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Running head:
Lymphedema in SLNB negative patients

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

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Conflict of interest

The authors have no conflict of interest to declare.

Reprints

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1 Running head:
2 Lymphedema in SLNB negative patients

3
4 Title:

5 **The incidence and time path of lymphedema in sentinel negative breast**
6 **cancer patients: a systematic review**
7

8 Abstract

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

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

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

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

23 **Data synthesis:** 28 articles were included, representing 9,588 SLNB negative patients. The overall
24 incidence of lymphedema in sentinel node negative breast cancer patients ranged from 0% to 63.4%.
25 The studies that have assessed lymphedema at predefined time points, instead of a mean follow-up
26 time, demonstrated an incidence range at ≤ 3 , 6, 12, 18 or > 18 months post-surgery of 3.2-5%, 2-10%,
27 3-63.4%, 6.6-7% and 6.9-8.2% respectively.

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

31

32 **Key words:**

33 Lymphedema, Breast neoplasms, Sentinel Lymph Node Biopsy, Systematic Review

34

35 Abbreviations

36

37 ALND Axillary Lymph Node Dissection

38 MeSH Medical Subject Heading

39 QoL Quality of Life

40 SLNB Sentinel Lymph Node Biopsy

41 WoS Web of Science

42 ARM Axillary Reverse Mapping

43

44 Breast cancer is known as the most common malignancy in women in the Western World.
45 Unfortunately, the incidence is still increasing¹. At some time during their life, breast cancer will be
46 diagnosed in 1 out of every 8 women². In the past breast surgery was very extensive; present-day
47 surgical procedures have become more refined. Many women underwent and still undergo axillary
48 lymph node dissection (ALND) which can cause several arm and shoulder morbidities like numbness,
49 pain, limitation of arm movement, also including lymphedema³. Over the years, surgical techniques
50 have changed dramatically with the introduction of breast conserving techniques and the sentinel
51 lymph node biopsy (SLNB). SLNB is widely used as a standard assessment procedure in breast cancer
52 patients. The number of patients treated with SLNB is increasing since women with limited SLN
53 involvement are no longer treated with ALND⁴. SLNB can reduce unnecessary axillary clearance;

54 therefore it is expected to substantially decrease arm and shoulder morbidity, including upper limb
55 lymphedema⁵. In the literature SLNB and ALND patients are often compared, with beneficial results
56 in favor of SLNB⁶. Despite a strong reduction in morbidity after the SLNB procedure, the
57 complication rate may be underestimated. The occurrence of lymphedema, a condition characterized
58 by fluid accumulation in the interstitial space⁷, is expected to be minimal in SLNB⁸. However, a
59 recent systematic review by Verbelen et al. demonstrated that lymphedema might be a morbidity in
60 SLNB negative patients to take into account⁹. The aim of this systematic review is to provide answers
61 concerning the following questions: 1) what is the incidence/prevalence of lymphedema related to
62 breast cancer surgery in sentinel node negative patients, 2) what is the time path of this lymphedema?

63

64

65 Methodology

66

67 The literature was systematically reviewed, based upon the PRISMA guidelines, addressing the
68 following research questions: 1) what is the incidence of lymphedema related to breast cancer surgery
69 in sentinel node negative patients, 2) what is the time path of lymphedema in SLN negative patients?
70 Four electronic databases were screened online to identify eligible studies: PubMed (October 14,
71 2013), Web of Science (October 22, 2013), Embase (October 23, 2013) and Cochrane clinical trials
72 (October 29, 2013). In order to retrieve eligible studies, Medical Subject Headings (Mesh-terms) and
73 key words were combined in a Boolean search strategy to describe the patient population (P: breast
74 cancer), the intervention (I: SLNB) and the outcome (O: Lymphedema). We did not define any
75 comparison (C: /) nor study design (S:/) and all papers had to be written in Dutch or English. The
76 specific search strategy used for PubMed is shown in detail in appendix 1. An equivalent search
77 strategy was used for the other three databases but included a number of modifications regarding the
78 differences in the use of indexing terms (MeSH for PubMed and Cochrane, EMTREE for EMBASE).

79 *Please insert appendix 1*

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

90

91 *Please insert figure 1*

92

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

96

97

98 **Quality assessment**

99

100 The methodological quality of the selected articles was assessed using checklists for cohort studies,
101 cross-sectional studies and randomized controlled trials
102 (<http://dcc.cochrane.org/beoordelingsformulieren-en-andere-downloads>). Three reviewers (G.N.,
103 D.T., C.D.) evaluated the selected articles independently. Items could be rated by “1”, “0” or “?”. An
104 item was rated “1” if sufficient information was available and bias was unlikely. An item was rated
105 “0” if sufficient information was available but the article did not meet a specific criterion. An item was

106 rated “?” if no information was available. If disagreement persisted about assigning a score to an item,
107 consensus was sought during a meeting. Nine items were scored for RCT and cohort studies, while
108 only five items were scored for the cross-sectional studies.

109

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111 Results

112

113 Initially the search yielded 635 citations. After the first screening and removal of duplicates, 96 full
114 text articles were retrieved. After the final screening based upon the full-texts, 28 studies were found
115 eligible and included in this review^{6, 8, 10-35}. The results of this systematic review are based on 21
116 cohort studies^{8, 14-20, 22-30, 32-35}, 3 RCT's^{6, 12, 21} and 4 cross-sectional studies^{10, 11, 13, 31}. Four studies^{16, 17,}
117 ^{24, 25} reported from the same sample of patients, these data were extracted only once. Consequently, the
118 selected studies represent a total of 9,588 SLNB negative patients. The literature search and study
119 selection process are shown in Figure 1.

120

121 *please insert table 1*

122

123 Overall, including all methods of assessment and all definitions used, the incidence/prevalence of
124 lymphedema is very broad, ranging from 0% to 63.4% (see table 1). When the included studies were
125 divided based upon the assessment methods, the following incidences were demonstrated. For the
126 studies that used a circumference measurement, the incidence varied between 1% and 63.4% (table 1)^{8,}
127 ^{10, 11, 15-27, 30-33}. When a water displacement method was used, the incidence varied from 0% to 15.8%
128 (table 1)^{12, 14, 30}. Water displacement and circumference measures are both objective assessments

129 whereas questionnaires and interviews are subjective tools. When looking at the studies that have used
130 these subjective tools, the incidence varied from 0% to 11% (table 1)^{6, 13, 17, 23, 25, 28-30, 32, 34, 35}.

131 In the above described results, no distinction was made based upon the different follow-up times or
132 measuring intervals. Next, the incidence at specific time-points will be described (see table 1). These
133 results were extracted from the studies that specifically reported the incidence at pre-defined time
134 points. Most commonly, lymphedema assessment was done at 3, 6, 12, 18 or >18 months post-surgery.
135 The longest follow-up time was 9.4 years in the study of Wernicke et al.³² The studies that have
136 assessed the lymphedema at predefined time points, instead of a mean follow-up time, demonstrated
137 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%
138 and 6.9-8.2% respectively^{6, 12, 15, 21, 23, 33, 35}.

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

144

145

146 Discussion

147

148 The results of our systematic review clearly demonstrate that lymphedema is a non-negligible
149 complication in SLNB negative breast cancer patients. The overall range of the lymphedema incidence
150 is very broad, namely 0 to 63.4%. Two studies are mainly responsible for this broad range^{11, 15}. Both
151 studies have clear limitations, their results should be appraised critically with regard to the incidences
152 found. Armer et al, reported from a very low number (n=9) of SLNB patients, of which two (22%)
153 were diagnosed with edema¹¹. Francis et al have used a very liberal definition, namely 5% volume

154 difference between preoperative and postoperative arm volumes. Additionally, weight alterations were
155 only corrected when patients' weight changed with 10 pounds or more. Therefore this approach is
156 totally different and incomparable with the other studies¹⁵. If both studies (Armer et al. and Francis et
157 al.) were to be discarded from the results, the incidence range would be 0-15.8%. The aforementioned
158 incidence rate is less in comparison with lymphedema after ALND with a reported range of 13.5% to
159 28.2%³⁶. The response to our first research question is that lymphedema is less incident in SLNB than
160 ALND. However, clinicians and/or therapists should still be aware of the possibility of lymphedema
161 formation in SLNB. Mostly, the lymphedema in SLNB negative patients has a mild character.
162 Untreated, this lymphedema will progress to a more severe lymphedema. The results of our review
163 reveal that severe lymphedema ($\geq 10\%$ diff. or $>5\text{cm}$ diff.) was encountered significantly less in
164 SLNB than in ALND. However, severe lymphedema was diagnosed in 0.2-9% of the SLNB patients
165 with lymphedema^{6, 12, 13, 15-17, 20, 24, 27, 30}.

166 Several limitations among the selected studies need to be discussed. Not surprisingly, a wide variation
167 of assessments and accompanying measuring protocols were used by the different research groups.
168 Four studies relied totally on subjective assessments as for example a questionnaires or an interview
169 (incidence of lymphedema 0-7%)^{13, 28, 29, 34}. Since lymphedema is a complex morbidity; it is doubtful
170 that a patient is able to correctly answer questions regarding the presence or absence of lymphedema.
171 Therefore, objective assessment methods like the water displacement or circumference measures are
172 recommended. However, we also found that the objective assessments used in the selected studies had
173 a number of limitations. In case of the circumference measurements and water displacement method, a
174 wide variety of definitions is used (e.g. $>1\text{cm}$ difference, 2cm difference, $>2\text{cm}$ difference, 5%
175 difference, $>10\%$ difference). It is clear that when a higher difference is needed to diagnose edema, the
176 incidence will decrease. On the contrary, a limited difference in circumference (e.g. >1 or 2cm
177 difference) can also be found in perfectly healthy subjects. The latter is very well demonstrated in two
178 studies that compared the incidence based upon common lymphedema definitions^{37, 38}. In the same
179 sample of breast cancer patients, the incidences varied between 21% and 70% ³⁷ or 41% and 94% ³⁸
180 based upon the chosen definition to diagnose lymphedema. It is essential that international consensus

181 among clinicians/therapists is established concerning the definition of lymphedema. In 2007 we have
182 proposed to use prediction formulas based upon water displacement to diagnose edema/lymphedema³⁹.
183 Another apparent limitation, none of the selected studies have mentioned to take into account the
184 patient's arm dominance when defining the lymphedema volume. In case of unilateral edema, most
185 researchers use the contralateral limb for comparison, stating that both limbs have the same volume.
186 Unfortunately, both arms are not identical. It was demonstrated that the dominant arm of a healthy
187 person is 3.3% (sd 3%) larger than the non-dominant arm³⁹⁻⁴². Based upon these findings, prediction
188 formulas for the upper limbs were presented to cope with dominance in unilateral edema³⁹. We suggest
189 taking into account these volume difference when assessing the edema volume in patients. Since none
190 of the studies corrected for dominance, it is plausible that the lymphedema incidences presented in this
191 review might still be underestimated.

192 Concerning the second research question regarding the time path of lymphedema after SLNB,
193 diverging results were found (see table 1). Again, if we omit the studies of Armer et al.¹¹ and Francis
194 et al.¹⁵ a more focused result can be displayed and discussed. Until three months post-surgery,
195 lymphedema after SLNB is relatively low (range 3.2% to 5%)⁶. At 6 months post-surgery an increase
196 in lymphedema incidence is demonstrated (range 2% to 10%)^{6, 21, 23}. The most common follow-up
197 period to assess lymphedema in SLNB was 12 months post-surgery with incidences between 3% and
198 12%^{6, 21, 23, 27}. Follow-up periods of 18 months and longer resulted in incidences between 6.9% to
199 8.2%. A follow-up of 5 years or longer was only seen in five studies^{16, 17, 24, 25, 32} of which four^{16, 17, 24, 25}
200 reported from the same cohort. Long term ($\geq 5y$) incidence was 5% to 5.4%^{17, 32}.

201 Clinicians and therapists need to be aware that lymphedema remains a complication to take into
202 account when assessing SLNB patients. As demonstrated by the different studies, 6- 12 months after
203 surgery is a critical moment in follow-up to assess the presence of lymphedema in SLNB.

204 Overall we have found that the incidence of lymphedema in SLNB is less when compared to ALND.
205 This can be well explained by the less-invasive surgery that needs to be performed. Nevertheless,
206 lymphedema does occur in SLN-negative patients. Therefore, new techniques are tested and

207 implemented by surgeons to further reduce the risk of breast cancer related lymphedema; for instance
208 the use of axillary reverse mapping (ARM), a technique first described in 2007⁴³. ARM provides a
209 way to visualize the lymphatic routing of the arm, breast and axilla. This way, surgeons are able to
210 preserve as much as possible the normal lymph pathways. The evidence on ARM is not yet
211 conclusive⁴³; however in SLNB patients the results are very promising⁴⁴⁻⁴⁷. We have found no
212 evidence that ARM was used in one of the studies presented in the current review of the literature.
213 However, ARM studies have also demonstrated that about 20% of the SLNB patients have a lymphatic
214 route from the upper limb that passes the same (sentinel) nodes. Sakurai et al, have demonstrated that
215 only these patients were at risk of developing lymphedema. Additionally, they demonstrated that 5 out
216 of 76 patients (6.6%), who had a lymphatic route from the upper limb involving the sentinel,
217 developed lymphedema. On the contrary, none of the patients with an alternative route from the upper
218 limb experienced lymphedema⁴⁵. This evidence demonstrates that in some patients it is almost
219 inevitable to prevent lymphedema after surgery.

220 The current systematic review reveals that lymphedema after breast cancer therapy remains a
221 complication even in SLNB-negative breast cancer patients. Lymphedema after breast cancer is a
222 complication that needs life-long attention⁴⁸. It is essential to treat the lymphedema, not only to
223 improve the QoL^{49, 50}, but also to prevent the worsening and additional complications related to
224 lymphedema^{50, 51}. Physicians and therapists need to be aware that lymphedema is a possible
225 complication in SLNB-negative breast cancer patients. The real problem exposed by the current
226 review is the lack of a uniform diagnostic definition of lymphedema. We have found subjective as
227 well as objective assessments. The incidence found by both assessments differ within a same sample
228 of patients; this can be explained by the fact that some patients will have complaints related to
229 lymphedema without the objective volume difference. Vice versa, some patients will demonstrate a
230 significant volume difference without complaining from the lymphedema. Therefore the authors
231 suggest to combine an objective assessment with a subjective assessment. We suggest the water
232 displacement method with correction for hand dominance as objective assessment³⁹. The subjective
233 assessment should be a questionnaire that relates to the limitations based upon the ICF-criteria, for

234 instance the LYMPH-ICF questionnaire⁵²; none of the selected studies have used such an approach.
235 Patients with a volume difference between 5-10% and limited complaints on the questionnaire are
236 instructed to self-management of their lymphedema whereas patients with severe complaints or severe
237 volume increase receive full treatment based upon compression, manual drainage and exercise⁵³. Not
238 only therapists but also the patients should be attentive to all possible complications, including
239 lymphedema, that could arise after breast cancer treatment, enhancing the early detection of these
240 complications⁹. Therefore, providing sufficient information, not only about lymphedema but all
241 possible complications^{9,54} after breast cancer treatment, is essential.

242

243 Study limitations

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

248

249

250 Conclusion

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

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257 Conflict of interest

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259 The authors have no conflict of interest to declare.

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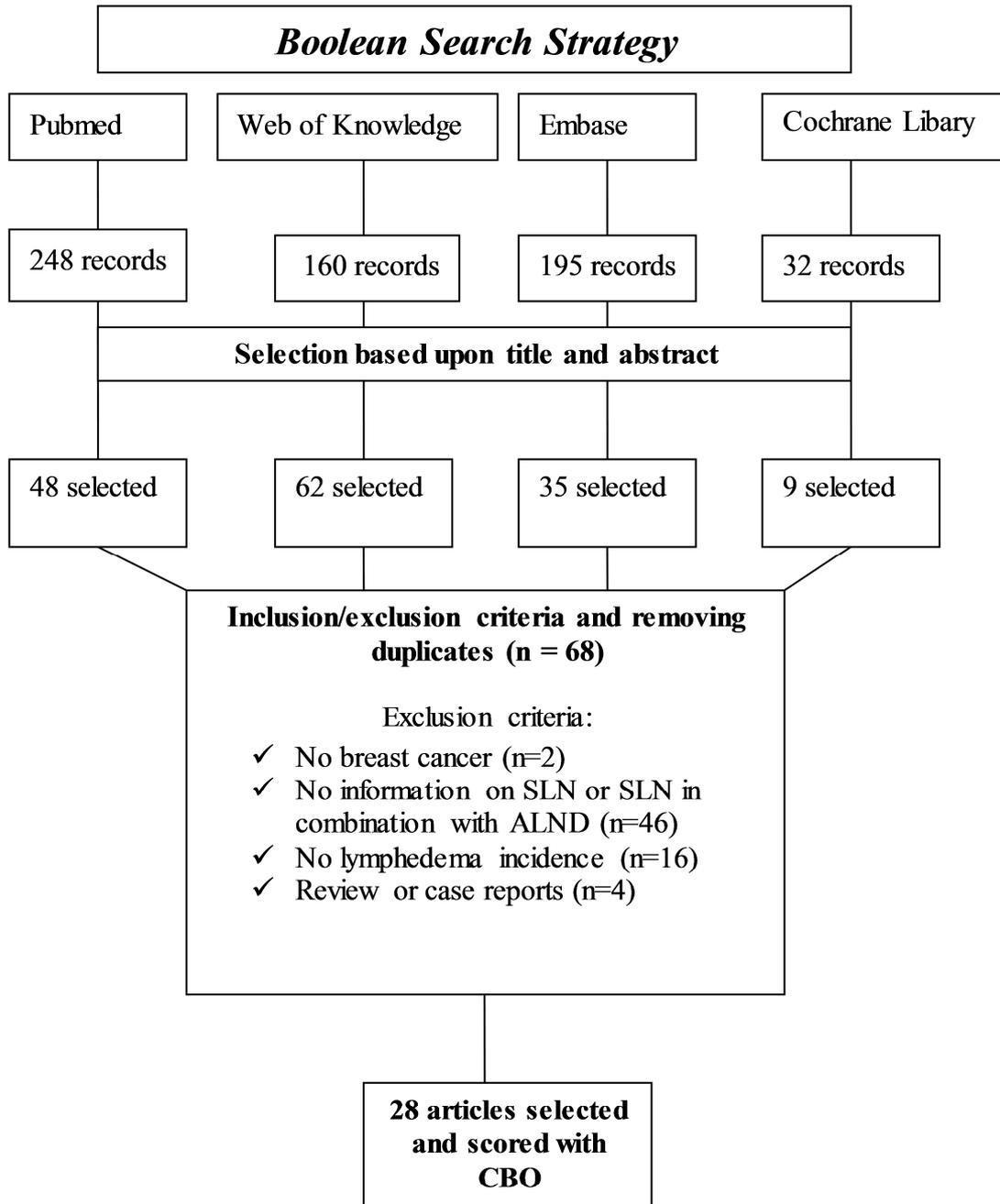
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420 Figure legend

421 **Figure 1: Search strategy flow chart**

422

Table 1: Summary of lymphedema incidence/prevalence and time path of the selected studies

Author, year ^{reference n°}	Lymphedema assessment method	Incidence of lymphedema in SLNB (percentages are in bold)	Time points/follow-up
Design (methodological score)	definition used		
n (n° of SLNB negative patients)			
Armer et al., 2004 ¹¹ Cross-sectional (5/9) n=9	Circumference measurements >2 cm of difference between sides	2/9 patients or 22.2%	4-14 months after surgery; median 8.5 months after surgery
Ashikaga et al., 2010 ¹² RCT (6/9) n=2008	Water displacement <5% diff /5-10% diff/>10% diff	16.7% of 1151 patients have excess volume after 3 year of follow-up (Pts with >5% diff who had <5% diff at baseline). >10% between 7-9%	>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%
Blanchard et al., 2003 ¹³ Cross-sectional (6/9) n=685	Questionnaire	39/683 patients or 6%	Mean follow-up was 2.4y (sd = 0.9y)
Celebioglu et al., 2007 ¹⁴ Cohort (6/9) n=30	Water displacement >10% diff between arms	0/30 patients or 0%	Follow-up: baseline- 1-2-3y
Goldberg et al., 2010 ¹⁷ , 2011 ¹⁶ Cohort (6/9) n=600	Circumference measurements Difference of >2cm = presence of edema Difference of >5cm = severe edema	5% (31/600) had edema of which 3/600 had severe edema	Median follow-up was 5y (2.7-8y)
	Interview	3% (18/600) reported edema	
Golshan et al., 2003 ⁸ Cohort (3/9) n=77	Circumference measurements Difference of >3cm between arms	2/77 or 2.6%	Minimum 1y post-op
Haid et al., 2002 ¹⁸ Cohort (5/9) n=57	Circumference measurements Difference of >2cm between arms	2/57 or 3.5%	mean follow-up time was 25 (range 14–60) months

Langer et al., 2007 ¹⁹ Cohort (7/9) n=449	Circumference measurements Difference of >2cm between arms	15/431 or 3.5%	Mean follow-up time was 31.0 (range 11–62)months
Leidenius et al., 2005 ²⁰ Cohort (4/9) n=92	Circumference measurements Difference of >2cm between arms	1/92 or 1%	3 years post-operative
Lucci et al., 2007 ²¹ RCT (6/9) n=446	Circumference measurements Difference of >2cm between arms	Range = 5.5% - 7.7%	Subjective assessment: 6 months 19/339 or 5.6% 12months 16/268 or 6% >12 months 14/253 or 5.5% Objective assessment: 30 days 17/272 or 6.3% 6 months 21/271 or 7.7% 12 months 14/226 or 6.2%
Lumachi et al., 2009 ²² Cohort (5/9) n=54	Circumference measurements Difference of >2cm between arms	2/54 or 3.7%	median follow-up was 22 months (range 18-28 months)
Husted Madsen et al., 2008 ³⁵ Cohort (6/9) n=164	Water displacement Questionnaire	Range 7-10% (questionnaire)	6 months 10% (questionnaire) 18 months 7% (questionnaire)
Mansel et al., 2006 ⁶ RCT (8/9) n=478	Circumference measurements Self-assessment	3.2% - 5% (self-assessment)	1 month 3.2% 3 months 5% 6 months 4.5% 12 months 5%
Mc Laughlin et al., 2008 ^{24,25} Cohort (6/9) n=600	Circumference measurements Difference of >2cm = presence of edema Difference of >5cm = severe edema Interview	5% (31/600) had edema of which 3/600 had severe edema 3% (18/600) reported edema	Median follow-up time was 5y (range 2.7-8y)

McLaughlin et al., 2013²³ Cohort (5/9) n=67	Circumference measurements 10% or more increase in volume	2-3%	6 months: 2% (1/67) had measured edema 5% (3/67) had edema based upon the questionnaire 11% had perceived edema based upon the interview 12months: 3% (2/67) had measured edema 6% (4/67) had edema based upon the questionnaire 6% had perceived edema based upon the interview
	Questionnaire	5-6%	
	Interview	6-11%	
Ozcinar et al., 2012²⁶ Cohort (8/9) n=80	Circumference measurement >2cm of difference between arms	1.9-8%	Mid-term (9-12 months post-op) 8% Late-term (> 12-64 months post-op) 1.9%
Paim et al., 2008¹⁰ Cross-sectional (3/5) n=48	Circumference measurement >1cm of difference between arms	4.2% (2/48)	Mean 23 months post-op (6-60 months)
Rönka et al., 2005²⁷ Cohort (7/9) n= 43	Circumference measurement Increase in limb volume of 5% or more	12% (5/43)	1 year after surgery
	Self-reported lymphedema (VAS- score)	Mild 9% Moderate 3.5%	
Roumen et al., 2001²⁸ Cohort (4/9) N=90	Questionnaire	0%	Median 24 (16-40) months
Schijven et al., 2003²⁹ Cohort (6/9) n=180	Questionnaire	1.1%	<1y – 3y post-op

Schulze et al., 2006³⁰ Cohort (7/9) n=31	Circumference measurement for the arm in combination with a water displacement for the volume of the hand >10% difference	15.8% (3/19)	Both incidence percentages are presented for long-term morbidities (>20 months post-op; mean 49 months for SLNB)
	Questionnaire	10.5% (2/19)	
Velloso et al., 2011³¹ Cross-sectional (3/5) n=45	Circumference measurements 10% or more increase in volume	4.4%(2/45)	Mean 21.3 (range 10-42) months
Wernicke et al., 2013³² Cohort (7/9) n=111	Circumference measurement >1cm of difference between arms	5.4% (6/111)	Mean 9.4y after surgery (range: 8.3-15.3y)
	Self-assessment by patients	9.1% (10/111)	
Wilke et al., 2006³³ Cohort (6/9) N=4069	Circumference measurement >2cm increase in comparison with baseline measurement	0-7%	0% at 30d of follow-up (n= 4069) 7% at 6month follow-up (n = 2904)
Yen et al., 2009³⁴ Cohort (6/9) n=319	Self-assessment by telephone survey	7%	Median 48 months post-surgery
Francis et al., 2006¹⁵ Cohort (6/9) n=41	Circumference measurements >5% difference in comparison with pre-operative volume	63.4% (26/41)	1 year post-surgery: >5% difference (17/41 or 41%) ≥10%difference (9/41 or 22%)

Table 2: Overview of the incidence ranges at predefined time points with regard to the diagnostic definition used.

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

*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

("Lymphedema"[Mesh] OR "Lymphedema"[All Fields] OR "lymphoedema" [All Fields]) AND ("Breast Neoplasms"[Mesh] OR "Breast Neoplasms"[All Fields] OR "breast cancer" [All Fields]) AND ("Sentinel Lymph Node Biopsy"[Mesh] OR "Sentinel Lymph Node Biopsy"[All Fields] OR "Sentinel"[All Fields] OR "Sentinel lymph node" [All Fields] OR "Sentinel lymph node dissection" [All Fields] OR " lymph node excision" [Mesh] OR " lymph node excision"[All Fields]) NOT review NOT case report