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Title: Axillary reverse mapping in N0 patients requiring sentinel lymph node biopdy – A systematic review of the literature and necessiry of a randomised study

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Abstract

Objectives

Axillary reverse mapping (ARM) is a technique to map and preserve arm lymphatics which may be damaged during surgery, resulting in lymphoedema.

This work systematically reviews the incidence of lymphoedema following sentinel lymph node biopsy (SLNB) + ARM, compared to SLNB alone, for clinically node negative disease, as well as recurrence rate, other morbidity and the feasibility and difficulties of ARM.

Materials and Methods

The following databases were searched: PubMed, Embase, Cochrane Library. Abstracts submitted to recognised societies dedicated to research in oncology were included. Studies were eligible if performed within the last 10 years; ARM was used in any form; ARM performed during SLNB +/- axillary lymph node dissection (ALND). Studies were analysed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

No studies were found meeting the initial inclusion criteria. Therefore, studies reporting use of SLNB + ARM (i.e. no comparison to SLNB) were reviewed. A second search was performed to identify studies reporting outcome following SLNB alone. Twelve studies reported data on patients undergoing SLNB + ARM and 23 studies on patients undergoing SLNB. Incidence of lymphoedema following SLNB + ARM was quoted between 0-4% and 0–63.4% following SLNB. Few studies commented on recurrence rate. Studies included were of mainly low level of evidence.

Conclusion

Evidence is beginning to emerge for the use of ARM in order to reduce lymphoedema following axillary surgery. However, data regarding oncological safety of ARM is not clear and randomised controlled trials, with adequate follow-up, need to be performed to determine this.

Introduction

History

At the turn of the century, breast cancer treatment in the UK moved from axillary lymph node dissection (ALND) [1] to four-node axillary sampling [3]. Even with this reduction in lymph node removal, it was estimated that 60-70% of patients with early breast cancer have no axillary disease and therefore, preservation of these lymph nodes outweighs removal [1, 4]. In the last ten years or so [5, 6] the concept of selecting only the first lymph node(s) draining the breast – the sentinel lymph node(s), has become commonplace. Current National Institute for Health and Care Excellence (NICE) guidance [7] states that minimally invasive surgery should be performed where possible for patients with no evidence of lymph node involvement and this should be by sentinel lymph node biopsy (SLNB).

Lymphoedema

The reported incidence of lymphoedema following ALND ranges from 6% to as high as 77% [1]. SLNB has helped to reduce the incidence of lymphoedema to between 2 - 7%, without impacting on overall survival [8, 9].

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) multicentre randomised trial in clinically node-negative breast cancer patients, compared those who underwent SLNB (n = 515) to those who received standard axillary staging procedure (n = 516) [10]. SLNB was associated with reduced arm morbidity and better quality of life over a 12-month period, with no compromise in efficacy, measured by axillary recurrence rate, local recurrence and survival.

Data on comparable survival between patients undergoing ALND and those having SLNB alone, has been demonstrated in the Phase III study Z0011 trial by The American College of Surgeons Oncology Group [11]. This prospective multi-centre trial compared overall survival between patients with positive sentinel lymph nodes, randomised to receive either ALND or no further axillary treatment

following SLNB. At 1 year, lymphoedema was reported subjectively by 13% (37 of 288) of patients after SLNB + ALND and 2% (6 of 268) after SLNB alone ($p<0.001$). There were no significant differences between the two groups for overall survival, disease-free survival, 5 year in-breast or nodal recurrence.

Concept of axillary reverse mapping

It is hypothesised that there are distinct non-overlapping nodes which drain the arm and the breast respectively [12]. Therefore, by tracing the two different pathways, a technique known as axillary reverse mapping (ARM), it is theoretically possible to resect axillary nodes alone and their draining lymphatics from the breast, subsequently leading to a reduced rate of lymphoedema occurrence following axillary surgery.

ARM involves injection of a radioactive substance, by blue dye, fluorescent dye or radioisotope into the axilla, to highlight the lymphatic drainage pattern of the upper limb. Therefore, lymphatics draining solely the arm can be avoided, as far as clinically able and lymphatics draining the breast alone can be removed as clinically indicated [13].

ARM can be used in N0 patients requiring SLNB or N+ patients requiring ALND.

Oncological safety of ARM

Studies to date suggest that ARM is feasible in clinical practice [13, 14]. Data regarding safety in terms of recurrence; disease-free survival; and absolute benefit in preventing lymphoedema, is lacking. The hypothesis of this review is that the incidence of lymphoedema following SLNB + ARM compared to SLNB alone will be significantly reduced, without increasing regional recurrence of the disease.

Methods and results

This research undertook the form of a systematic review of the literature.

Following the initial search strategy as will be described, there were no articles found making comparisons between SLNB + ARM and SLNB alone, for clinically node negative disease. However, there were studies which did investigate the use of SLNB + ARM on its own, either as descriptive studies or compared to ALND + ARM.

In order to compare the incidence of lymphoedema following SLNB + ARM to SLNB alone, a second literature review was conducted looking at SLNB alone and data collected on incidence of lymphoedema, recurrence rate and other reported morbidity.

The data from the two searches were then compared.

SEARCH 1 - Methods

Search strategy

Studies reporting use of ARM in SLNB procedures compared to SLNB alone, were reviewed. The following online databases were searched for relevant literature: PubMed, Embase, Cochrane Library. Abstracts submitted to recognised international societies dedicated to research in oncology, including the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium and the St. Gallen Oncology Conferences, available online, were included.

SLNB has become commonplace in routine practice in the last decade, therefore, the search was limited to those studies published within the past 10 years (1st December 2005 – 31st December 2015). Studies were restricted to those published in English language and performed in humans. The last search was conducted on 7th February 2016.

The search terms used were: axillary reverse mapping, breast cancer, lymphoedema, sentinel lymph node biopsy.

Inclusion criteria:

- Performance of ARM defined as simultaneous mapping of the breast and axilla
- ARM performed during SLNB with or without completion ALND
- Clinical trial using patient data
- Full-text article or abstract

Exclusion criteria:

- Studies which failed to fulfil inclusion criteria or ARM not used in methodology
- No relation to breast cancer
- Patient data not used

- Duplicate study
- Restricted access to study report/data
- Review article, letter to the editors, editorial report, case report

Data extraction

Data was extracted from the selected studies using a data extraction form. All data was extracted directly from the study text. No further statistical analysis was made where data was not presented.

Data was collected on: publication details; study design; number of participants; number undergoing SLNB/ALND; follow-up period; participant age; ARM technique; stage of tumour; primary breast cancer treatment; ARM node or lymphatics identification and preservations rate; ARM crossover node identification rate; excised ARM nodes and node-positive rate; method of measurement of lymphoedema, incidence of lymphoedema; in-breast and in-axillary recurrence rates; other reported morbidity following the procedure: sensory disturbance; pain; impairment of arm mobility; uniqueness of the study; limitations of study.

Critical appraisal

Once relevant studies were identified and data collected, the studies were assessed using the system proposed by Harbour and Miller [15]. The quality of cohort studies was assessed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. Risk of bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias [17].

Statistical analysis

All extracted data were tabulated and presented as percentages.

SEARCH 1 – Results

Using the initial search strategy, no studies were found meeting the inclusion criteria as outlined above (Figure 1).

As no studies were found comparing SLNB + ARM to SLNB procedures alone, studies which included a group of patients undergoing SLNB + ARM, without comparison to SLNB alone, were analysed. Twelve full-text articles or abstracts were therefore, analysed in further detail (Tables 1 and 2).

Summary Search 1

A total of 12 studies describing the use of ARM during SLNB were eligible for discussion. One of these was a systematic review. The remaining 11 studies were prospective cohort studies.

Overall incidence of lymphoedema following SLNB + ARM was reported between 0 and 6%. Recurrence rate was reported between 0 and 1.2% for local recurrence and between 0 and 6.4% for distant recurrence. Most studies reported semi-permanent tattooing from injection of blue dye in the arm, lasting for up to one year. There were no other major reported morbidities. All studies were able to successfully implement ARM into their clinical practice, without major difficulty.

SEARCH 2 – Methods

As no studies were identified comparing SLNB + ARM to SLNB alone, studies reporting incidence of lymphoedema following SLNB were reviewed. The following databases were used to obtain evidence: PubMed, Embase, Cochrane Library. The following search terms were used: incidence, sentinel lymph node biopsy, lymphoedema, breast cancer.

Again, the search was limited to those studies published within the past 10 years (1st December 2005 – 31st December 2015). Studies were restricted to those published in English language and performed in humans. The last search was conducted on 7th February 2016.

Inclusion criteria:

- Able to determine group on which SLNB was performed
- Clinical trial using patient data
- Full-text article or abstract

Exclusion criteria:

- Studies which failed to fulfil inclusion criteria or SLNB not used in methodology
- Duplicate study
- Patient data not used

Data extraction

Data was collected on: publication details; study design; number of participants; follow-up period; participant age; SLNB technique; stage of tumour; method of measurement of lymphoedema; incidence of lymphoedema; in-breast and in-axillary recurrence rates; other reported morbidity following the procedure: sensory disturbance; pain; impairment of arm mobility.

Critical appraisal and statistical analysis was performed as per Search 1 methodology.

SEARCH 2 - Results

Using the second search strategy, a total of 23 studies meeting the inclusion criteria were identified (Figure 2).

Summary – Search 2

23 studies are presented in this appraisal (Table 3). Two of these studies were systematic literature reviews and the remainder were cohort studies – 8 of these were performed retrospectively and 13 prospectively.

Overall incidence of lymphoedema in patients undergoing SLNB in these studies was quoted between 0 and 63.4%. Local recurrence rate was quoted between 0% and 1% with systemic recurrence at 8%.

A number of other morbidities following SLNB procedure have been documented, including: tattooing at site of blue dye injection; decreased arm function; seroma formation; sensory changes.

Discussion

The results from both Search 1 and Search 2 are discussed in comparison below.

General overview

Overall incidence of lymphoedema following SLNB + ARM was quoted between 0 and 4%. Incidence of lymphoedema following SLNB was found to be as high as 63.4%. The studies included in the initial literature review were generally of a low level of evidence; there was only one systematic literature review and no randomised controlled trials. The studies meeting the inclusion criteria for the second search were again of a relatively low level of evidence; two systematic literature reviews and no randomised controlled trials. It was felt that the data between the two searches were of similar levels of evidence and therefore, comparable.

Comparability of studies

It is noted that the role of ARM is different between studies; ARM can be used in N0 patients undergoing SLNB or N+ patients requiring ALND. Where this information is provided in the study literature, the authors have been able to differentiate between these two groups (see tables).

It is difficult to compare the individual studies included in the initial literature review due to differences in ARM methodology and measurement of lymphoedema. The studies by Kang S et al [25] and Tummel E et al [29] were presented in the form of abstracts, with the remainder being full-text articles. Therefore, less information regarding methodology and findings are given in these two studies.

Regarding the literature review by Ahmed M et al [18] it is difficult to draw conclusions about the overall rate of lymphoedema due to wide variation in methods and timing of measurement. Only one of the studies included was a randomised controlled trial. Recurrence rate was reported by few studies and length of follow-up mainly short-term. It was noted that when performing the ARM technique,

the standard SLNB technique of dual mapping with radioisotope and blue dye is not being used and use of ARM in less experienced units could therefore result in lower sentinel node detection rates.

It is difficult to make comparisons with studies which used less well known methods of ARM such as the study by Ding X [19] who used lymphoscintigraphy and Sakurai T et al [22] and Noguchi M et al [27] who used ICG fluorescence. Sakurai T et al [22] base their methodology and definition of lymphoedema on the literature published by the Japanese Breast Cancer Society [50], specific to characteristics of the Japanese population. Therefore, this may not translate to other cohorts.

It is noted that in the second search, again multiple methods were used for measurement of lymphoedema.

Lymphoedema

Data regarding incidence of lymphoedema was reported in 10 out of the 12 studies in the first search. In the cohort studies, detection of ARM nodes during SLNB (for N0 disease) ranged from 27-75% with overall incidence of lymphoedema reported as 0-4%. In the systematic review [18] figures for ARM detection were 27-100% and lymphoedema 0-6%. There was wide variation in method and timing of measurement of lymphoedema, as well as overall follow-up.

All 10 studies gave some description as to how lymphoedema was measured, ranging from brief description to repeatable, detailed instructions. The studies by Ochoa D et al [21], Tummel E et al; [23] and Boneti C et al [28] described using water volume displacement, with the remaining studies using some form of circumferential arm measurement. The methods used by Ochoa D et al [21] and Boneti C et al [28] appear to be similar. Ochoea D et al [21] used the protocol from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 for arm volume measurements and the International Society of Lymphology guidelines [53, 54] Boneti C et al [28] do not reference their method. Unfortunately, as Tummel E et al [23] present only an abstract, their methodology is not

given. Detection of ARM nodes in these three studies is 33.7%, 33.3% and 40.6% respectively, with incidence of lymphoedema at 2.5%, 0.33% and 0%.

For the studies using circumferential arm measurements, again there is much variation. Ding X [26] and Kang S et al [25] state that measurements are made but do not detail anatomical landmarks for these. The remaining studies detail anatomical landmarks with Kuusk U et al [20] and Casabona F et al [29] using an increase of >1cm from baseline as confirmation of lymphoedema and Sakurai T et al [22] and Connor C et al [24] using >2cm. Detection of ARM nodes in these studies ranges from 27-63.3% with lymphoedema incidence from 0-4%.

There appears to be greater detection of ARM nodes in the studies using circumferential arm measurements for lymphoedema monitoring, but increased rates of lymphoedema detected. This is converse to what would be expected; if more ARM nodes were detected (assuming they were preserved), there should be a lower rate of lymphoedema.

Sakurai T et al [22] and Noguchi M et al [27] use a method of SLNB/ARM which is unique to the study group [32], using preoperative lymphoscintigraphy and intraoperative radioisotope by ICG fluorescence for ARM detection. All other studies use the conventional method of subareolar injection of colloid and injection of blue dye into the arm. Sakurai T et al [22] report an ARM detection rate of 32.3% with no cases of lymphoedema detected, which is in keeping with the results from the other studies. They report 5 cases of lymphoedema which all occurred when the ARM was also the SLN. As this is a presented abstract only, exact incidence and individual cases are not discussed.

It is difficult to make comparisons between the above studies, as noted in the literature review by Ahmed M et al [18] due to the variation in methodology. However, different methods of SLNB/ARM produce similar results, but measurement of lymphoedema by water volume displacement compared to circumferential arm measurements, detects a lower rate of lymphoedema. It is unclear which method is the more accurate.

According to the international consensus ‘Best Practice for the Management of Lymphoedema [55]’, published in 2006 and in a more recent review by Armer J et al [56] several staging systems for lymphoedema have been devised, including the International Society of Lymphology System, which classifies lymphoedema according to visual changes. They admit that no one method of measurement has achieved international agreement and each has its limitations, but suggest that water volume displacement is the gold standard method for calculating limb volume, however, circumferential measurements are the most commonly used.

The consensus states that circumferential limb measurements can be reliable if a standard protocol is followed. They suggest taking the measurement on the ulnar aspect of the arm and recording the distance from the nail bed of the little finger to 2cm above the ulnar styloid (wrist) and thus at 4cm intervals from the starting point to 2cm below the axilla. A simplified method is also proposed that requires taking measures at: around dorsum of hand, 10cm below the point of the elbow (olecranon process); 10cm above the olecranon process.

The consensus states that lymphoedema is considered if the volume of the swollen limb is more than 10% greater than that of the contralateral unaffected limb and goes on to suggest classification into ‘mild’ ‘moderate’ or ‘severe’ categories, with limb volume <20%, 20-40% and >40% respectively.

It is clear from this present review, that some elements from the International Consensus are being considered when forming methodology for these studies, but not strictly adhered to.

Regardless of difficulty in comparing individual studies as mentioned above, there is a clear difference in reported rates of lymphoedema following SLNB alone (0-63.4%) compared to SLNB + ARM (0-4%). Looking at the studies commenting on lymphoedema following SLNB alone, 10 of the 22 studies (45%) had rates of ≤5%. In 7 out of 9 (78%) studies commenting on lymphoedema following SLNB + ARM, had rates of ≤5%. This may have significant clinical implications on axillary surgery, should the method prove to be oncologically safe.

Recurrence rate

A total of 8 of the studies in the first search gave information regarding number of nodes excised. For SLNB alone, number of nodes excised varied between 0 and 5. This compares to between 9 and 45 for ALND. Only 4 studies commented on recurrence rate.

Kuusk U et al [20] reported that there were no axillary recurrences in their study group. This group had a crossover rate (ARM node equivalent to SLN) of 9.6% and these nodes were positive for malignancy in 2% of cases. They report that one patient died before 24 months of an unrelated metastatic head and neck squamous cell carcinoma. This is the smallest study to report on recurrence rate.

The study by Ochoa D et al [21] provides information on axillary recurrence as well as distant and local recurrence. In this study crossover rate was 4.3% and these were positive for malignancy in 14.3%. Overall, ARM nodes were positive for malignancy in 18.5% of cases. Ochoa D et al [21] state that blue lymphatics were identified in a total of 173 patients and were able to be preserved in 79.2%. In this group where the lymphatics were preserved, there were 11 (6.4%) distant recurrences and 2 (1.2%) local recurrences. There was one axillary recurrence over an average follow-up of 12 months which was found at 17 months of follow-up in a patient in which blue dye was not identified and therefore no blue nodes were specifically preserved. The authors note that this patient underwent surgery for T2N1 disease and had known metastatic spread to the liver.

Tummel E et al [23] and Kang S et al [25] both present abstracts which identify no axillary recurrences and no locoregional recurrences respectively. Tummel E et al [23] is the largest study to report on recurrence rate. Due to the nature of these reports, details regarding positivity of ARM and crossover nodes are lacking.

It is difficult to make comparisons between these studies as they have different follow-up periods and comment on different measures of recurrence. The study by Ochoa D et al [21] provides us with the

most information and is of a generous sample size. Predicted recurrence rate is clearly related to stage of the disease and this is only reported in Ochoa's paper. However, the authors felt that this fairly large trial with good length of follow-up is a surrogate for the safety of ARM. This is particularly true for patients with 4N+ who receive radiation therapy anyway.

The Z0011 trial which has been previously mentioned [11] is a prospective multi-centre trial comparing patients who had SLNB alone or ALND, following positive sentinel lymph nodes. They report a local recurrence rate following SLNB of 1.8% and regional recurrence rate of 0.9% with no significant differences between the two groups for overall survival, disease-free survival and 5 year in-breast or nodal recurrence [11, 56]. These low figures are in keeping with the findings in this current review.

It is difficult to make comparisons between recurrence rate following SLNB compared to SLNB + ARM due to differences in how this was measured and the small number of studies which reported this. Following SLNB, local recurrence was reported between 0 – 3.6% and systemic recurrence at 1.5 - 8%. Following SLNB + ARM, local recurrence was reported between 0 – 1.2% with distant recurrence at 6.4%. From this data, it appears that recurrence rates are comparable for the two procedures, but more evidence is needed in this area.

Other morbidity

The most common morbidity mentioned other than lymphoedema following ARM, was presence of tattooing at injection site in the arm. Five of the studies, Kuusk U et al [20], Connor C et al [24], Deng H et al [26], Noguchi M et al [27] and Boneti C et al [28], reported temporary tattooing at the injection site for between a few days up to one year. Connor C et al [24] reported one case of skin necrosis at the site of blue dye injection which resolved with topical wound care. No allergic reactions or other problems were reported from method of ARM.

It was commented on in the study by Ding X [19] that there was some trend towards improved arm function in the group who had ARM success as opposed to ARM failure, however, this was not statistically significant.

No other morbidities were specifically reported or had data collected on in any of the studies.

A large number of morbidities were reported following SLNB alone including increased pain, decreased range of arm motion, change in sensation and seroma formation. These morbidities were not frequently mentioned in the SLNB + ARM studies, although it was not the intention of any of the SLNB + ARM studies to report this. As SLNB is a well-practiced procedure proven to be oncologically safe (when compared with ALND), it is suspected that more recent studies have been able to focus more on other reported morbidity following SLNB and that with time, this will be the same of SLNB + ARM.

Feasibility/difficulties

In general, all studies were able to carry out the ARM procedures in their institution and this was echoed in the systematic review [18]. The largest study in that review was the one presented by Ochoa D et al [21] and they reported a lymphoedema rate of 2.5% for SLNB alone and 2% when ARM is used. They propose that this very small difference suggests that the inability to identify ARM lymphatics is not necessarily a 'failed' ARM procedure, but rather provides reassurance that lymphatic drainages of the arm and breast are not in close proximity to the SLN and therefore, do not pose risk of lymphoedema.

It is important to recognise that when performing the ARM procedure, the standard SLNB technique of radioisotope and blue dye is not being used. Although in the majority of studies the SLN identification rate was within expected levels, use of the ARM procedure in less experienced units could result in lower SNB detection rates. A potential technique to overcome this would be the administration of different radioactive tracers for the ARM and SNB procedure or by the addition of

other dyes, for example indocyanine green, as in the studies by Sakurai T et al [22] and Noguchi M et al [27], to replace the blue dye in the upper limb mapping.

Limitations

As already discussed, there were no studies identified comparing SLNB to SLNB + ARM, as per the aim of this study, therefore, two sequential literature reviews were performed instead in order to answer the study objectives.

This systematic review is limited in its ability to accurately assess lymphoedema outcomes using ARM. The included studies used a range of definitions of lymphoedema, methodology of measurement of lymphoedema and generally of low levels of evidence, making it difficult to draw solid conclusions.

It is noted that many other factors affect rate of lymphoedema and these have not been specifically examined in this systematic review, for example, adjuvant radiotherapy and chemotherapy, body mass index, multiple surgeries.

It was not always possible in the studies to separate patients who had SLNB alone to those who had SLNB and later went on to have ALND. This means that lymphoedema rates may have been overestimated in this review.

There was only one systematic review included in search one and two included in search two, in this analysis and no randomised controlled trials, thereby the evidence base for this review is generally low.

Clinical relevance

This literature review reveals that there is some evidence to support introduction of ARM in addition to SLNB, in an attempt to reduce incidence of lymphoedema in breast cancer patients. ARM by a variety of methods, appears feasible and has not posed any particular problems to individual institutions. However, at present, it is unclear regarding the oncological safety of the procedure and the impact ARM has on local and regional recurrence. Data regarding other potential morbidities such as arm pain, sensory disturbance and reduced arm movements, is lacking. Therefore, at the present time, this literature review does not show enough evidence to mandate the introduction of ARM into current cancer guidelines.

Further work

In order to be able to introduce ARM into routine clinical practice, a large, randomised controlled trial specifically comparing SLNB + ARM to SLNB alone should be performed. All breast cancer patients who meet the criteria for SLNB would be eligible to participate. Participants would be randomised to either receive routine care of SLNB alone or to have SLNB + ARM. Lymphoedema should be measured by a well-defined, reproducible measure, by either water volume displacement or circumferential arm measurements, in accordance with the international consensus 'Best Practice for the Management of Lymphoedema' guidelines [30], as previously discussed. Arm volume/circumference should be measured preoperatively and then at defined intervals postoperatively, such as every 6 months. Length of follow-up must be adequate, for example, up to five years. As well as lymphoedema, local and regional recurrence rate should be examined.

This would be an opportunity to examine other factors which firstly may impact on lymphoedema and secondly may be an adverse feature of ARM procedure. Other factors include: administration of chemotherapy and/or radiotherapy pre- and postoperatively; need for further surgery; patient body weight/BMI; level of physical activity. Suggested adverse features of ARM may include: reduced arm movements, sensory disturbance and increased arm pain.

Patients included in the study should be stratified by stage of cancer and by age.

The benefit of this research would be the ability to counsel patients preoperatively on their comparative risks of lymphoedema should they proceed with SLNB + ARM, compared to SLNB alone, as well as possibility of metastatic involvement in crossover nodes and overall recurrence risk.

It is noted that there would be difficulties in performing a randomised controlled trial in this case for a number of reasons. A large number of patients will need to be recruited to show clinical difference between the two arms and patients would need to be followed up for a long time peroid. This is because there are currently very low rates of regional recurrence following SLNB for N0 disease, partly due to the efficacy of modern optimal adjuvant therapies. There is also a low rate of lymphoedema already following SLNB for N0 disease. As previously mentioned there are many discrepancies in the measurement of lymphoedema and this could propose a major bias to the study.

Conclusions

There is some evidence to support introduction of ARM in addition to SLNB for selected breast cancer surgical patients. However, the current literature is of mainly low level evidence and casts doubt over long-term oncological safety of ARM. Current studies are hampered by differing methodology of performance of ARM and measurement of lymphoedema.

Therefore, a prospective randomised controlled trial is required to formally assess SLNB + ARM compared to the current recommended axillary procedure of SLNB. This would be an opportunity to take into account other factors which impact on development of lymphoedema such as body weight and post-operative systemic treatments as well as to examine possible long-term negative consequences of ARM.

Legend to figures:

Figure 1: Search 1 - Selection of studies for review

Figure 2: Search 2 – Selection of studies for review

Legends to tables:

Table 1: Search 1 - Demographics from full-text articles and abstracts

Table 2: Search 1 - Results from full-text articles and abstracts

Table 3: Search 2 – Results from full-text articles and abstracts

Conflicts of interest

There are no conflicts of interest to declare

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Ethical approval was not required for this work

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Figure 1: Search 1 - Selection of studies for review

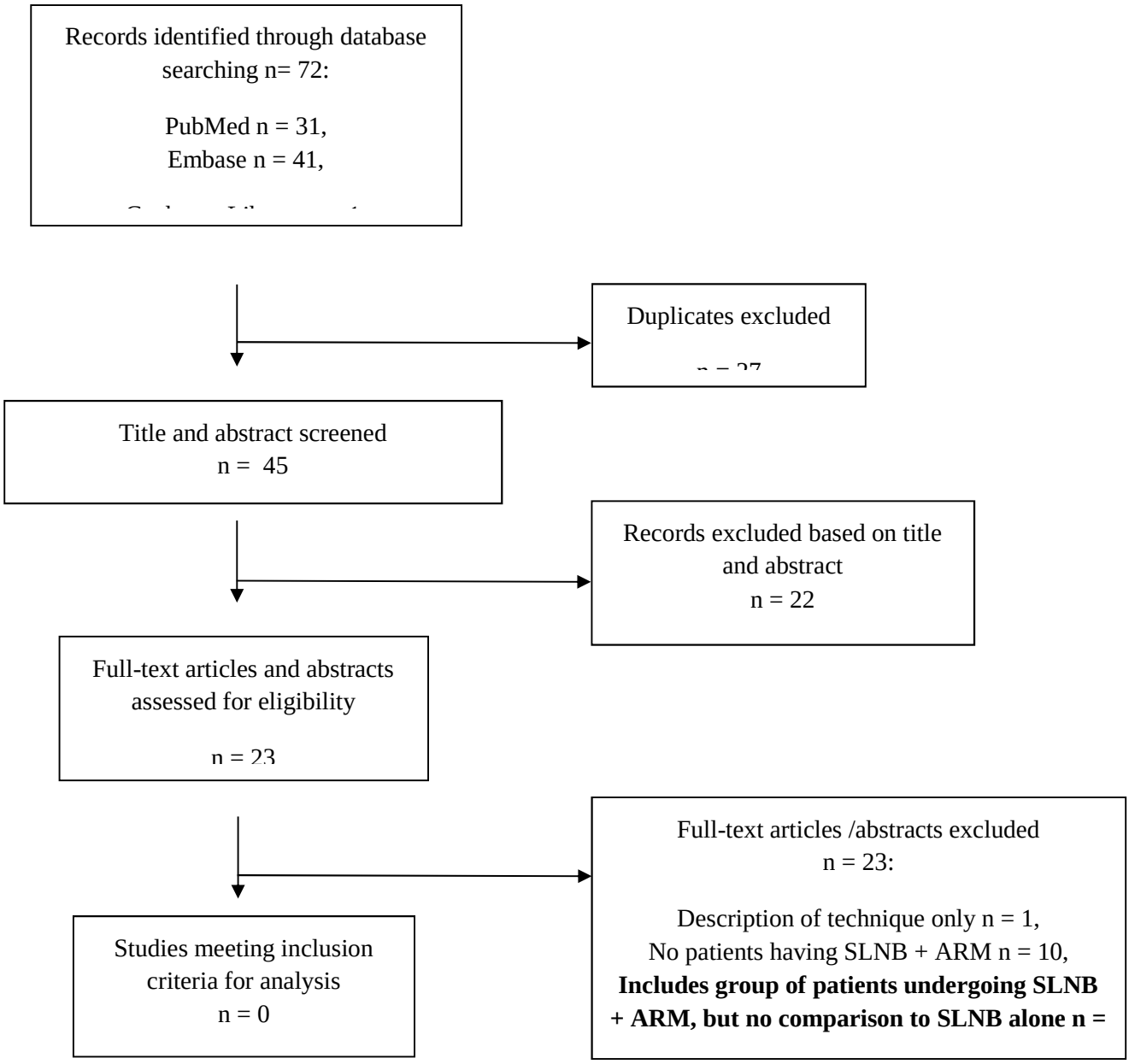

Table 1: Search 1 - Demographics from full-text articles and abstracts

Date	Study	Context	Lvl	N	Age (yrs)	Stage	Axillary status	Primary treatment	Method of SLNB	Method of ARM	Measurement of lymphoedema
Dec 2015	Ahmed M et al [18]	Systematic review of ARM used alongside SLNB or ALND	2	1142				SLNB or SLNB + ALND or ALND	Majority used radiolabeled nanocolloid subareolarly	Majority used 1-5ml blue dye SC, SD or IM in upper arm	Different definitions used in each study
Dec 2014	Kuusk U et al [20]	Single centre prospective study assessing ARM to preserve lymphatics	3	52	56 (30-74)	Locally advanced axillary disease excluded	28.8% known nodal breast cancer metastases	Partial Mx 56.6%; total Mx 42%; SLNB + ARM for N0 patients (n=37) or ALND + ARM for N+ patients (n=15)	Technetium-99 sulfur colloid subareolar	1-2ml patent blue dye into upper inner arm	Circumferential measurements of both arms 15cm above elbow, 10cm below elbow, at the wrist; defined as increase of 2cm
Nov 2014	Ochoea D et al [21]	Prospective, non-randomized cohort study to evaluate	3	360	56	93.3% invasive:	32.4% positive:	Mastectomy or lumpectomy. SLNB + ARM for N0 patients	Subareolar injection of technetium sulfur colloid and handheld gamma probe	5ml blue dye SC in volar surface of arm	Water volume displacement

		feasibility of ARM and effect on lymphoedema				T1 67%; T2 24.4%; T3 6.5%	N1 76.1%; N2 15.5%; N3 8.3%	(n=237); ALND + ARM for N+ after positive SLNB; (n=111); ALND for N+ patients detected preoperatively (n=12)			
May 2014	Sakurai T et al [22]	Prospective study to identify at-risk groups for postoperative lymphoedema following ARM + SNB. 'Corresponding [C]' group displayed upper extremity lymphatic	3	321: 'C' 76; 'Non-C' 245	'C': 59 (24-80); 'Non-C': 58 (28-88)	'C': Tis 16; T1 39; T2 19; T3 2. 'Non-C': Tis 54; T1 131; T2 52; T3 8.	Clinically negative	Surgery + SLNB + ARM for N0 patients (all patients)	Preoperative lymphoscintigraphy and intraoperative radioisotope (99mTc-phytate) + dye (indigocarmine)	ICG fluorescence SC into interdigital area and indigo carmine blue dye upper one third of the arm	Bilateral arm circumference based on international consensus of breast practices for management of lymphoedema. 1-2cm expansion defined as mild oedema and >2cm

		drainage into the breast SN									
Mar 2014	Tummel E et al [23]	Prospective assessment of use of ARM as a method to reduce rates of lymphoedema in axillary surgery	3	447			14 had positive axilla preoperatively	SLNB + ARM for N0 (n=303); ALND + ARM for N+ after positive SLNB (n=130); ALND + ARM for N+ preoperatively (n= 14)	Subareolar injection of technetium	5mls lymphazurin injected into upper arm	Volume displacement
Oct 2013	Connor C et al [24]	Prospective non-randomised trial to investigate ARM in a population of clinically node negative and node positive	3	184	60		SLNB all clinically negative; ALND group 25% clinically positive	SLNB + ARM for N0 (n=155): 25% received NAC, 22% performed during prophylactic mastectomy. ALND + ARM for N+ disease	Subareolar injection of technetium sulfur colloid and gamma probe detection + blue dye	2-5ml of blue dye into dermal/SC tissue into medial intramuscular groove	Bilateral measurements at levels of meta-carpal phalangeal joints, wrist, 10cm above the wrist, at the elbow, 10cm above the elbow; Increase >2cm from baseline considered positive.

		breast cancer patients						(n=57): 75% followed NAC			
Mar 2013	Kang S et al [25]	Prospective study to investigate the location and metastatic rate of the ARM node and evaluate differences in lymphoedema	3	116				ARM node preserved: SLNB + ARM for N0 disease (n=10), ALND + ARM for N+ disease (n=87); ARM node unpreserved: SLNB + ARM (n=4), ALND + ARM (n=15)		2.5ml blue dye injected into upper-inner arm	Measured pre- and post-operatively
Aug 2011	Deng H et al [26]	Prospective study to clarify risk factors for metastasis in arm lymphatic drainage in breast cancer	3	69	47.99	0 2.9%; I 44.9%; IIa 46.4%; IIb 5.8%	N0 73.9%; N1 17.4%; N2 7.2%; N3 1.4%	BCS 80.5%; SLNB + ARM for N0 (all patients)	0.5ml technetium-99m nanocolloid to nipple-areola complex	1ml methylene blue dye SC upper inner arm along medial intramuscular groove	

		patients with negative axillary nodes									
Mar 2010	M Noguchi et al [27]	A prospective feasibility study to improve identification of ARM nodes and/or lymphatics	3	20	63.3 (37-85)	T1 40%; T2 40%; T3 15%; T4 5%	N0 70%; N1 15%; N2 15%	Total Mx 11, partial Mx 9; SLNB + ARM for N0 (n=12), ALND + ARM for N+ (n=8).	2mCI Tc-99m-phytate into two peritumoral sites; lymphoscintigraphy.	0.1ml ICG subdermally inner wrist, 2ml ICG subdermally upper inner arm + near-infrared fluorescence imaging system	
Oct 2009	Boneti C et al [28]	A prospective study to assess efficacy of ARM to preserve lymphatics in order to reduce incidence of lymphoedema	3	220	60.3 ± 11.3		Clinically negative	SLNB + ARM for N0 (n=173), ALND + ARM for N+ (n=40)	Subareolar plexus injection 1.0 mCI of technetium sulfur colloid	2-5ml blue dye injected dermally and then later SC upper inner arm	Water volume displacement: immerse upper extremity to 10cm above elbow. Asymmetrical increase in volume >20% from baseline

Sept 2009	Casabona F et al [29]	Prospective study to evaluate feasibility of ARM during SLNB	3	72	57 (25-81)	SLNB: T1a 15.9%; T1b 27.0%; T1c 57.1% ALND: T1c: 100%	Clinically negative	Quadrantectomy 70.8%, Mx 8.3% WLE 20.8%; SLNB + ARM for N0 (n=63), ALND + ARM for N+ at SLNB (n=9)	Subareolar injection of 40 MBq technetium-99m nanocolloid.	2ml dermal blue patent injected intradermally, SC and IM in upper inner arm along medial intramuscular groove	Circumferential measurements. Lymphangioscintigraphy in patients who underwent LYMPHA. Measurements: starting at olecranus, then at 5, 10 and 15cm intervals distally and 5, 10, 15 and 20cm intervals proximally. Lymphoedema defined as >1cm difference.

Abbreviations: ALND, axillary lymph node dissection; ARM, axillary reverse mapping; BCS, breast conserving surgery; CT, chemotherapy; ICG, indocyanine green; IM, intramuscular; LYMPHA, lymphatic microsurgical preventing healing approach; Lvl, level of evidence; Mx, mastectomy; N, number of participants; NAC, neoadjuvant chemotherapy; SC, subcutaneous; SD, subdermal; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; Tis, in situ; WBI, whole breast irradiation; WLE, wide local excision

Table 2: Search 1 - Results from full-text articles and abstracts

Study	Follow-up (months)	Identification of ARM nodes/lymphatics	% of crossover (SLN = ARM)	# of LNs removed	Pathology result ARM nodes	Pathology result crossover nodes	Rate of lymphoedema	Other morbidity	Recurrence rate
Ahmed M et al [18]	SLNB 4.3–36; ALND 6.3-7.5	SLNB 27-100%; ALND 78.3-100%	SLNB 10%	SLNB 0-5; ALND 11-13		SLNB 14-20%; ALND 0-19%	SLNB 0-6%; ALND 0-6%		SLNB: 1.2% breast; 0.4% axillary
Ding X [19]		63.3%	8.3%		3.2%	40%	Higher rate in group of ARM failure ($p<0.05$)	ARM may improve upper limb function	
Kuusk U et al [20]	24 (6-36)	27%	SLNB 5.4%;	SLNB 2.8; ALND 11.5		SLNB 0%;	SLNB 2.1% (1/47)	Blue tattoo present for up	0%

			ALND 13.3%			ALND 6.6%		to 1 year in ‘most’ patients	
Ochoea D et al [21]	Total 12 (±13.6); lymphoedema assessment 10 (range 3-48)	SLNB 33.7%; ALND 75.4%	SLNB 4.3%		18.5%	14.3%	Overall: Subjective 8.4% (20/238); objective 2.9% (7/238): SLNB 2.5% (4/158), ALND 3.7% (3/80)	Subjective complaints of ‘lymphoedema’ resolved with pain management	Distant 6.4%; local 1.2%
Sakurai T et al [22]	28 (12-47)	32.3%	20.7% (Non-C group)	‘C’: 1.51 (1-6). ‘Non-C’: 1.80 (1-6)			‘C’: 5/76 ‘Non-C’: 0/245 This was statistically significant	Lymphoedema more likely associated with post-operative CT and WBI	
Tummel E et al [23]	24 (3-54)	SLNB 33.3%; ALND 77%	SLNB 3%; ALND 14%			SLNB 0%; ALND 15%	SLNB 0.33%; ALND 5.5%		SLNB 0%, ALND 0.7%

Connor C et al [24]	12	SLNB 47%; ALND 72%	SLNB 12%; ALND 10%	SLNB 3; ALND 20	SLNB 0%; ALND 18%	SLNB 0%; ALND 25%	SLNB 4% (6/137)	One patient experienced skin necrosis at site of blue dye injection at upper inner arm (0.5%)	
Kang S et al [25]	16.24 (3-24)	Mean number of identified blue stained nodes 1.41 +/- 0.66		1.41 ± 0.66	Unpreserved: 4.3%		SLNB: no difference between preserved and unpreserved group ALND: arm circumference greater in arm unpreserved group (p=0.066); 0% ARM node preserved group, 5.2% unpreserved group.		0%
Deng H et al [26]			27.5%		8.7%	31.6%		Mild blue mark at injection site for up to 4 weeks in the	

								‘majority’ of patients	
M Noguchi et al [27]	10 days	SLNB 75% ALND 88%	14%	SLNB 1.2 (1-2); ALND 23.5 (13-45)	SLNB 0%; ALND 43%	0%		Temporary tattoo at injection site for up to 10 days	0%
Boneti C et al [28]	6	SLNB 40.6%; ALND 47; SLNB + ALND 40 (18.7%)	2.8%	ALND 12.7 +/- 5.6	SLNB 0%	0%	5.4% overall; 0% SLNB	Temporary tattoo for up to few months in ‘most’ patients	
Casabona F et al [29]	9	SLNB 37.5% ALND 88.9%		SLNB 1.3 ALND 16 (9-24)	0%		0% (0/72)		0%

Abbreviations: ALND, axillary lymph node dissection; ARM, axillary reverse mapping; BCS, breast conserving surgery; CT, chemotherapy; ICG, indocyanine green; IM, intramuscular; LYMPHA, lymphatic microsurgical preventing healing approach; Lvl, level of evidence; Mx, mastectomy; N, number of participants; NAC, neoadjuvant chemotherapy; SC, subcutaneous; SD, subdermal; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; Tis, in situ; WBI, whole breast irradiation; WLE, wide local excision

Figure 2: Search 2 – Selection of studies for review

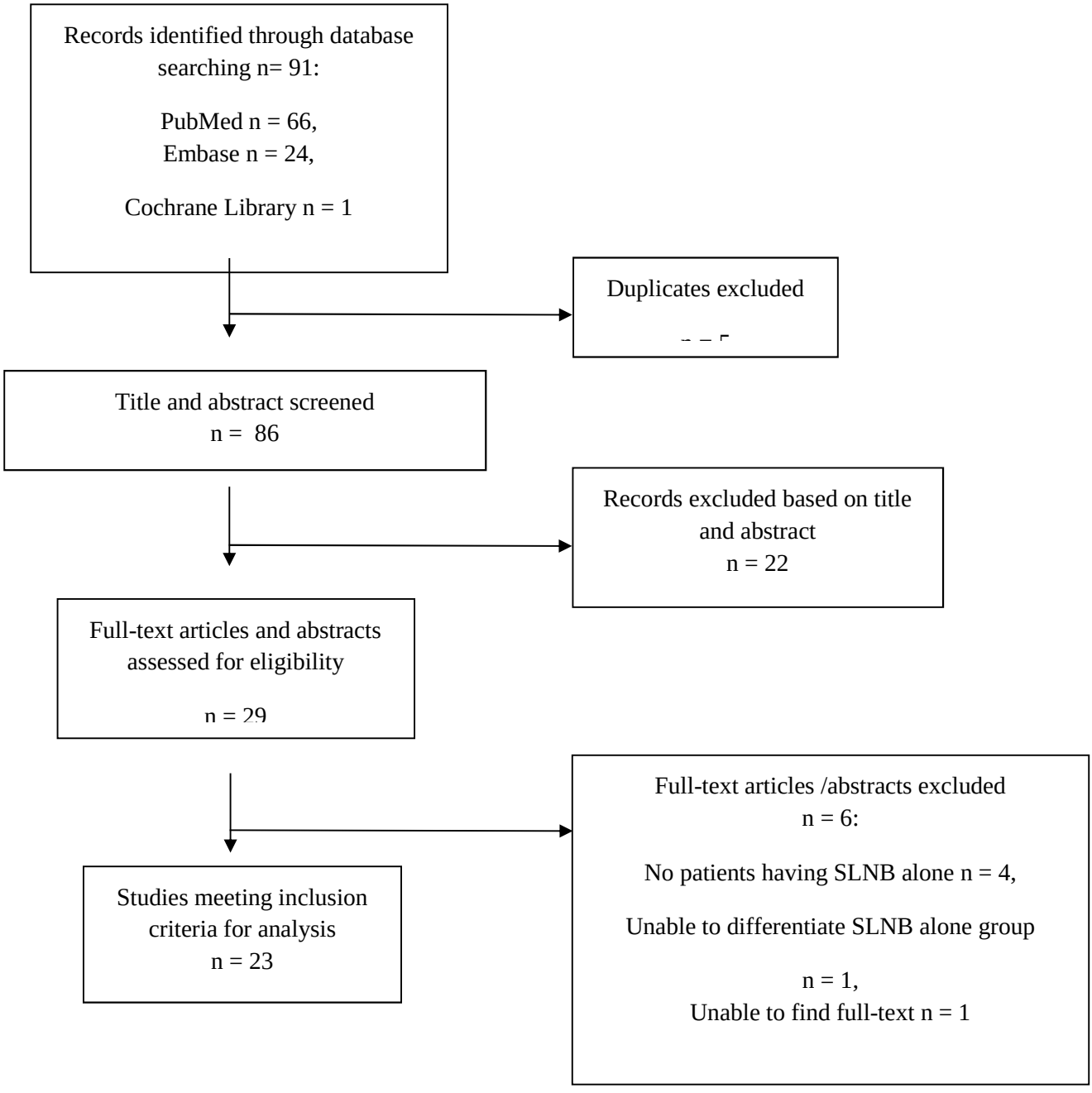

Table 3: Search 2 – Results from full-text articles and abstracts

Date	Study	Context	Lvl	N	Stage	Axillary treatment	Method of SLNB	Measurement of lymphoedema	Follow-up (months)	Rate of lymphoedema	Other morbidity	Recurrence rate
Dec 2015	Voss R et al [30]	Prospective cohort study to investigate risk factors for lymphoedema in breast cancer and melanoma	3	205	0 8%; I 43%; II 31%; III 12%; IV 3%	SLNB for N0 disease (n=107), ALND for N+ disease (n=98)	According to surgeon's preference	Perometry measured at 9, 6, 12 and 18 months. Moderate/severe lymphoedema defined as limb volume change ≥10%	18	36.5% overall	Upper-extremity numbness, tightness, aching, swelling, stiffness and heaviness	
Jun 2015	Li J et al [31]	Prospective study investigating accuracy of SLNB compared to partial ALND	3	289		SLNB for N0 (n=221), partial ALND following positive SLNB (n=59), partial ALND due to failed SLNB (n-9), partial ALND for	Methylene blue dye into tumour bed/areola	Arm circumference at the point of 10cm proximal to the medial epicondyle before surgery and at 12 months. Severe lymphoedema	12-33	0% following SLNB		Overall survival 97.2%; death 3%; local recurrence 0%

						patient choice (n=149)		diagnosed at increase ≥2cm				
Jun 2015	Gebruers N et al [32]	Systematic literature review to assess incidence of lymphoedema in node-negative breast cancer	2	9588		SLNB for N0 (all patients)		Variety of methods, at ≤3, 6, 12, 18 or >18 months		0-63.4%		
Dec 2014	Fu Y et al [33]	Retrospective analysis of primary breast cancer patients undergoing SLNB or ALND	3	214	T1 46.2%; T2 44.3%; T3 6.6%; Tx 2.8%	SLNB for N0 (n=39), ALND for N+ (n=112)	Peritumoral/periareolar injection of 99m Tc-labeled sulfur colloid and 1% isosulfan blue dye	Self-reported as well as circumferential measurement of both arms at wrist, forearm and upper arm	Median 43.6	7.7% following SLNB	Pain, limited range of motion	Local recurrence 0%
Oct 2014	Fu M et al [34]	Prospective cohort study to investigate lymphoedema risk reduction measures	3	134		SLNB for N0 (n=59), ALND N+ (n=75)		Perometer at baseline, 2-4 weeks, 6 months and 12 months. Lymphoedema		3% at 2-4 weeks following SLNB		

								defined as increase ≥10%.				
Aug 2014	Black D et al [35]	Retrospective study to determine racial differences in SLNB use among patients with node-negative breast cancer	3	27856 white, 1767 black		SLNB for N0 (n= 20530 white population, 1103 black population); ALND for N+		Variety of methods	5 years	6.8% white population; 8.8% black population following SLNB		
Aug 2014	Gärtner R et al [36]	Retrospective review of follow-up questionnaire study looking at lymphoedema in primary breast cancer patients	3	2293		SLNB for N0 disease + chemotherapy (n=45) or without chemotherapy (n=61), ALND for N+		Questionnaire: 'Does the armpit, the arm of the back of the hand, on the side where you were operated, sometimes or always feel swollen or heavy?'; severity on 0-10;	9-11 years	SLNB + chemotherapy 17%; SLNB alone 10%		

								frequency of symptoms				
May 2014	Sánchez P et al [37]	Retrospective observational study to analyse lymphoedema in breast cancer patients undergoing SLNB	3	145		SLNB for N0 (all patients)				8.4%	Seroma	
May 2014	Sagen A et al [38]	Prospective cohort study to examine upper limb function following ALND and SLNB	3	391	Early-stage primary breast cancer	SLNB for N0 (n=161), ALND for N+		≥10% increase in arm volume relative to control arm volume defined as lymphoedema	2.5 years	3% following SLNB	Grip strength reduction, shoulder abduction-provoked pain	
Feb 2014	Miller C et al [39]	Prospective study evaluating rates of lymphoedema in mastectomy patients	3	664		SLNB for N0 + no radiotherapy (n=34), SLNB + radiotherapy (n=58), ALND for N+ no radiotherapy		Perometer arm volume measurements pre and post-operatively; lymphoedema defined as ≥10%	2 years	SLNB + radiotherapy 10%; SLNB alone 2.19%		

						(n=229), ALND + radiotherapy (n=229)		increase in arm volume				
Jan 2014	Morcos B et al [40]	Prospective cross-sectional study assessing risk factors for developing lymphoedema following breast cancer	3	499		SLNB for N0 (n=90), ALND for N+		Mid-arm of forearm circumference difference between both limbs of 2cm of more	26.2	4.5% following SLNB		
Sept-Oct 2013	Burger A et al [41]	Retrospective review of prospectively maintained database of patients undergoing risk reducing mastectomy	3	83		SLNB for N0 (all patients)				0%		
May 2013	DiSipio T et al [42]	Literature review assessing lymphoedema	2	18 studies				Variety of methods		5.6% following SLNB		

		following breast cancer										
Mar 2013	McLaughlin S et al [43]	Prospective study evaluating lymphoedema following ALND and SLNB	3	120		SLNB for N0 (n=67), ALND for N+ (n=53)		Circumferential measurement at 4cm increments from nail bed base of middle finger to axillary fold		3% at 12 months following SLNB		
Feb 2013	Wernicke A et al [44]	Retrospective review of stage I-II breast cancer patients investigating complication rates	3	226	TI 82%, T2 18%	SLNB for N0 (n=111), ALND for N+ (n=115)		Objective measurement at baseline and each follow-up visit at antecubital fossa, 10cm superior, 10cm inferior and at the wrists. Lymphoedema defined as difference >1cm.	9.4 years (8.6 – 15.2)	5.4% following SLNB	Axillary web syndrome, seroma, wound infection, decreased range of shoulder movement, paraesthesia	In-breast recurrence 3.6%; distant metastases 1.5%.
Jun 2012	Ozcinar B et al [45]	Prospective observational study to examine	3	218	Early stage	SLNB for N0 (n=80), ALND for N+ (n=138)		10cm proximal and distal to olecranon, pre	Median 64	8% following SLNB		

		lymphoedema in early-stage breast cancer patients						and post-operative measurements. Lymphoedema defined as >2cm increase				
Nov 2011	El-Asir L et al [46]	Retrospective analysis of patients undergoing SLNB and/or ALND to determine incidence of lymphoedema	3	678		SLNB for N0 (n=365), ALND for N+ (n=313)				0.2% following SLNB		
Aug 2011	Aslani N et al [47]	Retrospective review of prospectively collected database comparing patients undergoing SLNB with	3	185	T1 54.7%; TII 41.1%; TIII 3.2%; TIV	All patients N+ at SLNB. Patients undergoing no further procedure (n=95) or ALND (n=90).			36 (median 1.9 years)	7% following SLNB	Pain, tethering or stiffness in the axilla, radiation pneumonitis	Locoregional recurrence 1%, systemic recurrence 8%

		completion ALND			1.1%							
Jan-Feb 2010	Helyer K et al [48]	Prospective study to determine predictors of lymphoedema in patients undergoing SLNB +/- ALND	3	137		SLNB for N0 (n=52), ALND for N+ (n=31). ALND for N0 to detect false-negative (n=54)	Radioactive colloid and/or isosulphan blue dye. Lymphoscintigraphy for patients who underwent radioactive colloid injection.	Arm volume measurements preoperatively and then every 6 months: arm submersed in 10cm above olecranon and volume recorded. Lymphoedema defined as measurement changes of >200cc.	Median 20 (6 – 36)	37.5% following SLNB		
Nov-Dec 2009	Lumachi F et al [49]	Retrospective review of patients who underwent curative surgery for primary breast cancer	3	205		SLNB for N0 (n=54), ALND following positive SLNB (n=48) using ultrasound scissors, ALND for N+ using				3.7% following SLNB		

						ultrasound scissors (n=53), ALND for N+ by traditional methods (n=50)						
Nov 2008	McLaughlin S et al [50]	Prospective study to compare incidence of lymphoedema in patients undergoing SLNB compared to SLNB + ALND	3	936	Tis 13%; TIa 17%; TIb 26%; Tic 35%; TII 8.3%	SLNB for N0 (n=600), ALND for positive SLNB (n=336)	Technetium-labeled sulfur colloid intradermally + isosulfan blue dye intraparenchymally	Circumferential measurements 10cm above and 5cm below olecranon process, preoperatively and at follow-up 3 to 8 years later. Lymphoedema defined as >2cm increase at any location. Severe lymphoedema at >5cm increase.	Median 5 years (2.7 – 8 years)	5% following SLNB		
Nov 2006	Francis W et al [51]	Prospective study investigating incidence and	3	209		SLNB for N0 (n=41), ALND for N+ (n=105)	Blue dye + radioisotope	Circumferential arm measurements at 10cm intervals	12	16.8% after SLNB		

		severity of lymphoedema during the first year after SLNB and ALND						starting at the hand. Measured quarterly for 12 months. Lymphoedema defined as increased measurement by at least 5%.				
Apr 2006	Wilke L et al [52]	Prospective multicentre trial to investigate prognostic importance of micrometastases in SLNB in early stage breast cancer	3	4069		SLNB for N0 (all patients)	Blue dye, or radioisotope or blue dye + radioisotope	Measurement at 10cm proximal and distal to medial epicondyle, compared to preoperative measurement. Defined as increase >2cm.	6	7%	Wound infection, haematoma, seroma, brachial plexus injury	

Abbreviations: ALND, axillary lymph node dissection; Lvl, level of evidence; N, number of participants in study undergoing SLNB; SLNB, sentinel lymph node biopsy; Tis, in situ; Tx stage unknown