 5y) incidence was 5% to 5.4%.

Clinicians and therapists need to be aware that lymphedema remains a complication to take into account when assessing SLNB patients. As demonstrated by the different studies, 6-12 months after surgery is a critical moment in follow-up to assess the presence of lymphedema in SLNB. Overall we have found that the incidence of lymphedema in SLNB is less when compared to ALND. This can be well explained by the less-invasive surgery that needs to be performed. Nevertheless, lymphedema does occur in SLN-negative patients. Therefore, new techniques are tested and
implemented by surgeons to further reduce the risk of breast cancer related lymphedema; for instance
the use of axillary reverse mapping (ARM), a technique first described in 2007\textsuperscript{43}. ARM provides a
way to visualize the lymphatic routing of the arm, breast and axilla. This way, surgeons are able to
preserve as much as possible the normal lymph pathways. The evidence on ARM is not yet
conclusive\textsuperscript{43}; however in SLNB patients the results are very promising\textsuperscript{44-47}. We have found no
evidence that ARM was used in one of the studies presented in the current review of the literature.
However, ARM studies have also demonstrated that about 20\% of the SLNB patients have a lymphatic
route from the upper limb that passes the same (sentinel) nodes. Sakurai et al, have demonstrated that
only these patients were at risk of developing lymphedema. Additionally, they demonstrated that 5 out
of 76 patients (6.6\%), who had a lymphatic route from the upper limb involving the sentinel,
developed lymphedema. On the contrary, none of the patients with an alternative route from the upper
limb experienced lymphedema\textsuperscript{45}. This evidence demonstrates that in some patients it is almost
inevitable to prevent lymphedema after surgery.

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

Study limitations

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

Conclusion

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

The authors have no conflict of interest to declare.
References


Figure 1: Search strategy flow chart

**Boolean Search Strategy**

<table>
<thead>
<tr>
<th>Source</th>
<th>Records</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubmed</td>
<td>248</td>
</tr>
<tr>
<td>Web of Knowledge</td>
<td>160</td>
</tr>
<tr>
<td>Embase</td>
<td>195</td>
</tr>
<tr>
<td>Cochrane Library</td>
<td>32</td>
</tr>
</tbody>
</table>

Selection based upon title and abstract

- 248 records
- 160 records
- 195 records
- 32 records

Inclusion/exclusion criteria and removing duplicates (n = 68)

Exclusion criteria:
- No breast cancer (n=2)
- No information on SLN or SLN in combination with ALND (n=46)
- No lymphedema incidence (n=16)
- Review or case reports (n=4)

28 articles selected and scored with CBO
Table 1: Summary of lymphedema incidence/prevalence and time path of the selected studies

<table>
<thead>
<tr>
<th>Author, year, reference n°</th>
<th>Design (methodological score)</th>
<th>n (n° of SLNB negative patients)</th>
<th>Lymphedema assessment method</th>
<th>Incidence of lymphedema in SLNB (percentages are in bold)</th>
<th>Time points/follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armer et al., 2004&lt;sup&gt;11&lt;/sup&gt; Cross-sectional (5/9) n=9</td>
<td>Circumference measurements &gt;2 cm of difference between sides</td>
<td>2/9 patients or <strong>22.2%</strong></td>
<td>4-14 months after surgery; median 8.5 months after surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ashikaga et al., 2010&lt;sup&gt;12&lt;/sup&gt; RCT (6/9) n=2008</td>
<td>Water displacement &lt;5% diff /5-10% diff/&gt;10% diff</td>
<td><strong>16.7%</strong> of 1151 patients have excess volume after 3 year of follow-up (Pts with &gt;5% diff who had &lt;5% diff at baseline). &gt;10% between 7-9%</td>
<td>&gt;10% diff at Baseline, 6-12-18-24-30-36 months follow-up are respectively 8%-9%-8.6%-6.6%-8.2%-6.9%-7.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blanchard et al., 2003&lt;sup&gt;13&lt;/sup&gt; Cross-sectional (6/9) n=685</td>
<td>Questionnaire</td>
<td>39/683 patients or <strong>6%</strong></td>
<td>Mean follow-up was 2.4y (sd = 0.9y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celebioglu et al., 2007&lt;sup&gt;14&lt;/sup&gt; Cohort (6/9) n=30</td>
<td>Water displacement &gt;10% diff between arms</td>
<td>0/30 patients or <strong>0%</strong></td>
<td>Follow-up: baseline- 1-2-3y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldberg et al., 2010&lt;sup&gt;15&lt;/sup&gt;, 2011&lt;sup&gt;16&lt;/sup&gt; Cohort (6/9) n=600</td>
<td>Circumference measurements Difference of &gt;2cm = presence of edema Difference of &gt;5cm = severe edema Interview</td>
<td>5% (31/600) had edema of which 3/600 had severe edema</td>
<td>Median follow-up was 5y (2.7-8y)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Golshan et al., 2003&lt;sup&gt;8&lt;/sup&gt; Cohort (3/9) n=77</td>
<td>Circumference measurements Difference of &gt;3cm between arms</td>
<td>3% (18/600) reported edema</td>
<td>Minimum 1y post-op</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haid et al., 2002&lt;sup&gt;18&lt;/sup&gt; Cohort (5/9) n=57</td>
<td>Circumference measurements Difference of &gt;2cm between arms</td>
<td>2/57 or <strong>2.6%</strong></td>
<td>mean follow-up time was 25 (range 14–60) months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Methodology</td>
<td>N</td>
<td>Population</td>
<td>Number (%)</td>
<td>Median follow-up time (range)</td>
</tr>
<tr>
<td>-------------------------------------------</td>
<td>-------------</td>
<td>------</td>
<td>------------</td>
<td>-------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>Langer et al., 2007¹⁹</td>
<td>Cohort (7/9)</td>
<td>n=449</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circumference measurements</td>
<td>Difference of &gt;2cm between arms</td>
<td>15/431 or 3.5%</td>
<td>31.0 months (range 11–62)months</td>
<td></td>
</tr>
<tr>
<td>Leidenius et al., 2005²⁰</td>
<td>Cohort (4/9)</td>
<td>n=92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circumference measurements</td>
<td>Difference of &gt;2cm between arms</td>
<td>1/92 or 1%</td>
<td>3 years post-operative</td>
<td></td>
</tr>
<tr>
<td>Lucci et al., 2007²¹</td>
<td>RCT (6/9)</td>
<td>n=446</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circumference measurements</td>
<td>Difference of &gt;2cm between arms</td>
<td>Range = 5.5% - 7.7%</td>
<td>Subjective assessment: 6 months 19/339 or 5.6% 12months 16/268 or 6% &gt;12 months 14/253 or 5.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Objective assessment: 30 days 17/272 or 6.3% 6 months 21/271 or 7.7% 12 months 14/226 or 6.2%</td>
</tr>
<tr>
<td>Lumachi et al., 2009²²</td>
<td>Cohort (5/9)</td>
<td>n=54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circumference measurements</td>
<td>Difference of &gt;2cm between arms</td>
<td>2/54 or 3.7%</td>
<td>Median follow-up was 22 months (range 18-28 months)</td>
<td></td>
</tr>
<tr>
<td>Husted Madsen et al., 2008³⁵</td>
<td>Cohort (6/9)</td>
<td>n=164</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Water displacement</td>
<td>Questionnaire</td>
<td>Range 7-10% (questionnaire)</td>
<td>6 months 10% (questionnaire) 18 months 7% (questionnaire)</td>
<td></td>
</tr>
<tr>
<td>Mansel et al., 2006⁶</td>
<td>RCT (8/9)</td>
<td>n=478</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circumference measurements</td>
<td>Self-assessment</td>
<td>3.2% - 5% (self-assessment)</td>
<td>1 month 3.2% 3 months 5% 6 months 4.5% 12 months 5%</td>
<td></td>
</tr>
<tr>
<td>McLaughlin et al., 2008²⁴,²⁵</td>
<td>Cohort (6/9)</td>
<td>n=600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Circumference measurements</td>
<td>Difference of &gt;2cm = presence of edema</td>
<td>Difference of &gt;5cm = severe edema</td>
<td>5% (31/600) had edema of which 3/600 had severe edema</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median follow-up time was 5y (range 2.7-8y)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3% (18/600) reported edema</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Cohort</td>
<td>Study Design</td>
<td>Sample Size</td>
<td>Measurement Method(s)</td>
</tr>
<tr>
<td>---------------------</td>
<td>------</td>
<td>--------</td>
<td>--------------</td>
<td>-------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>McLaughlin et al., 2013&lt;sup&gt;23&lt;/sup&gt;</td>
<td>2013</td>
<td>5/9</td>
<td>Cohort</td>
<td>67</td>
<td>Circumference measurement 10% or more increase in volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Questionnaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Interview</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozcinar et al., 2012&lt;sup&gt;26&lt;/sup&gt;</td>
<td>2012</td>
<td>8/9</td>
<td>Cohort</td>
<td>80</td>
<td>Circumference measurement &gt;2cm of difference between arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mid-term (9-12 months post-op) 8% Late-term (&gt; 12-64 months post-op) 1.9%</td>
</tr>
<tr>
<td>Paim et al., 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>2008</td>
<td>3/5</td>
<td>Cross-sectional</td>
<td>48</td>
<td>Circumference measurement &gt;1cm of difference between arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mean 23 months post-op (6-60 months)</td>
</tr>
<tr>
<td>Rönka et al., 2005&lt;sup&gt;27&lt;/sup&gt;</td>
<td>2005</td>
<td>7/9</td>
<td>Cohort</td>
<td>43</td>
<td>Circumference measurement Increase in limb volume of 5% or more</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Self-reported lymphedema (VAS-score) Mild 9% Moderate 3.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 year after surgery</td>
</tr>
<tr>
<td>Roumen et al., 2001&lt;sup&gt;28&lt;/sup&gt;</td>
<td>2001</td>
<td>4/9</td>
<td>Cohort</td>
<td>90</td>
<td>Questionnaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Median 24 (16-40) months</td>
</tr>
<tr>
<td>Schijven et al., 2003&lt;sup&gt;29&lt;/sup&gt;</td>
<td>2003</td>
<td>6/9</td>
<td>Cohort</td>
<td>180</td>
<td>Questionnaire</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;1y – 3y post-op</td>
</tr>
<tr>
<td>Study</td>
<td>Sample</td>
<td>Methodology</td>
<td>Observation</td>
<td>Incidence (%; n)</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>Schulze et al., 2006</td>
<td>Cohort (7/9)</td>
<td>n=31</td>
<td>Circumference measurement for the arm in combination with a water displacement for the volume of the hand &gt;10% difference</td>
<td>15.8% (3/19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Questionnaire</td>
<td>10.5% (2/19)</td>
<td></td>
</tr>
<tr>
<td>Velloso et al., 2011</td>
<td>Cross-sectional (3/5)</td>
<td>n=45</td>
<td>Circumference measurements 10% or more increase in volume</td>
<td>4.4% (2/45)</td>
<td></td>
</tr>
<tr>
<td>Wernicke et al., 2013</td>
<td>Cohort (7/9)</td>
<td>n=111</td>
<td>Circumference measurement &gt;1cm of difference between arms</td>
<td>5.4% (6/111)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Self-assessment by patients</td>
<td>9.1% (10/111)</td>
<td></td>
</tr>
<tr>
<td>Wilke et al., 2006</td>
<td>Cohort (6/9)</td>
<td>N=4069</td>
<td>Circumference measurement &gt;2cm increase in comparison with baseline measurement</td>
<td>0-7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0% at 30d of follow-up (n= 4069) 7% at 6month follow-up (n = 2904)</td>
<td></td>
</tr>
<tr>
<td>Yen et al., 2009</td>
<td>Cohort (6/9)</td>
<td>n=319</td>
<td>Self-assessment by telephone survey</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Francis et al., 2006</td>
<td>Cohort (6/9)</td>
<td>n=41</td>
<td>Circumference measurements &gt;5% difference in comparison with pre-operative volume</td>
<td>63.4% (26/41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 year post-surgery: &gt;5% difference (17/41 or 41%) ≥10%difference (9/41 or 22%)</td>
<td></td>
</tr>
</tbody>
</table>

Both incidence percentages are presented for long-term morbidities (>20 months post-op; mean 49 months for SLNB)
Table 2: Overview of the incidence ranges at predefined time points with regard to the diagnostic definition used.

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

*only the studies that provided data on predefined time points were used to create this table. Studies with an mean or median follow-up were omitted because of the potential bias that is created by mixing different follow-up times.
Appendix 1: Boolean search strategy performed in Pubmed