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Review

Late morbidity associated with a tumour-negative sentinel lymph node biopsy in primary breast cancer patients: A systematic review

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ABSTRACT

Aims: To evaluate the relationship between late morbidity (i.e. ≧6 months) and a tumour-negative sentinel lymph node biopsy (SLNB) in primary breast cancer patients by using a systematic review approach, and to identify the predictors of late morbidity.

Methods: We performed a systematic review of the literature for studies concerning the late morbidity of patients who had undergone SLNB alone or SLNB followed by ALND when SLN metastases were found. A literature search over the last 16 years (1993–2008) was performed in the databases MEDLINE and EMBASE. The methodological quality of the selected studies was assessed according to a list of predefined criteria. The data of assessment and predictors of late morbidity were collected.

Results: We identified a total of 32 papers reporting 27 independent cohort studies, of which 17 were high quality studies and were further analysed in this review. There was a great variation in the prevalence of pain (7.5–36%), impairment of range of motion (0.0–31.0%), oedema (0.0-14.0%), decreased strength (11.0–19.0%) and sensory disorders (1.0–66.0%). Factors such as time after surgery and young age were strong predictors of late morbidity. Breast surgery, radiation to axilla, tumour location, body mass index (BMI) and two-step procedure, especially lymph mapping techniques, could also predict the late morbidity to different extents.

Conclusions: SLNB-associated late morbidity, even with a low prevalence, remains a clinical problem which cannot be neglected in primary breast cancer patients. Time after surgery and young age are the important predictors for late morbidity in primary breast cancer patients after SLNB; breast surgery, radiation to axilla, tumour location, BMI and two-step procedure also have limited prognostic value.

1. Introduction

Sentinel lymph node biopsy (SLNB), first reported by Krag et al. using radio-guided technique,[1] is now widely used as a safe and effective procedure after routine axillary lymph node dissection (ALND) in patients with early breast cancer.[2] SLNB has been proven to be feasible and accurate to improve the staging of the axilla.[3–5] A recent meta-analysis of 69

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studies (comprising 8059 SLNB procedures) demonstrated the rapid and widespread acceptance of SLNB as a minimally invasive alternative to stage the axilla.[6] Furthermore, many long-term studies have proven that the prevalence of axillary recurrences after negative SLNB was much lower than expected.[7–10] Another meta-analysis reported that the axillary recurrence rate after a tumour-negative SLNB in breast cancer patients was 0.3%, and the sensitivity of SLNB was 100%.[11] Reportedly, the survival of patients following SLNB was equivalent to that of patients following ALND.[2,12]

SLNB also results in less upper limb morbidity since it can reduce unnecessary ALND that may result in considerable arm morbidity. Several papers have reported that SLNB was associated with reduced morbidity and better quality of life compared with standard ALND procedure.[13–16] However, it is not clear how strong the relationship is between late morbidity (pain, lymphoedema, range of motion, loss of strength and sensory disorders) and SLNB alone. As late morbidity may interfere with activities of daily life (ADL) and quality of life (QOL),[17–19] recently the SLNB-associated late morbidity has drawn increasing attention despite its safety and accuracy. Prevalence of late morbidities after SLNB, including pain, lymphoedema, range of motion, loss of strength, and sensory disorders, was found to be variable in different studies, probably due to differences in study population, surgical procedures and assessment methods.[20] Thus, the primary aim of this systematic review is to identify the prevalence of the late morbidity after SLNB alone by evaluating the results of relevant studies, and also to discuss the predictors of late morbidity after SLNB.

2. Methods

2.1. Search strategy

A computerised search of the literature was performed in databases MEDLINE and EMBASE from 1993 to May 2008. A search strategy that combined disease-specific search terms (e.g. 'breast neoplasms'), the axillary management-class terms (e.g. 'SLNB') and terms related to treatment outcomes (e.g. 'morbidity', 'pain', 'range of motion', 'oedema', 'lymphoedema', 'muscle strength' and 'sensory disorders') or quality of life (e.g. 'well-being', 'activities of daily living', 'QOL' and 'ADL'). The search strategy employed relevant medical subject headings (MeSH) and Excerpta Medica Tree (EMTREE) terms as well as text words. We used the search terms simultaneously by 'OR' and combined them with 'AND' in the syntax of the databases. The reference lists/bibliographies of relevant papers/books were also hand searched for additional citations.

2.2. Selection criteria

The abstracts of publications which were found were screened and selected by the first author (Liu CQ) on the basis of the following criteria:

1. The patients must have primary clinical node-negative breast cancer, must not have received neoadjuvant therapy and not be pregnant.
2. All patients in the study group must receive sentinel lymph node biopsy. The cancer treatment must either be a modified radical mastectomy or be a breast-conserving therapy (BCT) alone or in combination with radiotherapy and/or chemotherapy/endocrine therapy.
3. Late morbidity of the SLNB group must be studied with a more than six-month follow-up after the surgical treatment.
4. The author must provide the data of the late morbidity after SLNB (measurement or percentage).

All articles meeting our four criteria were included in the present analysis. The criteria were applied independently by the two reviewers (LIU CQ and GUO Y) to the full text of the articles that had passed the first eligibility screening. In case of disagreement, a consensus was reached by means of discussion. When the disagreement persisted, a third

Table 1 – Criteria list for assessing the methodological quality of studies on post-SLNB morbidity of breast cancer patients.

Criteria
A. Socio-demographic and medical data are described (e.g. age, sex, tumour stage at diagnosis and menopausal status).
B. There is a clear statement of inclusion criteria or exclusion criteria for the study population.
C. The process of data collection is described (e.g. physical examination, interview and self-report).
D. A clear description of cancer treatment strategy is described (e.g. breast surgery, chemotherapy, radiation therapy and hormone therapy).
E. The study design is randomised.
F. The study size has to be more than 100 patients.
G. The results are compared between two groups or more groups (e.g. SLNB versus ALND and SLNB versus SLNB + ALND).
H. Mean or median and range or standard deviation of time since diagnosis or treatment are given.
I. Participation and response rates for patient groups have to be described and have to be more than 75%.
J. Information on patient/disease characteristics of dropouts is presented.
K. The measurement instrument to assess morbidity or quality of life has been reported by the authors or has been established in studies cited by the authors.
L. More than one type of symptoms associated with post-SLNB morbidity is assessed in the results.
M. Besides physical morbidity, results are also described for additional assessment (e.g. quality of life, activities of daily life and the psychological or social domain).
N. Frequencies of the most important outcome measures are presented.
O. Data are presented for clinically relevant prognostic factors of late morbidity after SLNB.
P. Informed consent is obtained from all participants before study.

independent reviewer (Sheng Y.) made the final decision. Trials were excluded if they were published in a language other than English, as translation capabilities were not available.

2.3. Quality assessment

Two of the authors (Liu C.Q. and Guo Y.) assessed the articles independently using a modified version of an established criterion list (Table 1).[21–24] The final list of the modified version consisted of 16 items. Each item of a selected study, which met our criteria, was assigned one point. If an item did not meet our criteria or was not described clearly or not at all, zero point was assigned. So the highest possible score was 16. Studies scoring 75% or higher of the maximum attainable score (i.e. ≧12 points) were arbitrarily considered as 'high quality'; studies scoring between 50% and 75% were rated as 'moderate quality' and studies scoring lower than 50% were considered as 'low quality'. If articles were based on the same cohort, one quality score was given based on the information from all the available publications. The scoring results of the two reviewers were compared, and the discrepancies were resolved by discussion to achieve consensus. If agreement could not be achieved, a third reviewer (Sheng Y.) was invited to evaluate the article.

2.4. Analysis

Data extracted from the selected studies included the study population, design, setting, follow-up time, outcome measures and rate of late morbidity in patients undergoing SLNB alone. We presented predictors that were described in at least one study and showed RR or OR above 2.0 or below 0.5 with a statistically significant association ($P < 0.05$). We did not depend solely on statistical significance, as many cohorts included in our review had a rather small sample size, and the relevant association between the prognostic factors and outcomes may have remained undetected. Findings were considered consistent if ≧75% of the studies reported of a factor showing the same direction of the association. Totally, we defined five levels of evidence.[21–24] If consistent findings (≧75%) were found in at least two high quality studies, we defined it as strong evidence. If consistent findings (≧75%) were found in one high quality study and in at least one low quality study, we defined it as moderate evidence. If findings were found in one high quality study or consistent findings (≧75%) were found in at least three or more low quality studies, we defined it as weak evidence. If inconsistent findings or less than three low quality studies were available, we defined as it inconclusive evidence. If no data were presented, we defined it as no evidence.

3. Results

3.1. Selection of studies

Initially, the search yielded 957 citations (MEDLINE 492, EMBASE 437, and 28 by reference checking). After the first screening, 109 non-duplicate abstracts were selected and the full publications were retrieved. Two reviewers assessed the full publications, and finally a total of 32 papers reporting on 27 independent cohort studies were included in this review.

Table 2 – Results of the methodological assessment of studies on late morbidity after SLNB.

Study	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Total
Mansel 2006[13], Fleissig 2006[25]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	–	1	15
Purushotham 2005[26]	1	1	1	1	1	1	1	1	1	1	1	1	1	1	–	1	15
Bianco 2008[27],Zavagno 2008[28]	1	1	1	1	1	1	1	1	1	–	1	1	1	1	–	1	14
Madsen 2008[15]	1	1	1	1	–	1	1	1	1	1	1	1	–	1	1	1	14
Langer 2007[14]	1	1	1	1	–	1	1	1	1	1	1	1	–	1	1	1	14
Lucci 2007[29]	1	1	1	1	1	1	1	1	–	1	1	1	–	1	1	1	14
Rietman 2004[30],2006[31]	1	–	1	1	–	1	1	1	1	1	1	1	1	1	1	1	14
Swenson 2002[32]	1	1	1	1	–	1	1	1	1	–	1	1	1	1	1	1	14
Barranger 2005[33]	1	1	1	1	–	1	1	1	1	1	1	1	1	1	–	–	13
Peintinger 2003[34]	1	1	1	1	–	–	1	1	1	1	1	1	1	1	–	1	13
Temple 2002[35]	1	1	1	1	–	1	1	1	1	–	1	1	–	1	1	1	13
Okada 2008[16]	1	1	1	1	–	1	1	1	1	–	1	1	–	1	–	1	12
Husen 2006[36]	1	–	1	1	–	1	1	1	1	–	1	1	1	1	1	–	12
Wilke 2006[37]	1	1	1	1	–	1	–	1	–	1	1	1	–	1	1	1	12
Leidenius 2005[38]	1	–	1	1	–	1	1	1	–	–	1	1	1	1	1	1	12
Rönkä 2005[39]	1	–	1	1	–	–	1	1	1	1	1	1	1	1	–	1	12
Veronesi 2003[2]	1	1	1	1	1	1	1	1	–	–	1	1	–	1	–	1	12
Baron 2002, 2004, 2007[40–42]	1	1	1	–	–	1	1	1	–	–	1	1	1	1	–	1	11
Schijven 2003[43]	1	–	1	1	–	1	1	1	–	–	1	1	1	1	1	–	11
Burak 2002[44]	1	1	1	1	–	–	1	1	1	–	–	1	1	1	–	1	11
Schrenk 2000[45]	1	–	1	1	–	–	1	1	1	1	–	1	1	1	–	1	11
Schulze 2006[46]	1	–	1	1	–	1	1	1	–	–	1	1	1	1	–	–	10
Blanchard 2003[47]	1	–	1	1	–	1	1	1	–	1	1	1	–	1	–	–	10
Haid 2002[48]	1	–	1	1	–	1	1	1	–	–	1	1	1	1	–	–	10
Haid 2002[49]	1	–	1	1	–	1	1	–	1	–	1	1	–	–	1	1	10
Sener 2001[50]	–	–	1	–	–	1	1	1	1	1	1	–	–	1	1	1	10
Golshan 2003[51]	1	–	1	–	–	1	1	–	–	–	1	–	–	1	–	1	7

3.2. Methodological quality

The results of the quality assessment are presented in Table 2. The overall quality scores ranged from 7 to 15 points, with the median score being 12.1 points (75.5%). In the end, 17 studies with a score of 12 points or more of the methodological criteria were further analysed in our review.[2,13–16,25–39]

3.3. Study characteristics

There were five randomised controlled trials (RCTs) in the review, and 14 of all the 17 studies were in a prospective approach; both RCTs and prospective studies were of high quality. Many studies described the technique of SLNB, including the type of radiopharmaceutical, the injection site, use of lymphoscintigraphy and use of blue dye, including the injection site. Besides, most studies described the assessment methods of pain, lymphoedema, range of motion and sensory disorders. All studies had different patient groups; and cancer treatment (breast surgery, radiation therapy, chemotherapy or hormonal therapy) and variable late morbidity were described. The collected the data are presented in Table 3.

3.4. Late morbidity

3.4.1. Pain

Totally 12 studies assessed the prevalence of pain. The assessment instruments varied from self-designed questionnaires, subjective rating scales, McGill Pain Questionnaire[34] and VAS[30,31] scores to validated pain questionnaires. The prevalence of pain one year or later after treatment of breast cancer ranged from 8.0% to 36.0% among the studies. During the second year, the prevalence of pain decreased to 7.5–21.2%. A five-year study on unilateral breast cancer reported that the prevalence of pain was 9.3% after surgery.[16] Working, needlework, carrying things and pressure of clothes were the most common pain inducers; and the pain led to sleep disturbances in 9.0% of the patients.[39]

3.4.2. Range of motion

The assessment of the range of arm motion was mostly performed by physical examination,[14,15,26,37–39] subjective rating scales[2,16,27,32,33,49] and Shoulder Disability Questionnaire.[30] A goniometer was also used in six articles.[15,26,30,38,39,49] The prevalence of restricted range of motion of the affected arm varied from 6.4% to 31% of the patients one year after treatment. Two years later, the prevalence decreased to 0.0–9.4%. However, a reduction in the upper extremity range of motion was found in 3.8% (117 of 3071) patients receiving SLNB alone in a prospective international cooperative group trial.[37] Range of motion interfered more with daily life in patients who had undergone an ALND than in those who had undergone an SLNB immediately after surgery, but the interference had no difference at 6 and 12 months after surgery.[32]

3.4.3. Oedema

Thirteen studies assessed the swelling of the affected arm. Different criteria were used for oedema. Most studies defined the oedema of the arm as an increase of 2 cm in the circumference from the pre-surgery arm measurement when compared with the contralateral arm. Some studies used a questionnaire to assess oedema by self-report. One study used the Measure of Arm Symptom Survey (MASS) questionnaire.[32] The prevalence of arm oedema varied from 3.0% to 10.0% at 6 months. At the time of one year or later, the prevalence was still between 6.0% and 14.0%. After a five-year follow-up, lymphoedema was still reported in 6.8% patients who had received SLNB alone. It is suggested that oedema is a long-term problem, even in patients receiving no total ALND.[16]

3.4.4. Strength

Muscle strength of the arms of the patients was assessed in six studies. The assessment methods varied from physical assessment of grip strength using a dynamometer[30] to subjective reported weakness.[16,33,36,39,49] The prevalence of strength reduction ranged from 17.0% to 19.0% at the time of one year or later. After a five-year follow-up, the prevalence of weakness was still reported as 11.0%.[16] In one study, ALND was considered a predictor of strength of shoulder abductors and grip strength.[30] In subjective evaluation, the prevalence of strength reduction may be underestimated because older women were prone to attribute their symptoms to ageing rather than to operation sequelae; therefore they do not consider the reduced strength, although present, to be of any significance.[36]

3.4.5. Sensory disorders

Symptoms of sensory disorders were described in 17 studies. Sensory disorders included numbness, paresthesias, dysesthesias and stiffness. The main assessments were physical examination, self-designed questionnaires and Breast Sensation Assessment Scale (BSAS). Some reported that SLNB even had a significant sensory morbidity, though the prevalence was approximately half that of ALND.[35] The prevalence of sensory disorders at one year or later after treatment of breast cancer ranged from 2.0% to 66.0% in the studies. Two years after treatment it was still 1.0–22.0%. A large prospective study (Z0010)[37] reported that 8.6% (307 of 3573) patients had axillary paresthesias after SLNB alone. One study reported that after a five-year follow-up the rate of self-reported arm numbness was 5.1%,[16] which was much lower than that reported in another comparison study,[42] also with a five-year follow-up but with moderate quality (score = 11).

3.5. Predictors of late morbidity

Consequently, time after surgery, young age, breast surgery, axillary radiation, tumour location, tumour stage, two-step procedures, BMI, radiopharmaceutical, trauma/infection and chemotherapy were investigated. Some factors were examined in several studies, while others in just one study. So their prognostic value remained uncertain.

3.5.1. Strong evidence

Strong evidence was found for the predictive value of time after surgery and young age for late morbidity. The prevalence of morbidity decreased over time in patients who underwent SLNB alone.[32,35,43] Another important predictor of late morbidity was young age. Schijven[43] reported that patients

Table 3 – Study characteristics of 17 selected studies.

Reference	Centre	Sample size			Treatment of cancer/SLNB					Blue dye	Design	Follow-Up (months)	Assessment	Late morbidity of SLNB alone (%)				
		SLNB	SLNB+	ALND	BCT	MRM	RT	CT	HT					Pain	Oedema	ROM	Strength	Sensory disorders
Swenson 2002[32]	Multi(2)	169	78		141	28	132	67	119	Yes ib	Prospective	12	MASS: Pain/ROM/Oedema	28.7	3.5	6.4		24.9
Temple 2002[35]	Single	171	62		171	0	163	65	–	–	Prospective	12	BSAS: Pain/Sensory disorders	25.0				25.0
Veronesi 2003[2]	Single	100		100	–	–	–	–	–	No	Prospective	24	Phys exam: Oedema/ROM Questionnaire: Pain/ROM Paresthesias	8.0	7.0	0.0		1.0
Peintinger 2003[34]	Multi(2)	25	31		25	0	25	5	17	Yes pb	Prospective	12	EORTC QLQ-C30 EORTC QlQ-BR23 MPQ: Pain KPS: Mobility	36.0				4.0
Rietman 2004[30], 2006[31]	Multi(2)	66	58	80	49	17	49	10	10	Yes pb	Prospective	24	Phys exam: Oedema/ROM VAS: Pain SDQ:ADL GARS:ADL					18.0
Purushotham 2005[26]	Multi(2)	143[a]		155	133	10	132	43	114	Yes pb	Prospective	12	Phys exam: Oedema/ROM SF-36:physical and social function, pain					66.0
Leindenius 2005[33]	Single	92		47	84	8	84	8	12	Yes pb	Retrospective	36	Phys exam: Oedema/ROM Questionnaire: Pain/ Sensory disorders	12.0	5.0	7.0		14.0
Barranger 2005[33]	Single	54		61[b]	54	0	54	15	40	Yes pb	Prospective	20	EORTC QLQ-C30 EORTC QLQ-BR23	21.2	0.0	9.4	17.3	5.9
Rönkä 2005[39]	Single	43		40[b]	35	8	36	6	18	Yes pb	Prospective	12	Phys exam: Oedema/ROM Questionnaire(Pain/Oedema/ Numbness)	28.0	13.0	31.0		19.0
Wilke 2006[37]	Multi(126)	4160			4160	0	3472	–	–	Yes pb/mb	Prospective	6	Phys exam: Oedema/ROM / Paresthesias		6.9	3.8		8.6
Mansel 2006[13] Fleissig 2006[25]	Multi(11)	495[a]		496	457	38	–	–	–	Yes pb	Prospective	18	Phys exam: Oedema/ROM/ Sensory disorders/Shoulder function Arm functioning subscale. FACT-B+4: QOL TOI :QOL		7.0			8.7
Husen 2006[36]	Single	203	167		147	54	134	35	90	Yes pb	Retrospective	24	Questionnaire: Arm morbidity/Oedema	16.0	4.0	12.0	18.0	6.0
Lucci 2007[29]	Multi(110)	446	445		446	0	446	–	–	Yes ib/pb	Prospective	12	Phys exam: Oedema/ Paresthesias		6.0			9.0
Langer 2007[14]	Multi(13)	449	210		411	38	411	124	355	Yes ib/pb	Prospective	31	Phys exam: Oedema /ROM Questionnaire: Pain/ Numbness	15.3	3.5	3.5		10.9
Madsen 2008[15]	Multi(7)	164	174	57	137	27	133	41	60	–	Prospective	18	Phys exam: Oedema/ROM/ Sensibility Subjective arm score	18.0	7.0	14.0		15.0
Bianco 2008[27] Zavagno 2008[28]	Multi(18)	336		341	286	49	–	–	–	No	Prospective	24	Phys exam: Oedema Questionnaire: Pain/ROM/ Numbness SF-36/PGWB	7.5	5.0	2.5		9.0
Okada 2008[16]	Multi(4)	119		68	119	0	115	43	–	–	Retrospective	59	Phys exam: Oedema/ROM Questionnaire: Sensory disorders/ Arm symptoms	9.3	6.8		11.0	5.1

Abbreviations: SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; SLNB+, SLNB + ALND; SNB[a], SNB group includes patients under SLNB+ALND; ALND[b], ALND group includes patients under SLNB + ALND; BCT, breast conservative therapy; MRM, modified radical mastectomy; RT, radiation therapy; CT, chemotherapy; HT, hormone therapy; QOL, quality of life; ADL, Activities of daily life; phys exam, physical examination; ROM, range of motion; –, unknown or not mentioned; pb, patent blue; ib, isosulphan blue; mb, methylene blue; BMI, body mass index; MASS, Measure of Arm Symptom Survey; BSAS, Breast Sensation Assessment Scale; KPS, Karnofsky performance status scale; MPQ, McGill Pain Questionnaire; SDQ, Shoulder Disability Questionnaire; GARS, Groningen Activity Restriction Scale; VAS, visual analogue scale; FACT-B + 4, Functional Assessment of Cancer Therapy-Breast + 4 questionnaire; TOI, trial outcome index; SF-36, the MOS 36-item short-form health survey; PGWB, the Psychological General Well Being Index; EORTC QLQ-C30, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-C30; EORTC QLQ-BR23, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire QLQ-BR23.

younger than 50 had a 3.4-fold higher risk for numbness compared with patients over 65 years of age. Younger women were also reported to have significantly more sensory morbidity regardless of the type of surgery when compared with elder women.[35] Patients at young ages were also at risk to have more pain and reduced strength.[36] In contrast, it was found that elder women were less likely to suffer pain, numbness and limitation in ROM.[32]

3.5.2. *Moderate evidence*

Moderate evidence was found for the predictive value of breast surgery, axillary radiation and tumour location. Breast surgery, including BCT and mastectomy, appeared to be another important predictor. Women who underwent mastectomy were more likely to report of numbness and limitation in ROM than those who had breast-conserving surgery. The advantage of SLNB over ALND was independent of whether the women had breast-conserving surgery or mastectomy.[32] In patients undergoing total mastectomy, the difference was only significant for pain sensation.[49]

Patients who underwent radiation therapy to the axilla were 2.4 times higher at risk of lymphoedema and 2.6 times higher prone to impaired use of the arm.[43] Additional radiation on the axilla predicted a further decrease in shoulder range of motion due to radiation-induced subcutaneous fibrosis.[30] A third important predictor was tumour location. For lymph node-negative patients who underwent sentinel lymphadenectomy alone, tumour location in the upper outer quadrant was associated with increased risk of lymphoedema.[50] Another study found that tumour location in upper outer quadrant seemed to increase numbness in all patients.[36]

3.5.3. *Weak evidence*

Weak evidence was found for the predictive value of two-step procedure, BMI and the use of radiopharmaceutical alone. One study suggested that the two-step axillary clearance represented the most important influential factor for arm morbidity symptoms of swelling and numbness.[36] The second predictor was the BMI of patients. It was found that women of larger BMI were more likely to report of pain and infection, and of interference with daily life from pain and infection.[32] The use of radiopharmaceutical alone was considered a significant predictor of late morbidity in one study.[37] Patients who were mapped with the radiopharmaceutical technique alone were associated with the presence of paresthesias and decrease in the range of motion of their upper extremity.

3.5.4. *Inconclusive evidence*

Inconclusive evidence was found for tumour stage, trauma/infection and chemotherapy. The pathologic stage of the patients was an important indicator for loss of full active motion range of arm (higher stage indicating a 2.1-fold higher risk).[43] Interestingly, it was found that patients with chemotherapy reported of less arm/hand numbness than patients without chemotherapy.[43] The presence of trauma and/or infection had been identified in one study as a factor associated temporally with the onset of lymphoedema.[50]

4. Discussion

Only a few studies have described the late morbidity in patients with primary breast cancer after SLNB alone over the last 16 years (1993–2008); and the majority of them showed much lower morbidity compared with ALND group. This systematic review assessed the late morbidity of breast cancer patients after SLNB alone (i.e. $\geqslant$6 months) from a total of 17 eligible studies, all of them reported that the morbidity after SLNB alone was much lower compared with that after levels I and II ALND, but should not be neglected. And strong evidence has been found that the time after surgery and young age were the predictors for late morbidity after SLNB. There were only five RCTs in our study[2,13,25–29] because few publications were conducted in a randomised approach for women's choice between SLNB and ALND had to be considered.[52,53] We noticed that studies have reported various methods and standards for assessing the morbidity (pain, impairment of range of motion, oedema, decreased strength and sensory disorders) in breast cancer surgery, which may contribute to the different morbidities after breast cancer surgery, which also prevented us from performing a meta-analysis. Different assessing methods can lead to difficulties in the process of assessment, making it impossible to obtain the data of more patients with breast cancer, not to mention the management and statistical analysis of the data, stopping us from carrying out further research. Therefore, uniform, standardised assessment criteria for assessing the upper limb function after breast cancer are very important, and a consensus is needed to be reached urgently among the organisers of large clinical trails and societies of breast cancers.

4.1. *Assessment of late morbidity after SLNB*

As mentioned earlier, there are no uniform criteria for impairments in pain, range of motion, oedema, muscle strength or sensory disorder[20]; and it is difficult to find a suitable questionnaire for the above-mentioned morbidities in breast cancer patients associated with SLNB, which may partly explain the variation in prevalence of pain (7.5–36%), impairment of range of motion (0.0–31.0%), oedema (0.0–14.0%), decreased strength (11.0–19.0%) and sensory disorders (1.0–66.0%).[2,13–16,25–39]

Researchers like to make comparisons between different groups, such as SLNB alone versus ALND, patients who received SLNB alone versus patients who received a secondary ALND after an initial SLNB (i.e. SLNB + ALND), and patients with sentinel node metastases undergoing delayed ALND (two-step ALND) versus patients with sentinel node metastases undergoing immediate ALND (i.e. one-step ALND). In this review, seven studies assessed the morbidity between SLNB alone and SLNB + ALND, and found that the morbidity after SLNB alone was much lower than that after SLNB+ALND.[14,15,29,32,34–36] But once the lymph node metastasis was found, a complete axillary clearance was suggested.[54] Moreover, RT to the axilla is another option instead of ALND for patients with positive SLNs.[55] Comparison between efficacies of axillary RT and ALND for preventing axillary recurrence in patients is ongoing in the AMAROS trial.[56]

4.2. *Predictors of late morbidity after SLNB*

We have identified 11 predictors for late morbidity associated with SLNB in the present review. However, the results described in this review were partially inconclusive, even though most studies included in this review were of high quality. In general, it can be concluded that breast cancer patients with low prevalence of late morbidity after SLNB alone are probably those who experienced it long time after surgery. Besides, patients at young ages were prone to report of higher morbidity (mostly sensory disorders) than the elderly, while increased age ($\geqslant$60 years) has been found to be related to a higher prevalence of post-operative lymphoedema formation.[57] The chance of experiencing late morbidity gets even lower under following conditions: when patients also undergo BCT instead of mastectomy, when patients receive irradiation on breast or chest wall, but not on axillary/supraclavicular region; when the tumour is not in the upper outer quadrant; when patients have lower BMI or when delayed ALND (two-step procedures) is avoided. The roles of other variables are less clear.

In particular, the Z0010 trial [37] found that the use of radiopharmaceutical alone was associated with late morbidity. A combination of a radiopharmaceutical injection, lymphoscintigraphy, blue dye injection and a gamma camera detection-probe was used in most studies. An exclusive blue dye technique can be viewed as not fully fulfilling the primary goal of morbidity reduction that SLNB promises.[58] Lymphoscintigraphy imaging is also very useful in further reducing morbidity during sentinel lymph node biopsy, even there is no RCT to confirm it.[59]

4.3. *Limitations of this review*

Firstly, in this review we only collected reports published in English. Language bias might exist, even its effect has not been firmly established.[60–62] Secondly, very few studies had evaluated the risks of late morbidity after SLNB alone, probably due to the low prevalence of morbidity, thus we have chosen the positive predictors (RR or OR above 2.0 or below 0.5, $P < 0.05$) either from SLNB group or from all the participants (including SLNB group) in the study. Finally, we did not assess the predictors for different kinds of late morbidities separately, which may influence our finding.

4.4. *Conclusion*

In patients with early stage primary breast cancer, SLNB has been proven to be a safe and minimally invasive procedure. In this review, we found that the late morbidity under SLNB alone is lower than expected, but not negligible, especially in the view of sensory disorders. We also found that time after surgery and young age are strong evidences in predicting late morbidity after SLNB. And more attention should be paid to breast surgery, radiation to axilla, tumour location, BMI, two-step procedure and especially lymph mapping techniques. All these predictors are identified in the development of late morbidity that should be taken into account in clinical practice. More long-term prospective randomised clinical trials are warranted to investigate the late morbidity of early stage breast cancer patients under SLNB, and the relationship with quality of life and activity of daily life.

Conflict of interest statement

None declared.

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REFERENCES

1. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. *Surg Oncol* 1993;**2**:335–9.
2. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *New Engl J Med* 2003;**349**:546–53.
3. Giuliano AE, Kirgan DM, Guenther JM, Morton DL. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. *Ann Surg* 1997;**225**:126–7.
4. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer – a multicenter validation study. *New Engl J Med* 1998;**339**:941–6.
5. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymphnodes. *Lancet* 1997;**349**:1864–7.
6. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma. *Cancer* 2006;**106**:4–16.
7. de Kanter AY, Menke-Pluymers MM, Wouters MW. 5-Year follow-up of sentinel node negative breast cancer patient. *Eur J Surg Oncol* 2006;**32**:282–6.
8. Domènech A, Benitez A, Bajén MT, Pla MJ, Gil M, Martín-Comín J. Patients with breast cancer and negative sentinel lymph node biopsy without additional axillary lymph node dissection: a follow-up study of up to 5 years. *Oncology* 2007;**72**:27–32.
9. Veronesi U, Galimberti V, Mariani L, et al. Sentinel node biopsy in breast cancer: early results in 953 patients with negative sentinel node biopsy and no axillary dissection. *Eur J Cancer* 2005;**41**:231–7.
10. Naik AM, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. *Ann Surg* 2004;**240**:462–8.
11. van der Ploeg IM, Nieweg OE, van Rijk MC, Valdés Olmos RA, Kroon BB. Axillary recurrence after a tumour-negative sentinel node biopsy in breast cancer patients: a systematic review and meta-analysis of the literature. *Eur J Surg Oncol* 2008;**34**:1277–84.
12. Kuijt GP, van de Poll-Franse LV, Voogd AC, Nieuwenhuijzen GA, Roumen RM. Survival after negative sentinel lymph node biopsy in breast cancer at least equivalent to after negative extensive axillary dissection. *Eur J Surg Oncol* 2007;**33**:832–7.
13. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. *J Natl Cancer Inst* 2006;**98**:599–609.

14. Langer I, Guller U, Berclaz G, et al. Morbidity of sentinel lymph node biopsy (SLNB) alone versus SLNB and completion axillary lymph node dissection after breast cancer surgery: a prospective Swiss multicenter study on 659 Patients. *Ann Surg* 2007;**245**:452–61.
15. Husted Madsen A, Haugaard K, Soerensen J, et al. Arm morbidity following sentinel lymph node biopsy or axillary lymph node dissection: a study from the Danish Breast Cancer Cooperative Group. *Breast* 2008;**17**:138–47.
16. Crane-Okada R, Wascher RA, Elashoff D, Giuliano AE. Long-term morbidity of sentinel node biopsy versus complete axillary dissection for unilateral breast cancer. *Ann Surg Oncol* 2008;**15**:1996–2005.
17. Bruner DW, Wasserman T. The impact on quality of life by radiation late effects. *Int J Radiat Oncol Biol Phys* 1995;**31**:1353–5.
18. Swedborg I, Borg G, Sarnelid M. Somatic sensation and discomfort in the arm of post-mastectomy patients. *Scand J Rehab Med* 1981;**13**:23–9.
19. Tobin MB, Lacey HJ, Meyer L, Mortimer PS. The psychological morbidity of breast cancer-related arm swelling. *Cancer* 1993;**72**:3248–53.
20. Rietman JS, Dijkstra PU, Hoekstra HJ, et al. Late morbidity after treatment of breast cancer in relation to daily activities and quality of life: a systematic review. *Eur J Surg Oncol* 2003;**29**:229–38.
21. Scholten-Peeters GG, Verhagen AP, Bekkering GE, et al. Prognostic factors of whiplash-associated disorders: a systematic review of prospective cohort studies. *Pain* 2003;**104**:303–22.
22. Borghouts JA, Koes BW, Bouter LM. The clinical course and prognostic factors of non-specific neck pain: a systematic review. *Pain* 1998;**77**:1–13.
23. Kuijpers T, van der Windt DA, van der Heijden GJ, Bouter LM. Systematic review of prognostic cohort studies on shoulder disorders. *Pain* 2004;**109**:420–31.
24. Mols F, Vingerhoets AJ, Coebergh JW, van de Poll-Franse LV. Quality of life among long-term breast cancer survivors: a systematic review. *Eur J Cancer* 2005;**41**:2613–9.
25. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat* 2006;**95**:279–93.
26. Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. *J Clin Oncol* 2005;**23**:4312–21.
27. Del Bianco P, Zavagno G, Burelli P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. *Eur J Surg Oncol* 2008;**34**:508–13.
28. Zavagno G, De Salvo GL, Scalco G, et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg* 2008;**247**:207–13.
29. Lucci A, McCall LM, Beitsch PD, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol* 2007;**25**:3657–63.
30. Rietman JS, Dijkstra PU, Geertzen JH, et al. Treatment-related upper limb morbidity 1 year after sentinel lymph node biopsy or axillary lymph node dissection for stage I or II breast cancer. *Ann Surg Oncol* 2004;**11**:1018–24.
31. Rietman JS, Geertzen JH, Hoekstra HJ, et al. Long term treatment related upper limb morbidity and quality of life after sentinel lymph node biopsy for stage I or II breast cancer. *Eur J Surg Oncol* 2006;**32**:148–52.
32. Swenson KK, Nissen MJ, Ceronsky C, Swenson L, Lee MW, Tuttle TM. Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. *Ann Surg Oncol* 2002;**9**:745–53.
33. Barranger E, Dubernard G, Fleurence J, Antoine M, Darai E, Uzan S. Subjective morbidity and quality of life after sentinel node biopsy and axillary lymph node dissection for breast cancer. *J Surg Oncol* 2005;**92**:17–22.
34. Peintinger F, Reitsamer R, Stranzl H, Ralph G. Comparison of quality of life and arm complaints after axillary lymph node dissection vs sentinel lymph node biopsy in breast cancer patients. *Br J Cancer* 2003;**89**:648–52.
35. Temple LK, Baron R, Cody 3rd HS, et al. Sensory morbidity after sentinel lymph node biopsy and axillary dissection: a prospective study of 233 women. *Ann Surg Oncol* 2002;**9**:654–62.
36. Husen M, Paaschburg B, Flyger HL. Two-step axillary operation increases risk of arm morbidity in breast cancer patients. *Breast* 2006;**15**:620–8.
37. Wilke LG, McCall LM, Posther KE, et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. *Ann Surg Oncol* 2006;**13**:491–500.
38. Leidenius M, Leivonen M, Vironen J, von Smitten K. The consequences of long-time arm morbidity in node-negative breast cancer patients with sentinel node biopsy or axillary clearance. *J Surg Oncol* 2005;**92**:23–31.
39. Rönkä R, von Smitten K, Tasmuth T, Leidenius M. One-year morbidity after sentinel node biopsy and breast surgery. *Breast* 2005;**14**:28–36.
40. Baron RH, Fey JV, Raboy S, et al. Eighteen sensations after breast cancer surgery: a comparison of sentinel lymph node biopsy and axillary lymph node dissection. *Oncol Nurs Forum* 2002;**29**:651–9.
41. Baron RH, Fey JV, Borgen PI, Van Zee KJ. Eighteen sensations after breast cancer surgery: a two-year comparison of sentinel lymph node biopsy and axillary lymph node dissection. *Oncol Nurs Forum* 2004;**31**:691–8.
42. Baron RH, Fey JV, Borgen PI, Stempel MM, Hardick KR, Van Zee KJ. Eighteen sensations after breast cancer surgery: a 5-year comparison of sentinel lymph node biopsy and axillary lymph node dissection. *Ann Surg Oncol* 2007;**14**:1653–61.
43. Schijven MP, Vingerhoets AJ, Rutten HJ, et al. Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. *Eur J Surg Oncol* 2003;**29**:341–50.
44. Burak WE, Hollenbeck ST, Zervos EE, Hock KL, Kemp LC, Young DC. Sentinel lymph node biopsy results in less postoperative morbidity compared with axillary lymph node dissection for breast cancer. *Am J Surg* 2002;**183**:23–7.
45. Schrenk P, Rieger R, Shamiyeh A, Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. *Cancer* 2000;**88**:608–14.
46. Schulze T, Mucke J, Markwardt J, Schlag PM, Bembenek A. Long-term morbidity of patients with early breast cancer after sentinel lymph node biopsy compared to axillary lymph node dissection. *J Surg Oncol* 2006;**93**:109–19.
47. Blanchard DK, Donohue JH, Reynolds C, Grant CS. Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer. *Arch Surg* 2003;**138**:482–7.
48. Haid A, Köberle-Wührer R, Knauer M, et al. Morbidity of breast cancer patients following complete axillary dissection

or sentinel node biopsy only: a comparative evaluation. *Breast Cancer Res Treat* 2002;**73**:31–46.
49. Haid A, Kuehn T, Konstantiniuk P, et al. Shoulder-arm morbidity following axillary dissection and sentinel node only biopsy for breast cancer. *Eur J Surg Oncol* 2002;**28**:705–10.
50. Sener SF, Winchester DJ, Martz CH, et al. Lymphedema after sentinel lymphadenectomy for breast carcinoma. *Cancer* 2001;**92**:748–52.
51. Golshan M, Martin WJ, Dowlatshahi K. Sentinel lymph node biopsy lowers the rate of lymphedema when compared with standard axillary lymph node dissection. *Am Surg* 2003;**69**:209–11.
52. Asaad M, Tamer M, Mokbel K. British women's choice between sentinel node biopsy and axillary node clearance for breast cancer. *Curr Med Res Opin* 2003;**19**:570–4.
53. Gan S, Magarey C, Schwartz P, Papadatos G, Graham P, Vallentine J. Women's choice between sentinel lymph node biopsy and axillary clearance. *ANZ J Surg* 2002;**72**:110–3.
54. Krag DN. Is axillary dissection needed when the sentinal node is positive? Yes! *J Surg Oncol* 2008;**97**:197–8.
55. Galper S, Recht A, Silver B, et al. Is radiation alone adequate treatment to the axilla for patients with limited axillary surgery? Implications for treatment after a positive sentinel node biopsy. *Int J Radiat Oncol Biol Phys* 2000;**48**:125–32.
56. <http://research.nki.nl/amaros/start.htm>.
57. Sakorafas GH, Peros G, Cataliotti L, Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. *Surg Oncol* 2006;**15**:153–65.
58. Krynyckyi BR, Shafir MK, Kim SC, et al. Lymphoscintigraphy and triangulated body marking for morbidity reduction during sentinel node biopsy in breast cancer. *Int Semin Surg Oncol* 2005;**2**:25.
59. Kim SC, Kim DW, Moadel RM, et al. Using the intraoperative hand held probe without lymphoscintigraphy or using only dye correlates with higher sensory morbidity following sentinel lymph node biopsy in breast cancer: a review of the literature. *World J Surg Oncol* 2005;**3**:64.
60. Egger M, Zellweger-Zähner T, Schneider M, Junker C, Lengeler C, Antes G. Language bias in randomised controlled trials published in English and German. *Lancet* 1997;**350**:326–9.
61. Moher D, Fortin P, Jadad AR, et al. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. *Lancet* 1996;**347**:363–6.
62. Moher D, Pham B, Klassen TP, et al. What contributions do languages other than English make on the results of meta-analyses? *J Clin Epidemiol* 2000;**53**:964–72.