



**NATIONAL BREAST
AND OVARIAN
CANCER CENTRE**

**SENTINEL NODE BIOPSY FOR
EARLY BREAST CANCER:
A SYSTEMATIC REVIEW**

JULY 2007

Prepared by National Breast and Ovarian Cancer Centre

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LIST OF ABBREVIATIONS

AC	Axillary Clearance
ACOSOG	American College of Surgeons Oncology Group
ACTR	Australian Clinical Trials Registry
AD	Axillary Dissection
ADRAC	Australian Drug Reactions Advisory Committee
ALMANAC	Axillary Lymphatic Mapping Against Nodal Axillary Clearance
ALND	Axillary Lymph Node Dissection
ASCO	American Society of Clinical Oncology
BCT	Breast Conserving Therapy
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
CCO	Cancer Care Ontario
DFS	Disease Free Survival
ESMO	European Society for Medical Oncology
FACT-B	Functional Assessment of Cancer Therapy-Breast
FN	False Negative
GSI	Global Severity Index
H&E	Haematoxylin & Eosin
ICSI	Institute for Clinical Systems Improvement
ID	Intradermal
IHC	Immunohistochemical
IMN	Internal Mammary Node
IP	Intraparenchymal
ITT	Intention to Treat
MAC	Mental Adjustment to Cancer Scale
MSAC	Medical Services Advisory Committee
MERGE	Method for Evaluating Research Guideline Evidence
NBCC	National Breast Cancer Centre
NBOCC	National Breast and Ovarian Cancer Centre
NSABP	National Surgical Adjuvant Breast and Bowel Project
NA	Not Applicable
NR	Not Reported

NS	Not Significant
NZ	New Zealand
OR	Odds Ratio
OS	Overall Survival
PA	Periareolar
PPN	Post-test Probability Negative
PT	Peritumoural
PGWB	Psychological General Well-Being
QoL	Quality of Life
RACS	Royal Australasian College of Surgeons
RCT	Randomised Controlled Trial
SA	Subareolar
SABCS	San Antonio Breast Cancer Symposium
SF-36	36-Item Short Form Health Survey
SIGN	Scottish Intercollegiate Guidelines Network
SNAC	Sentinel Node vs Axillary Clearance
SN	Sentinel Node
SLNB	Sentinel Lymph Node Biopsy
SNB	Sentinel Node Biopsy
SNR	Sentinel Node Resection
SSSS	SNAC Study Specific Scale
STAI	State-Trait Anxiety Inventory
TGA	Therapeutic Goods Administration
TOI	Trial Outcome Index
UK	United Kingdom

EXECUTIVE SUMMARY

Sentinel node biopsy (SNB) has been identified as an alternative to axillary lymph node dissection (ALND) in determining if early breast cancer cells have spread to the surrounding lymph nodes.

The primary research questions of this systematic review assessed

- the benefits and harms of using SNB compared to ALND to detect cancer spread in early (operable) breast cancer
- cancer recurrence and survival outcomes for patients receiving SNB.

The secondary research questions of this review assessed:

- the optimal technique for SNB in early (operable) breast cancer including different detection agents and different injection sites
- different treatments after a positive sentinel node (SN) is detected.

The review included randomised controlled trials (RCTs) published from January 2000 to July 2007 in women with clinically node negative, operable breast cancer. The search retrieved a total of 167 references from electronic databases, conference sites, clinical trial registries and guideline sites. After rigorous methods of inclusion and exclusion of articles, 12 trials remained for the review: six addressing the primary questions and six addressing the secondary questions.

RESULTS

Localisation

The trials reported high localisation rates of the SN in both SNB and ALND groups, although the SNB group was found to have slightly higher rates.

Overall and disease-free survival

Overall and disease-free survival was reported in three of the trials,¹⁻³ with a similar number of deaths found between the SNB and ALND across the trials and no statistically significant difference reported. Among these three trials axillary local recurrences were rare.

Morbidity

Morbidity was found to be lower in the SNB group compared with ALND group particularly in relation to arm morbidity (for example, lymphoedema).

Quality of Life

Patients having SNB had shorter hospital stays. Patients having SNB had similar, if not better quality of life (QoL) in comparison to patients having ALND.

Optimal technique for performing SNB

Lymphatic mapping using a combination of blue dye and radioisotope was superior to blue dye alone in detecting the SN.^{4,5} Two RCTs examined differences between injection sites. Further investigation is needed to determine the most effective injection route.

Surgical procedures after positive sentinel node detection

One RCT reported on treatment of patients with one or two positive SNs, although only morbidity outcomes were reported. Investigation is continuing on how to treat patients with micrometastases in the SN.

CONCLUSION

Overall SNB appears to be an adequate alternative to ALND in identifying whether cancer cells have spread to the surrounding lymph nodes in early (operable) breast cancer. SNB and ALND have similar localisation rates, overall and disease-free survival. SNB was found to have less morbidity, especially lymphoedema, and improved QoL. While studies showed a combined use of blue dye and radioisotope to be superior to blue dye alone, further information is needed to determine the best method of detection of the SN and surgical procedures after positive SN detection.

BACKGROUND

Treatment of early breast cancer involves surgery to remove the tumour (a lumpectomy or mastectomy) and management of the axilla. The axilla is assessed to determine if the cancer has spread to surrounding lymph nodes (usually in the axilla or armpit) and to determine treatment options and prognosis. Traditionally, a lumpectomy or mastectomy with axillary lymph node dissection has been the surgical standard of care used to manage early breast cancer. Axillary lymph node dissection (either level I, II or III) involves surgically removing a substantial number of the lymph nodes in the axilla. Axillary dissection has been associated with morbidity, particularly lymphoedema.⁶ Only about 30% of women with early breast cancer will have positive axillary nodes, and therefore around two thirds of women receive no benefit from axillary dissection and are at risk of morbidity associated with the procedure.⁷

Sentinel node biopsy (SNB) is a minimally invasive surgical technique used to assess the axilla. SNB is **not** a form of unguided axillary sampling. The sentinel node (SN) is the first lymph node to which cancer cells are likely to spread from the primary tumour in the breast. The SN can be located by injecting a detection agent (for example, blue dye or radioactive isotopes) around the cancer and locating the lymph node(s) to which the detection agent has travelled. Once detected, the SN(s) is/are surgically removed and investigated by a pathologist to determine if cancer cells are present. If cancer cells are found (a positive SN), further surgery to remove more lymph nodes, and/or radiotherapy to the area may be required.

National Breast Cancer Centre (NBCC)^{*} released a position statement supporting the Royal Australasian College of Surgeons (RACS) SNB statement in October 2005. The position statement considers several aspects of SNB, including morbidity, false negative rates and pathological evaluation of the SN. The RACS statement identified four large randomised trials: the Milan trial, the Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC), the National Surgical Adjuvant Breast and Bowel Project (NSABP B-32) trials and the RACS Sentinel Node vs. Axillary Clearance (SNAC I) trial. At the time this position statement was released the Milan trial was the only trial with published results, ALMANAC and NSABP B-32 had presented initial results and the SNAC I trial had yet to report. The current review (up to July 2007) includes updated data from these trials, as well as additional, randomised controlled trials (RCTs) which have been published since this position statement was released.

^{*} In February 2008, National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

METHODS

The objective of this review is to compare SNB to standard ALND in early breast cancer.

The primary research questions to be addressed are:

- the benefits and harms of using SNB compared to ALND to detect cancer spread in early (operable) breast cancer
- cancer recurrence and survival outcomes for patients receiving SNB.

Secondary questions to be addressed:

- the optimal technique for SNB in early (operable) breast cancer including different detection agents and different injection sites
- different treatments after a positive SN is detected.

INCLUSION CRITERIA

Participants

Patients with clinically node-negative, operable invasive breast cancer.

Intervention

SNB defined as the removal and examination of the SN (the first lymph node to which cancer cells are likely to spread from the primary tumour). Radioactive isotope and/or blue dye may be used to detect the SN. True SNB should result in only 1–4 nodes being removed.

Comparison

ALND, defined as the removal of the axillary lymph nodes. True ALND should result in more than 10 nodes being removed.

Note: Many of the trials performed SNB before ALND. Therefore the comparison arm is actually SNB+ALND.

Types of outcome measures

- overall survival (OS)
- disease-free survival (DFS)
- morbidity (e.g. lymphoedema)
- quality of life (QoL)
- adverse events

LITERATURE SEARCH

A systematic literature search was conducted in May 2007 to identify phase III randomised controlled trials which addressed the inclusion criteria. The search was updated in July 2007. The search was conducted over several databases/sources (see Appendix 1), including:

- Medline (Ovid)
- EMBASE
- Pubmed
- EBM reviews (Ovid)
- CINAHL (Ovid)
- Cochrane Library, Issue 2 April 2007.

In addition to the above databases, several conferences, guidelines and health technology assessment websites were searched for relevant information.

Conference sites searched included:

- San Antonio Breast Cancer Symposium (SABCS)
- American Society for Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)
- International Sentinel Node Society Meetings
- International Conference on Primary therapy for Early Breast Cancer, St Gallen.

A list of the guidelines, clinical trials and health technology assessment websites searched can be found in Appendix 2. Additional papers identified from personal files and the reference lists of included papers were also sourced.

The search strategy used combined key terms which described breast cancer, SNB, ALND and RCTs (see Appendix 3). The search was limited to trials conducted in humans which were published between January 2000 and July 2007 in the English language.

After the removal of duplicate citations and the addition of further citations sourced, a total of 167 unique citations remained. The titles and abstracts of these citations were assessed by two independent reviewers to determine eligibility for the current review based on the criteria described above. Ineligible studies were classified using the exclusion criteria below. For citations which provided insufficient information to assess eligibility, the full text was retrieved for assessment.

Exclusion Criteria

Papers were excluded if they were:

- not an original clinical study — publications not reporting the findings of original clinical studies including non-systematic reviews, editorials, opinion pieces and letters
- wrong population — studies conducted in a population other than patients with early breast cancer
- wrong intervention — studies not investigating SNB
- wrong design — not phase III randomised controlled trials
- not published in the English language.

Based on these criteria, 77 articles were excluded. The full texts of the remaining 90 citations were retrieved and assessed to identify which met the inclusion criteria for the review. After full text assessment, 31 citations were identified as eligible for the current review (see Appendix 4). Of the included citations, there were two systematic reviews, three topic specific guideline recommendations, six trials which addressed the primary questions and a further six trials which addressed secondary questions (some trials were reported by multiple citations). NSABP B-32 published further results⁸ after the completion of this review, but during the development of guideline recommendations based on this review.

QUALITY ASSESSMENT

The two included systematic reviews and 12 trials were assessed for quality by two independent reviewers and verified by a third reviewer. This involved assessment of specific aspects of the studies according to the NSW Health Method for Evaluating Research Guideline Evidence (MERGE) tool. Aspects of systematic reviews which were assessed included the adequacy of the search strategy used, whether study quality assessment was performed and whether a point estimate was calculated. Aspects of the studies which were assessed included randomisation and allocation concealment methods, consideration of benefits and harms, and how well potential bias was minimised.

The systematic reviews provided enough information to determine that the methods used were of sound methodological quality.

All trials included were RCTs; however, the method of allocation and/or allocation concealment was often not reported. Two trials reported in abstracts only and therefore it is difficult to assess the quality of these trials.

For all trials the baseline patient characteristics were well balanced between study arms. It is unlikely that the trials included are significantly influenced by bias or confounding factors due to the studies being well designed RCTs.

DATA EXTRACTION

Data extraction was performed independently by two reviewers and verified by a third reviewer to ensure accuracy and consistency. Any discrepancies were discussed by all three reviewers until a consensus decision was made. Where multiple citations existed for one trial, data was extracted from the latest available publication. However if additional information of interest was reported in a previous publication this was also included. Descriptive data extracted from the studies included characteristics such as patient population, SN detection method, and primary end points. Outcome data extracted from the studies included accuracy of SNB, localisation rates, disease-free and overall survival. QoL data was also extracted, as well as outcomes relating to lymphoedema, arm morbidities, sensory deficit and psychological morbidity. Adverse events were also extracted from the papers.

RESULTS

INTERNATIONAL GUIDELINES

Various international guidelines were identified either through the literature search or on health technology assessment and guidelines websites.

American Society of Clinical Oncology⁹

In 2005, the American Society of Clinical Oncology (ASCO) produced guideline recommendations for SNB in early stage breast cancer. The guideline recommendations were developed following a literature review conducted in 2003 (included in this review). Overall, the ASCO recommendations concluded that:

- SNB is an appropriate initial alternative to routine staging (ALND) for patients with early breast cancer with clinically negative nodes
- SNB results in less morbidity than ALND
- completion ALND remains the standard treatment for axillary metastasis; however, it can be avoided if SNB correctly gives a negative result.

Institute for Clinical Systems Improvement¹⁰

In 2002, the US Institute for Clinical Systems Improvement (ICSI) updated the 1998 *Lymphatic mapping with Sentinel Lymph Node Biopsy for Breast Cancer* Technology Assessment Report. The updated conclusions were that:

- SNB is a safe and appropriate alternative to ALND with less morbidity and adverse effects for patients with solitary invasive breast cancer under 5cm
- SNB should be performed by an experienced surgeon and in a multidisciplinary setting
- no long term survival data is available
- there is a learning curve with regards to locating the SN
- serial sectioning with immunohistochemical (IHC) staining may be effective in detecting occult nodal metastasis.

Canadian Medical Association¹¹

The Canadian Medical Association guidelines on sentinel lymph node biopsy, published in the *Canadian Medical Association Journal* in 2001, are based on a systematic review which includes

information published between 1991 and 2000. The recommendations in this publication were based on consensus, given the lack of data from RCTs at this time. The recommendations were:

- axillary dissection is recommended as standard of care
- if SNB is requested or offered, risks and harms should be outlined
- for surgeons to perform SNB, they should be familiar with the technique and follow a defined protocol
- positive SN or failure to identify SN should prompt full axillary dissection.

Additional guidelines

The NBCC's *Clinical practice guidelines for the management of early breast cancer* (2001)⁶ stated that until further evidence is available, use of SNB should only be in a clinical trial setting or as a prelude to axillary node dissection.

Cancer Care Ontario (2003)¹² and the Scottish Intercollegiate Guidelines Network (SIGN) (2005)¹³ also produced broad guidelines on the surgical management of early breast cancer. These guidelines included small sections regarding SNB with similar conclusions: that SNB is not for standard practice but may be used in a clinical trial setting or following an evaluated training program.

SYSTEMATIC REVIEWS

Two systematic reviews were identified, one commissioned by the Australian Medical Services Advisory Committee (MSAC)¹⁴ and the other the review which supported the ASCO guidelines.¹⁵ A Cochrane protocol on axillary staging for operable primary breast cancer was also identified; however, this review has yet to be published.

MSAC¹⁴

MSAC published a review in March 2005, which included studies published up to June 2004. This significant review included 301 studies and reports on the diagnostic accuracy of SNB, including localisation and false negative rates, as well as safety, effectiveness and cost-effectiveness. Comparative studies (both randomised and non-randomised) were included as well as case series. Only one randomised trial was published at the time of the MSAC review,¹⁶ and therefore included in this SNB review.

The pooled localisation rate was calculated from 192 studies (228 sets of data) as 94.1% and the false negative rate (calculated from 130 studies, 136 sets of data) was 4.7%. The authors noted that

the available evidence was of moderate quality; however, significant heterogeneity was seen between studies. Test protocols which used the combination of dye and radioisotope were associated with higher localisation rates (estimated mean difference 8.5%, $p < 0.0001$) and lower false negative rates (estimated mean difference 2.9%, $p = 0.005$) compared to use of dye alone. Both subareolar and intradermal injection sites for radioisotope were associated with higher localisation rates than peritumoural injection sites. Subareolar injection of blue dye was associated with higher localisation rates than peritumoural injection sites. No differences in the false negative rate were observed for different injection sites of radioisotope or blue dye.

Lymphoedema, postoperative range of motion limitation, sensory morbidities and pain were more common in patients receiving ALND compared to SNB. Low rates of allergies to blue dye were reported (0–1.6%). There was not sufficient evidence to assess the relative effect of SNB on survival. In 29 cases series, the axillary recurrence rate did not exceed 1% in patients who were node negative at the time of SNB (follow up 8–47 months).

MSAC found that SNB is an effective and safe procedure to identify SNs, resulting in fewer complications compared to ALND (with longer term outcomes uncertain). MSAC recommended that interim funding should be provided for SNB pending the outcomes of current trials and should be reviewed in five years.

Kim *et al* 2005¹⁵

The meta-analysis on SNB in early stage breast cancer performed by Kim *et al* contributes to the 2005 ASCO guidelines. The review included RCTs, meta-analyses and single and multi-centre trials which addressed four key questions:

- i) utilization of results in clinical practice
- ii) role of SNB in special circumstances
- iii) factors which affect the success of SNB
- iv) potential benefits and risks of SNB.

The Kim *et al* review¹⁵ included data from 69 trials (including one RCT) which reported between 1970 and 2003, representing 8059 patients who were offered SNB followed by complete ALND. Primary outcomes included measures of test performance, including false negative (FN) rate, post-test probability negative (PPN) rate, and proportion of patients with successfully mapped SNs.

FN rates ranged from 0% to 30% (average 8.5%), with lower rates observed for larger studies (6.7% for studies ≥ 100 patients compared to 9.0% for studies < 100 patients, $p=0.007$). PPN rate ranged from 1% to 25% (average 5.7%), with the rate increasing as the percentage of positive lymph nodes identified at ALND increased ($p=0.033$). Among patients who completed the planned studies, 96.4% had successfully mapped SN.

The Kim *et al* review revealed a wide variation in test performance of SNB. The variation may be due to early experience with the procedure, as institutions/investigators with greater experience reported higher localisation rates and lower false negative rates.

INCLUDED STUDIES

The primary research question of this review was to compare SNB to ALND in relation to the defined outcomes (OS, DFS, morbidity, QoL and adverse events). Additional trials identified by the search which addressed secondary questions regarding SNB (such as differences in injection site or tracing agent, injections sites and treatment after a positive SN) are reported later in this review.

SNB vs. Axillary Dissection

Description of studies

In total, six RCTs were identified which compared SNB to ALND. Characteristics of these trials are described in Table 1. Results for most of these trials have been published and/or presented since the previous systematic reviews were conducted. The only RCT that was included in the previous reviews^{14,15} is the Milan trial,¹⁶ which has more recently published results on overall and disease-free survival.² Two of the trials have reported results in abstracts only (SNAC I, NSABP B-32). The remaining four trials have reported results in full-text peer-reviewed publications.

The single-centre Milan trial,^{2,16} conducted by Veronesi and colleagues, enrolled 516 women and was the first RCT to report on SNB compared to ALND. The ALMANAC trial^{1,17} is the largest multicentre trial (N=991) to have published results. Of the larger trials, the Australasian SNAC I trial¹⁸ (N=1088) and the US NSABP B-32 trial^{19,20} (N=5611) have only reported results in abstracts. The Cambridge trial²¹ is the smallest RCT to have reported, including only 198 patients. The GIVOM trial^{3,22} has enrolled 697 patients and is the latest trial to publish full results.

Patients with operable, invasive breast cancer who were clinically node negative were included in the trials. In the six included RCTs, a total of 9201 patients have been randomised to either SNB (n=4597) or ALND (n=4604). Most trials randomised patients to receive either SNB alone or SNB

followed by ALND. The Cambridge trial²¹ randomised patients to SNB alone or ALND alone. The ALMANAC trial^{1,17} randomised patients to SNB alone or standard axillary treatment (either ALND or 4-node axillary sampling). In these two trials patients in the control arm did not undergo SNB. In this review the ALND group refers to the arms which were randomised to receive ALND (either alone or with SNB) and the SNB group is for the arms which were randomised to have SNB performed alone. For all trials, in the SNB alone arms, ALND was performed if the SN was positive or if the SN could not be detected. Both SNB and ALND dissection were referred to by different names in each trial. For example, SNB was also referred to as SN resection (SNR) and ALND was referred to as axillary clearance (AC) or axillary dissection (AD).

Trials excluded patients with a primary tumour >3cm (the Milan trial^{2,16} excluded those >2cm), except for the ALMANAC trial^{1,17} and the NSABP B-32 trial.^{8†} These two trials included tumours of all sizes, however, up to 80% of patients in these two trials had tumours equal to or less than two centimetres in diameter. Only 2% of patients in the NSABP B32 trial⁸ had tumours more than four centimetres in diameter and 2% of patients in the ALMANAC trial¹ had tumours more than five centimetres in diameter. All trials excluded patients with multicentric cancers. Other exclusion criteria included clinically involved nodes, pregnancy or breastfeeding, known allergies to radioisotope or dye, previous breast or axillary surgery, and inability to complete questionnaires in English.

† Paper published after review completed

Table 1: Characteristics of included trials comparing sentinel node biopsy with axillary dissection

Trial	Country	Population	Patient Numbers		SNB group (method of SN detection)	ALND group	Outcomes measured
			SNB	ALND			
MILAN ^{2,16}	Italy	Women aged 40–75yrs with primary breast cancer ≤2cm, and BCT performed before SNB or ALND.	259	257	SNB (isotope)	SNB ⇒ ALND	Axillary metastases, DFS, OS, detection rate.
ALMANAC ^{1,17}	UK	Female and male patients aged <80yrs with clinically node negative invasive breast cancer	495 (478 ITT)	496 (476 ITT)	SNB (blue dye and/or isotope)	Standard axillary treatment (ALND or 4-node sampling)	Arm & shoulder morbidity, QoL, detection rate
SNAC I ^{18,23}	Australia and NZ	Women with histologically or cytologically confirmed invasive breast cancer ≤3cm	544	544	SNB (blue dye and/or isotope) ⇒ ALND if SN positive	SNB ⇒ ALND	Arm volume, QoL, detection of SN
NSABP B-32 ^{19,20,24}	USA	Women with operable invasive breast cancer and clinically negative nodes	2804	2807	SNB (blue dye and isotope)	SNB ⇒ ALND	QoL, FN, detection rate
CAMBRIDGE ²¹	UK	Patients with ≤3cm invasive breast cancer node negative breast cancer	143	155	SNB (blue dye and isotope) ⇒ ALND if SN positive.	ALND	Physical and psychosocial morbidity
GIVOM ^{3,22}	Italy	Patients aged <80yrs with ≤3cm node negative breast cancer	352	345	SNB (isotope) ⇒ ALND if SN positive	SNB ⇒ ALND	Detection, accuracy, QoL, OS, DFS

Notes: ALND=axillary lymph node dissection, BCT=breast conserving therapy, DFS=disease-free survival, FN=false negative, ITT=intention to treat, OS=overall survival, QoL=quality of life, SN=sentinel node, SNB=sentinel node biopsy.

Surgical training

Three of the trials, ALMANAC,^{1,25} SNAC I²⁶ and NSABP B-32,²⁷ reported that prior to participation in the trial, surgeons must have been trained and accredited in the SNB technique to ensure optimal performance. Training was measured differently; however, generally each surgeon had to perform a certain number of SNBs and meet set criteria (e.g. localisation rates >90%, FN rate <5%; see Table 2).

Table 2: Surgical training requirements

Trial	Training requirements	Trial results	
		Accuracy	False negative
ALMANAC ^{1,25}	SNB course 40 consecutive cases: Identify SN in ≥90% Maximum of 2 FN results Observed by principle investigator of trial	NA	NA
NSABP B-32 ^{19,27}	Training manual Site visit Minimum of 5 training cases	97.2%	9.7%
SNAC I ^{18,26}	20 consecutive cases: Identify SN in >90% Site visit Observed by surgeon experienced in SNB	NR	8.2%
Cambridge ²¹	Not specified	NA	NA
GIVOM ³	15 cases with no FN results No formal training course nor site visits	94.4%	16.7%
Milan ^{2,16}	No training specified however trial reported that surgeons were very experienced	96.9%	8.8%

Notes: FN=false negative, NA=not applicable, NR=not reported, SN=sentinel node, SNB=sentinel node biopsy

Method of SNB

Two trials used radioactive isotope alone to identify the SN.^{2,16,3} The remaining trials used a combined method of blue dye and radioisotope. The blue dye most commonly used was Patent Blue V. The radioisotopes used ranged from 5 to 40 MBq technetium 99m labelled albumin or sulphur colloid. Injections of dye and/or isotope were given peritumourally in the ALMANAC,¹ NSABP B-32²⁸ and SNAC I²⁶ trials. The Milan trial^{2,16} injected radioisotope subdermally for superficial tumours and peritumourally for deep tumours. GIVOM trial³ injected radioisotope subdermally. Details of the SN detection methods for each trial are described in Table 3.

The SN was identified as the blue stained node(s) and/or radioactive node(s) (radioactive count 10 times the background count) depending on which method of detection was used.

Pathological examination

The pathological methods used to examine the SN differed for each trial. The Milan^{2,16} and GIVOM^{3,22} trials used frozen section evaluation, and GIVOM followed this by staining with haematoxylin-eosin (H&E) and cytokeratin antibody for definitive histology. NSABP B-32¹⁹ undertook intraoperative cytology and H&E staining of serial sections. ALMANAC¹ examined the lymph nodes by H&E staining of serial sections only. The SNAC I²⁶ and Cambridge²¹ trials used H&E staining of serial sections, followed by immunohistochemistry to detect smaller metastases.

Table 3: Detection agents used to detect sentinel node

Trial	Colloid	Injection site	Dosage/time	Dye
MILAN ^{2,16}	Technetium 99m Albumin colloid (50-200nm in diameter in 2ml saline)	Subdermal if tumour was superficial or peritumoural if tumour was deep	5-10MBq injected either evening before (79% pts) or morning of surgery (21% pts).	NA
ALMANAC ¹	Technetium 99m Albumin colloid	Four sites peritumourally	40MBq day before surgery or 20MBq on the day of surgery	Intraoperatively 2ml of Patent Blue V dye diluted with 5ml saline injected peritumourally
SNAC I ²⁶	Technetium 99m anatomy-labelled sulphur colloid (in 2-4ml of solution)	Around the tumour at four sites	20-40MBq injected either day of or day preceding surgery	Intraoperatively 2-4ml of patent blue V dye injected peritumourally in four sites
NSABP B-32 ²⁸	Technetium 99m Sulphur colloid	Injected around and on the tumour	Injected 30mins to 8hrs before surgery	Blue dye injected around tumour 5mins before surgery
CAMBRIDGE ²¹	Technetium 99m Albumin colloid	NR	40MBq	2.5% Patent blue V
GIVOM ³	Technetium 99m Albumin nanocolloids (in 0.2 cc of saline)	Subdermal (using 25-G needle)	30-50MBq day before surgery	NA

Notes: NA=not applicable, NR=not reported

Adjuvant therapy

All patients were treated by radiotherapy, the majority of patients also received hormonal therapy and/or chemotherapy in line with standard guidelines/protocols.

Overall Results

Localisation and false negative rates

The trials reported high rates for localising the SN for both the SNB and ALND groups. Rates reported ranged from 93% to 98% with slightly higher rates observed in the SNB arms (see Table 4). Statistical significance was not reported.

Table 4: Detection of sentinel node

Trial	SNB group	ALND group
Successfully mapped SN		
ALMANAC ¹	98%	
SNAC I ¹⁸	95%	93%
NSABP B-32 ¹⁹	97%	97%
GIVOM ³	95.1%	94.9%
Positive sentinel nodes		
Milan ²	35.5%	32.3%
ALMANAC ¹	26%	23%
SNAC I ¹⁸	29%	25%
NSABP B-32 ¹⁹	26%	26%
Cambridge ²¹	34%	26%
GIVOM ²²	30%	32%

Notes: ALND=axillary lymph node dissection, SN=sentinel node, SNB=sentinel node biopsy

The accuracy of SNB in the detection of the SN could only be reported in trials which performed SNB followed by ALND in the control arm. Trials reported on accuracy, FN rate, sensitivity and negative predictive value (see Table 5). The Milan trial² reported a FN rate of 8.8%, similarly the SNAC I¹⁸ and NSABP B-32¹⁹ trials reported a FN rate of 8.2% and 9.7% respectively. The GIVOM trial³ reported a higher FN rate of 16.7%.

Table 5: Accuracy of SNB in detection of sentinel node

Trial	Accuracy	False negative rate	Sensitivity	Negative predictive value
Milan ²	96.9%	8.8%	91.2%	95.4%
SNAC I ¹⁸		8.2%	92%	97%
NSABP B-32 ¹⁹	97.2%	9.7%		96.1%
GIVOM ³	94.4%	16.7%	83.3%	92.3%

Notes: SNB=sentinel node biopsy

Two trials^{3,19} reported on the FN rates of frozen section examination/intraoperative cytology. The GIVOM trial³ reported a FN rate for frozen section examination as 24.7%. The NSABP B-32 trial¹⁹ reported a FN rate for intraoperative cytology as 38.5%.

Positive sentinel node

Rates of positive SNs ranged from 23% to 35.5% (see Table 4). Similar rates of positive nodes were reported in SNB and ALND groups.

The Milan trial² reported that a SN was more likely to be positive if peritumoural vascular invasion was present (OR: 6.4, 95% CI: 3.9 to 10.8). A higher percentage of positive SNs were found in tumours larger than 1 cm (38%) compared to tumours smaller than 1 cm (22%).

The NSABP B-32 trial²⁰ reported that clinical tumour size, lymphovascular invasion, tumour location (upper outer quadrant vs. all others) and proposed surgery (lumpectomy vs. mastectomy) were directly and significantly associated with SN metastases. Age was inversely and significantly related to SN metastases, with older patients less likely to have metastases compared to younger patients.

Overall & disease-free survival

Three of the RCTs have reported on overall survival (OS): ALMANAC¹ (median follow-up 12 months), Milan² (median follow-up 79 months) and GIVOM³ (median follow-up 48 months), all of which showed similar numbers of deaths in both the SNB arm and the control arm (see Table 6). In these three trials (including a total of 2184 patients) there were 65 deaths, 32 in the ALND arms and 33 in the SNB arms. The Milan² and GIVOM³ trials reported 5-year rates for SNB and ALND for OS and disease-free survival (DFS). The Milan trial² reported slightly higher overall and disease-free survival for the SNB group (however the difference was not statistically significant). The GIVOM³ trial reported slightly lower rates for overall and disease-free survival in the SNB group; the differences between the SNB and ALND arms were not statistically significant. The ALMANAC trial did not report on significance.

Table 6: Overall and disease-free survival

Trial	Median follow-up	N		Overall survival				Disease-free survival			
				Deaths		5-yr OS		Events		5-yr DFS	
		SNB	ALND	SNB	ALND	SNB	ALND	SNB	ALND	SNB	ALND
ALMANAC ¹	12 mths	495	496	7	7						
Milan ²	79 mths	259	257	5	11	98.4%	96.4%	16	18	92.2%	88.9%
GIVOM ³	48 mths	336	341	21	14	94.8%	95.5%	32	23	87.6%	89.9%

Notes: ALND=axillary lymph node dissection, DFS=disease-free survival, OS=overall survival, SNB=sentinel node biopsy

Axillary local recurrences were rare. The ALMANAC trial¹ reported three axillary recurrences in the standard axillary dissection arm and one in the SNB arm after 12 months, the Milan² and GIVOM³ trials each reported no cases of axillary recurrence in the ALND arm and one case in the SNB arm. Statistical significance was not reported.

Morbidity

The trials reported on a variety of physical morbidity outcomes, which were often measured differently. Commonly reported outcomes included arm morbidity such as lymphoedema, arm volume and shoulder functioning as well as sensory deficits such as numbness/paresthesia. Morbidity was also measured at multiple time points. Detailed tables of morbidity data may be seen in Appendices 5 and 6.

Lymphoedema was reported subjectively and/or measured by comparing arm volume/swelling of the arm on the operation side with the contralateral arm. All trials which reported on lymphoedema, swelling or arm volume had significantly lower levels of lymphoedema and/or arm swelling in the SNB groups compared to ALND groups (see Table 7). Higher levels of lymphoedema in the ALND arms compared to the SNB arms continued at 24 months after surgery.

The Cambridge trial²¹ also stratified morbidity results by nodal status. Decreases in arm volume changes and subjective lymphoedema in the SNB groups (compared to the ALND group) were statistically significant in the node-negative patient group but not in the node-positive patient group.

Arm and/or shoulder functioning were reported differently in each trial. However, functioning impairment was worse in ALND groups compared to SNB groups.

Sensory deficit/numbness/paresthesia were reported more often in the ALND groups compared to the SNB groups.

Pain was reported in the Milan¹⁶ and GIVOM²² trials and reported more often in the ALND groups at 6 months after surgery compared to SNB groups. Pain subsided at 24 months, with closer rates reported between the two treatment arms (still higher in ALND group for Milan trial).

The NSABP B-32 trial²⁴ compared self-reported outcomes with arm functional measurements for SNB patients and found that correlations between the two are weak to moderate and suggested both types are important to assess.

Length of hospital stay

Patients receiving axillary dissection stayed in hospital longer than those who received SNB alone. The Milan trial¹⁶ reported that patients who underwent axillary dissection had an average hospital stay of 4.3 days compared to patients who had SNB having an average stay of 2.1 days. The ALMANAC trial¹ reported patients with axillary dissection were in hospital for 5.4 days compared to 4.1 days for SNB patients ($p < 0.001$).

Table 7: Reported lymphoedema outcomes

Trial	Time after	SNB group		ALND group		p-value
		n	%	n	%	
Lymphoedema						
ALMANAC ^{1,17}	1mth	14	3.2	50	12	
	6mth	19	4.5	71	17	
	12mth	20	5	53	13	<0.001
GIVOM ²²	6mth		4		10	0.005
	12mth		4.5		9	0.03
	24mth		4.5		7	
Reported swelling						
ALMANAC ^{1,17}	1mth		12		28	<0.001
	6mth		7.5		15.8	
	12mth		5.2		11.8	0.002
	18mth		7		14	
MILAN ¹⁶	6mth	11	11	69	69	
	24mths	7	7	75	75	
SNAC I ¹⁸ (SSSS)	6mths and 12mths	3.4*		7.4*		<0.0001
Increased arm volume						
SNAC I ¹⁸			2.8		4.2	
Cambridge ²¹	1mth	8.1ml		49.6ml		0.001
	6mth	22.1ml		45.5ml		0.2
	12mth	18.6ml		56.4ml		0.03
	Mean	17.7		53.1		0.004
	Maximum	78.4		113.7		0.02

*Scale 0–10, 10 being worst

Notes: ALND=axillary lymph node dissection, SNB=sentinel node biopsy, SSSS=SNAC study specific scale

Quality of life - psychological morbidity

Quality of life (QoL) was assessed in these trials using various validated scales and questionnaires, including the FACT-B questionnaire, the Beck Depression Index (BDI) and the State-Trait Anxiety Inventory (STAI). The SNAC I¹⁸ trial used a SNAC study specific scale (SSSS). Descriptions of the different scales/questionnaires used in these trials are provided in Table 8.

The ALMANAC trial^{1,17} assessed QoL using the FACT-B questionnaire and TOI. Using both of these scales, QoL was statistically significantly better in the SNB group compared to ALND. There was no difference in the STAI scores between the treatment groups, indicating that no increase in anxiety in those who had SNB performed compared to ALND.

The SNAC I trial¹⁸ used a unique scoring system with significantly higher scores (indicating worse outcome) reported in the ALND arm for overall QoL, symptoms and dysfunction, compared to the SNB arm.

The Cambridge trial²¹ reported no significant differences between the groups for the STAI, BDI and MAC scores. However the SNB group reported better outcomes on the BSI, SF-36, GSI scales.

These were mostly significant immediately after surgery (baseline). Stratification by nodal status only found significant differences in the vitality component of SF-36 in the node-negative patient group with a higher level (immediately after surgery) for the vitality SF-36 component in the SNB group compared to the ALND group.

The GIVOM trial²² introduced the QoL component of the trial two years after the start of the study and therefore information is only available for 310 patients. While the physical and mental component summary scales from the SF-36 were lower at all time points (6, 12, 24 months after surgery) compared to baseline, there were no significant differences between the SNB and ALND groups. The mean scores of the PGWB questionnaire were significantly better in the SNB arm compared to ALND (p=0.01). However, this was not evident at 24 months after surgery.

Table 8: Quality of life scale descriptions

Scale	Description
FACT-B+4	The Functional Assessment of Cancer Therapy – Breast (FACT-B) is a comprehensive measure of overall quality of life that contains one item on arm morbidity. FACT-B+4 is the FACT-B plus four additional arm morbidity items. The trial outcomes index (TOI) score is derived from the sum of the scores on the physical and well-being subscales and on the breast cancer concerns subscale. Higher scores indicate a better quality of life and lower scores indicate a worse quality of life.
STAI	The state and trait anxiety index (STAI) is a self-report assessment device which includes separate measures of state and trait anxiety. Scores on the STAI have a direct interpretation: high scores on their respective scales indicate more trait or state anxiety and low scores indicate less anxiety.
BSI	The brief symptom inventory (BSI) assesses more serious psychiatric disturbance and its subscales are sensitive to morbidity in cancer patients. The global severity index (GSI) is the sum of the subscales in BSI, and is a measure of overall distress.
MAC	The mental adjustment to cancer (MAC) scale assesses coping responses via four subscales, including fighting spirit, helpless/hopeless, anxious preoccupation and fatalism. Internal consistency of the subscales ranges from .65 (fatalism) to .84 (fighting spirit).
BDI	The Beck depression inventory (BDI) assesses degree of depression. When the test is scored, a value of 0 to 3 is assigned for each answer and then the total score is compared to a key to determine the depression's severity. Higher total scores indicate more severe depressive symptoms.
SF-36	Short form 36 (SF-36) is a 36 item questionnaire which assesses subjective quality of life in terms of physical and social functioning, pain, mental and general health, vitality and role limitations due to physical health and emotional problems.
PGWB	Psychological General Well-Being (PGWB) scale has 22 items rated on a scale from 0 (most negative) to 5 (most positive), related to anxiety, depressed mood, positive well-being, self-control, general health and vitality. PGWB is highly correlated to the BDI.
SSSS	SNAC Study Specific Scale (SSSS) has 15 items rated on a scale from 0 (none) to 10 (worst imaginable) relating to arm symptoms, dysfunctions, and disabilities.

Adverse events

The NSABP B-32 trial¹⁹ is the only RCT to report on adverse events. Allergic reactions occurred in 0.7% of patients (0.2% grade 3 or 4).

The RCTs excluded patients with known allergies to blue dye or isotope.

Secondary Questions

Six additional RCTs were identified which investigated secondary research questions. Secondary research questions explored:

- different use of detection agents (dye, radioisotope) to detect SN
- different injection sites of the detection agents
- different treatment after a positive SN is detected (ALND vs. no further surgery).

Characteristics of these trials are described in Table 9.

Patients included in these trials were similar to those included in the previously mentioned studies: patients with early stage operable breast cancer, clinically node negative (with the exception of ACOSOG Z0011²⁹).

Table 9: Characteristics of trials addressing secondary questions

Trial	Country	Population	Intervention	Outcomes measured
Detection agent used				
Radovanovic ³⁰	Serbia	Women clinically T1-2 NOM0 breast cancer	i) Blue dye only n=50 ii) Blue dye and radiotracer n=100	Accuracy, FN rate, Specificity, Sensitivity
Hung ⁴	Hong Kong	Women <70yrs early breast cancer <3cm.	i) Blue dye only n=57 ii) Blue dye and isotope n=61	Accuracy, FN rate, Detection rate
Meyer-Rochow ⁵	New Zealand	Malignant palpable breast lump stage I or II breast cancer	i) Blue dye alone n=63 ii) Triple modality (preoperative lymphoscintigraphy, intraoperative gamma probe and blue dye) n=41	Accuracy, FN rate, Specificity, Sensitivity
Injection site				
FRANSENODE ³¹	France	T0-1 invasive breast cancer Clinically negative axilla.	i) Peritumoural injection of radiotracer and/or blue dye n=224 ii) Periareolar injection of radiotracer and/or blue dye n=225	Detection rate
Povoski ³²	US	Females >18yrs T1-2,N0,M0 BC (invasive or non-invasive)	i) Intradermal injection of radioisotope* n=133 ii) Intraparenchymal injection of radioisotope* n=134 iii) Subareolar injection of radioisotope* n=133 *for all patients blue dye was injected intraparenchymally	Detection rate
Sentinel node positive				
ACOSOG Z0011 ²⁹	US	undergoing BCT clinical T1-2, N0, M0 BC, 1 or 2 positive SNs	i) SNB (blue dye and/or isotope) ⇒ no further surgery n=445 ii) SNB (blue dye and/or isotope) ⇒ ALND n=446	QoL, detection rate

ALND=axillary lymph node dissection, BC=breast cancer, BCT=breast conserving therapy, DFS=disease-free survival, FN=false negative, QoL=quality of life, SN=sentinel node, SNB=sentinel node biopsy.

Detection agent used

Three RCTs investigated the use of different detection agents to identify the SN. Two trials investigated the use of blue dye alone compared to combination of blue dye and radioisotope.^{4,30} One trial investigated blue dye alone versus triple modality,⁵ preoperative lymphoscintigraphy, intraoperative gamma probe and intraoperative blue dye. After SNB, patients underwent level I and II ALND to verify axillary status. These trials primarily reported on the accuracy (including sensitivity, specificity and false negative rates) of the agents used.

The RCTs investigating differences in using blue dye alone compared to combined techniques were small, including 100–150 patients in total.^{4,5,30}

The trials used different blue dyes and radioisotopes. The Serbian trial³⁰ used Patent Blue V and 11.1 MBq technetium 99m antimony sulphide, the Hong Kong trial⁴ used Patent Blue dye and unfiltered technetium sulphur colloid (mean particle size 500nm) and the New Zealand (NZ) trial⁵ used Patent Blue V and 40 MBq technetium 99-antimony sulphur colloid. The Serbian³⁰ and New Zealand⁵ trials injected the tracing agent peritumourally, the Hong Kong trial injected subdermally.

Results

The varying success of the detection agents are reported in Table 10. Two trials reported on the SN detection rates^{4,5} with the combination arms reporting significantly higher rates (98–100%) than the blue dye alone arms (86–90%). The differences in detection rates between combination and blue dye alone were statistically significant for both trials.

The trials reported high rates of positive nodes (34–56%), with greater proportions reported in the combination arms (differences were either non-significant or not reported). In the NZ trial,⁵ triple modality took longer to identify the SN than blue dye alone (14 min vs. 11 min, $p<0.05$).

The accuracy of using either blue dye alone or combination reported in the Hong Kong⁴ and NZ⁵ trials was high (95–100%) and similar between treatment arms. The Serbian trial³⁰ reported lower accuracy rates overall with a higher rate in the combination arm compared to blue dye alone (83% vs. 68%, $p=0.048$).

Sensitivity and specificity were reported in two of the three trials^{5,30} with no significant difference observed between the treatment arms.

Although the rates of FNs varied between trials (0–18%), there was no significant difference for the FN rates observed between treatment arms in any of the three trials. The Serbian trial³⁰ reported a significantly higher negative predictive value for combination compared to blue dye alone (95.3% vs. 87%, $p=0.033$).

Table 10: Success of detection agents

Trial (first author – country)	Blue dye and isotope	Blue dye only	p-value
SN detection rate	%	%	
Hung – Hong Kong ⁴	100	86	0.002
Meyer-Rochow - NZ ⁵	98	90	<0.05
SN positive			
Radovanovic - Serbia ³⁰	44	34	
Hung – Hong Kong ⁴	54	44	0.266
Meyer-Rochow - NZ ⁵	56	37	
Accuracy	%	%	
Radovanovic - Serbia ³⁰	83	68	0.048
Hung – Hong Kong ⁴	100	98	0.262
Meyer-Rochow - NZ ⁵	95	98	NS
False negative rate	%	%	
Radovanovic - Serbia ³⁰	4.5	17.6	0.127
Hung – Hong Kong ⁴	0	5	0.216
Meyer-Rochow - NZ ⁵	9	4	NS
Sensitivity	%	%	
Radovanovic - Serbia ³⁰	95	82	0.129
Meyer-Rochow - NZ ⁵	91	96	NS
Specificity	%	%	
Radovanovic - Serbia ³⁰	73	60	0.244
Meyer-Rochow - NZ ⁵	100	100	NS
Negative predictive value	%	%	
Radovanovic - Serbia ³⁰	95.3	87	0.033

Notes: NS=not significant, SN=sentinel node

Injection Sites

Two RCTs investigated differences in injection sites. One trial³¹ investigated the differences between peritumoural and periareolar injection sites (N=454). The other³² investigated three routes of injection at intradermal (ID), intraparenchymal (IP) and subareolar (SA) sites (N=400).

The FRANSENODE trial³¹ randomised patients to receive their injection of unfiltered technetium 99m-labeled sulphur colloid and Patent Blue Dye in either the peritumoural (PT) or periareolar (PA) region. The US study³² randomised patients to receive injections of 99m-Tc-sulfur colloid at either intradermal (ID), intraparenchymal (IP) or subareolar (SA) sites; isosulfan/methylene blue dye was injected intraparenchymally for all patients.

In both trials, ALND was only performed if the SN was not found or if the SN was positive for metastases.

Results

The FRANSENODE trial³¹ reported that the detection of axillary SN by pre-operative lymphoscintigraphy was higher in the PA group than the PT group (85.2% vs. 73.2%, p=0.03; see

Table 11). The detection rate was high in both arms for blue dye and/or gamma probe (99.1%), with good concordance between identification by blue dye and gamma probe.

Pre-operative lymphoscintigraphy axilla localisation rates for the US trial³² were significantly higher in the ID injection site compared to IP and SA injection sites (see Table 12). The study also reported that the ID injection route had the highest success of intraoperative localisation of an SN, and shortest time to harvest the first SLN compared to the other injection routes.

The US study³² reported that there were no allergic reactions to 99m-technetium-sulfur colloid in any of the three injection routes. Allergic reactions to isosulfan blue dye were reported in 1.03% of patients. However, there were no reported reactions to methylene blue dye.

The FRANSENODE trial³¹ reported no adverse perioperative effects, especially anaphylactic reaction, after blue dye injection.

Table 11: Results of the FRANSENODE trial³¹

Outcome	PT		PA		p-value
	n	%	n	%	
Detection of SN (axilla, IMN & other) by pre-operative lymphoscintigraphy	169	78.2	184	85.2	0.11
Detection of axillary SN by pre-operative lymphoscintigraphy	158	73.2	184	85.2	0.03
Mean SN detected (range)	1.67 (1–5)		1.88 (1–6)		0.01
Detection rate by blue dye and/or gamma probe	222	99.1	223	99.1	0.99
SN identified by blue dye	210	93.8	215	95.6	0.24
SN identified by gamma probe	215	96	221	98.2	0.16

Notes: IMN=internal mammary node, PA=periareolar, PT=peritumoural, SN=sentinel node

Table 12: Results of the US study³² comparing three injection routes

Outcome	ID		IP		SA		p-value
	n	%	n	%	n	%	
Pre-operative lymphoscintigraphy localisation to axilla	126	95	82	62	96	72	ID vs. IP: <0.001 ID vs. SA: <0.001 IP vs. SA: 0.081
Intraoperative identification of SN	133	100	121	90	126	95	ID vs. IP: <0.001 ID vs. SA: 0.014 IP vs. SA: 0.168
Mean intraoperative time to harvest first SN (minutes)	9 ± 4		13 ± 6		12 ± 6		ID vs. IP: <0.001 ID vs. SA: <0.001 IP vs. SA: 0.410
Mean number of SN identified	2.5 ± 1.4		2.2 ± 1.2		2.6 ± 1.6		Overall: 0.234
Identification of “blue” SN	93	71	83	62	91	68	Overall: 0.304
Identification of “hot” SN	133	100	121	90	126	95	ID vs. IP: <0.001, ID vs. SA: 0.014 IP vs. SA: 0.168
Identification of “blue” and “hot” SN	90	97	82	99	87	96	Overall: 0.462

Notes: ID=intradermal, IP=intraparenchymal, SA=subareolar, SN=sentinel node

Surgical procedures after positive sentinel node detection

American College of Surgeons Oncology Group Z0011²⁹

The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial investigated a separate question of whether a person with only one or two positive SNs can be treated safely with no further surgery.

The trial enrolled breast cancer patients who had an SNB and had one or two positive SNs. SNB was performed with blue dye (isosulfan blue) and/or radioisotope. Patients with previous cancer history, bilateral breast cancer, multicentric disease, three or more positive SNs, contraindications to ALND or who are breastfeeding were excluded from the study. Patients were randomised to further treatment with axillary lymph node dissection (n=446) or no further surgery (n=445) before given breast radiation therapy and/or systemic adjuvant therapy.

Results

Patient characteristics were similar between groups. Adverse surgical effects were measured. Seventy percent of patients in the SNB plus ALND group reported an adverse surgical effect compared to 25% of SNB alone patients (p<0.001).

Higher rates of wound infections (8% vs. 3%, $p=0.0016$) and axillary seromas (14% vs. 6%, $p=0.0001$) were found in the SNB+ALND group compared to the SNB alone group. Greater BMI was associated with a small increase of wound infections.

Axillary paresthesias were present at 30 days, 6 months and 12 months, with significantly higher rates in the ALND group than the SNB alone group at all times. Age was associated with axillary paresthesias with younger patients more likely to have paresthesia at one year.

Lymphoedema was measured both subjectively (patient self-report or physician diagnosis) and objectively (comparing arm circumferences). Interestingly, only the subjective measurements were statistically different between the two treatment groups (at 12 months ALND: 13%, SNB alone: 2%, $p<0.001$; after 12 months ALND: 19%, SNB alone: 6%, $p<0.001$). The objective measurements approached significance at 12 months with 11% of patients with lymphoedema from ALND group and 6% from the SNB alone group ($p=0.0786$). Age was associated with subjective measurements of lymphoedema with younger patients more likely to report lymphoedema.

This trial did not report any data on axillary recurrence, DFS or OS.

ONGOING TRIALS

The following clinical trials websites were searched to identify any additional SNB studies which have not yet reported.

- Australian Clinical Trials Registry (ACTR) <http://www.actr.org.au/>
- Clinical Trials.gov <http://www.clinicaltrials.gov/>
- Current Controlled Trials <http://www.controlled-trials.com/>
- National Research Register <http://www.nrr.nhs.uk/>
- National Cancer Institute <http://www.cancer.gov/clinicaltrials>.

Two RCTs^{33,34} were identified as ongoing trials with each currently recruiting patients. Details of the trials are presented in Table 13 below. Both trials are investigating treatment following identification of a positive SN/micrometastases from SNB. Both trials are multicentre RCTs. The AMAROS trial³³ is being conducted throughout Europe and at November 2006 had recruited 61% of the total number of patients needed for the trial. The IBCSG-23-01 trial³⁴ is an international trial with two participating centres in Australia. There is currently no indication when these trials are likely to report results.

An additional ongoing trial, SNAC II is an extension of SNAC I, with broader inclusion criteria to include women with tumours larger than 3cm and/or multifocal tumours.³⁵

Table 13: Ongoing studies investigating sentinel node biopsy

Title/trial name	Location/s	Status	Participants	Treatment	Objectives
Phase III Randomised Study of Complete Axillary Lymph Node Dissection Versus Axillary Radiotherapy in Sentinel Lymph Node-Positive Women With Operable Invasive Breast Cancer					
EORTC-10981-AMAROS , NCT0001461 ³³	France, Italy, Netherlands, Poland, Slovenia, Switzerland, Turkey, UK (Wales)	Currently recruiting	<ul style="list-style-type: none"> • N=3485 • 1394 SN positive • 2091 SN negative • SNB performed in all patients 	<p>Arm I: SN -ve patients undergo no further surgery</p> <p>Arm II: SN +ve patients undergo complete ALND</p> <p>Arm III: SN +ve patients undergo radiotherapy 5 days a week for 5 weeks</p>	<p>Primary outcome: Axillary recurrence rates</p> <p>Secondary outcomes: morbidity, DFS, OS</p>
A randomised trial of axillary dissection versus no axillary dissection for patients with clinically node negative breast cancer and micrometastases in the sentinel node.					
CDR0000339581 IBCSG-23-01 EU-20319 NCT00072293 ³⁴	Australia, Brazil, Denmark, Italy, Peru, Slovenia, Switzerland	Currently recruiting	<ul style="list-style-type: none"> • N = 1960 • Female • any age • Clinically node negative cancer • Micrometastases in SN 	<p>Arm I: Surgical resection of primary tumour with ALND</p> <p>Arm II: Surgical resection of primary tumour without ALND</p>	<p>Do micro-metastases in the SN warrant axillary clearance?</p> <p>Outcomes: DFS, OS, QoL</p>
A randomised phase III study to determine in women with early breast cancer whether SN based management increases the risk of loco-regional recurrence and in particular, axillary recurrence, compared with axillary clearance in any subgroup of women					
SNAC II ³⁵	Australia & New Zealand	Currently recruiting	<ul style="list-style-type: none"> • N = 1012 • Female • Single or multiple ipsilateral BC • Primary BC may be less than or greater than 3cm 	<p>Arm I: Sentinel node biopsy with immediate standard axillary clearance</p> <p>Arm II: Standard axillary clearance</p>	<p>To determine if sentinel node based management increases the risk of loco-regional recurrence compared with axillary clearance in any subgroup of women</p> <p>Outcomes: OS, DFS</p>

Notes: ALND=axillary lymph node dissection, BC=breast cancer, DFS=disease-free survival, OS=overall survival, QoL=quality of life, SN=sentinel node

DISCUSSION

SENTINEL NODE BIOPSY COMPARED TO AXILLARY LYMPH NODE DISSECTION

In all but two of the trials SNB was compared to SNB+ALND rather than ALND alone and therefore the observed effects may be due to an additive effect of having both surgeries rather than a direct comparison of SNB to ALND.

The ALMANAC trial¹ did not perform SNB in the control arm; however, this control arm included both ALND and axillary sampling. This may have led to an underestimation of the benefit of SNB compared to axillary dissection alone; however, a benefit of SNB was still observed. The ALMANAC trial is expected to report at a later date on the comparison between axillary sampling and SNB.

Trials which used an intention-to-treat analysis may also have underestimated the benefit of SNB compared to ALND, as approximately 30% of patients in the SNB group were node positive and therefore received ALND as well. The Cambridge trial²¹ (which also did not perform SNB in the control arm) analysed node-negative and node-positive patients separately so that the node-negative patients represented the comparison of ALND only with SNB only and the node-positive patients represented a comparison of immediate ALND with delayed ALND. This trial found differences in morbidity data in the node-negative group, showing that patients receiving SNB alone reported less physical morbidity than those who received ALND alone. No significant differences were seen in the node-positive group, indicating that receiving ALND, immediately or delayed, did not impact morbidity.

The localisation and FN rates reported in the RCTs are consistent with the previously reported systematic reviews. The localisation rates of 93%–98% are comparable with the pooled rate reported in the MSAC review (94%).¹⁴ The FN rates reported in the RCTs are slightly higher (8.2–16.7%) than that reported in the MSAC review (4.7%),¹⁴ however are similar to the average rate reported in the Kim review for ASCO (8.5%).¹⁵ The GIVOM trial³ reported a high FN rate (16.7%); however this trial stated that not all surgeons in this trial had been appropriately trained and/or were familiar with the SNB technique. Surgeons participating in the ALMANAC, NSABP B-32, and SNAC I trials received prior training in SNB and therefore lower FN rates were expected.

Three of the included RCTs reported on OS and DFS, with equivalent rates in both the SNB and the ALND groups. However, the Milan² and GIVOM³ trials are small and the ALMANAC trial¹ has only reported a median follow-up of 12 months, so it is difficult to draw firm conclusions based on these results. Longer follow-up is needed from the larger RCTs to determine the effects of SNB on OS and DFS compared to ALND.

The reported rates of axillary recurrence in the trials are low, with a relatively short follow-up. Further results from longer follow-up are needed to determine the effect of SNB on axillary recurrence rates compared to ALND.

Physical morbidity outcomes including lymphoedema, shoulder and arm functioning, numbness and pain were reported less often in the SNB groups than the ALND groups.

QoL was measured by a variety of measures and scales. Most trials used validated questionnaires such as the FACT-B or SF-36 (except Milan). The SNAC I¹⁸ trial created its own scale which was validated internally. The ALMANAC trial^{1,17} used a breast cancer specific questionnaire FACT-B which showed improved QoL in the SNB arm compared to ALND. The other trials which used broad, general scales did not report a difference in QoL between treatment arms which may reflect the numerous aspects assessed by these questionnaires, only some of which may be affected by the different surgical procedures.

Morbidity data was not reported for every patient in the Milan trial;¹⁶ 100 consecutive patients from each group were evaluated at 6 and 24 months after surgery. The GIVOM²² trial initiated the QoL subsection two years after the trial had started and therefore data is not available for all members of the trial.

The RCTs excluded patients with a known allergy to blue dye or isotope. Only NSABP B-32¹⁹ reported rates of allergic reaction (0.7%). The MSAC review¹⁴ found case series to report small percentages of allergic reactions (0-1.6%) to blue dye. Up to August 2002, the Australian Drug Reactions Advisory Committee (ADRAC) had received 42 reports of reactions to Patent Blue V dye.³⁶ Five cases of anaphylaxis have been reported between October 2000 and August 2002 in women undergoing breast surgery, four of which were considered severe. The Australian Therapeutic Goods Administration (TGA) has stated that surgeons and anaesthetists should be aware of the potential for severe allergic reactions to Patent Blue V and that testing for hypersensitivity is recommended by the Product Information.³⁶

SECONDARY QUESTIONS

Three trials investigated differences in detection agents.^{4,5,30} Comparisons were made between blue dye alone and combination blue dye and radioisotope, with suggestions that using the combined technique is superior. Each of these trials contained small numbers of patients. Further information is needed to determine optimal detection agent(s).

Two RCTs have investigated differences in injection sites.^{31,32} Each trial investigated different injection routes. The majority of the RCTs reporting on the primary question of this review injected peritumourally. Further information is needed to determine the optimal injection site for SNB.

One randomised trial has reported on treatment of patients with positive SNs (ACOSOG Z0011²⁹). Two large ongoing RCTs will also investigate the question of the treatment of micrometastases in the SN (AMAROS,³³ IBCSG-23-01³⁴). It is unknown when these trials are likely to report.

CONCLUSIONS

SENTINEL NODE BIOPSY VS. AXILLARY LYMPH NODE DISSECTION

Both SNB and ALND are associated with high rates of localisation of the SN (~94%).

SNB can however produce false negative results, but no worse than ALND. Experience of the surgeon performing the procedure may influence false negative rates. SNB achieves equivalent localisation, OS and DFS rates compared to ALND at 5 year follow-up. However, further results are needed to confirm and to determine if SNB provides an OS and/or DFS benefit compared to ALND. SNB results in lower morbidity compared to ALND, both immediately following surgery and up to 24 months after, including lower rates of lymphoedema, arm morbidity and sensory deficit. Patients receiving SNB report shorter stays in hospital compared to ALND. SNB results in similar, if not better, QoL outcomes compared to ALND. The RCTs did not report on adverse events. However, allergic reactions to Patent Blue V have been reported in Australia and therefore SNB teams should be aware of the potential for allergic reactions to blue dye.

SECONDARY QUESTIONS

A combination of blue dye and radioisotope are superior at detecting the SN compared to blue dye alone. Accuracy, sensitivity, specificity and false negative rates appear to be similar between blue dye alone and combination methods.

Further research is needed to determine the optimal injection site of blue dye/radioisotope for SNB.

Investigation is continuing on how to treat patients with micrometastases in the SN.

APPENDICES

Appendix 1.

Literature databases searched

Source	Results/Retrievals
Medline (Ovid)	88
CINAHL (Ovid)	7
EBM Reviews (Ovid)	7
Embase	40
Pubmed	112
Additional papers (sourced from reference lists and conference sites)	12

Appendix 2.

Health technology assessment, guidelines and clinical trials websites searched

Country	Acronym	Organisation	Website
Australia	ACTR	Australian Clinical Trials Registry	http://www.actr.org.au/
	ANZBCTG	Australian New Zealand Breast Cancer Trials Group	http://www.anzbctg.org/
	NICT	National Institute of Clinical Trials	http://www.nhmrc.gov.au/nics/asp/index.asp?
Canada	CCO	Cancer Care Ontario	http://www.cancercare.on.ca/
International	HTAi	Health Technology Assessment International	http://www.htai.org/
Scotland	SIGN	Scottish Intercollegiate Guidelines Network	http://www.sign.ac.uk/
UK	CRD	Centre for Reviews and Dissemination	http://www.york.ac.uk/inst/crd/
	CCT	Current Controlled Trials	http://www.controlled-trials.com/
	NICE	National Institute for Health and Clinical Excellence	http://www.nice.org.uk/
	NRR	National Research Register	http://www.nrr.nhs.uk/
US		ClinicalTrials.gov	http://www.clinicaltrials.gov/
	NCI	National Cancer Institute Clinical Trials	http://www.cancer.gov/clinicaltrials
	NGC	National Guideline Clearinghouse	http://www.guideline.gov/

Appendix 3.

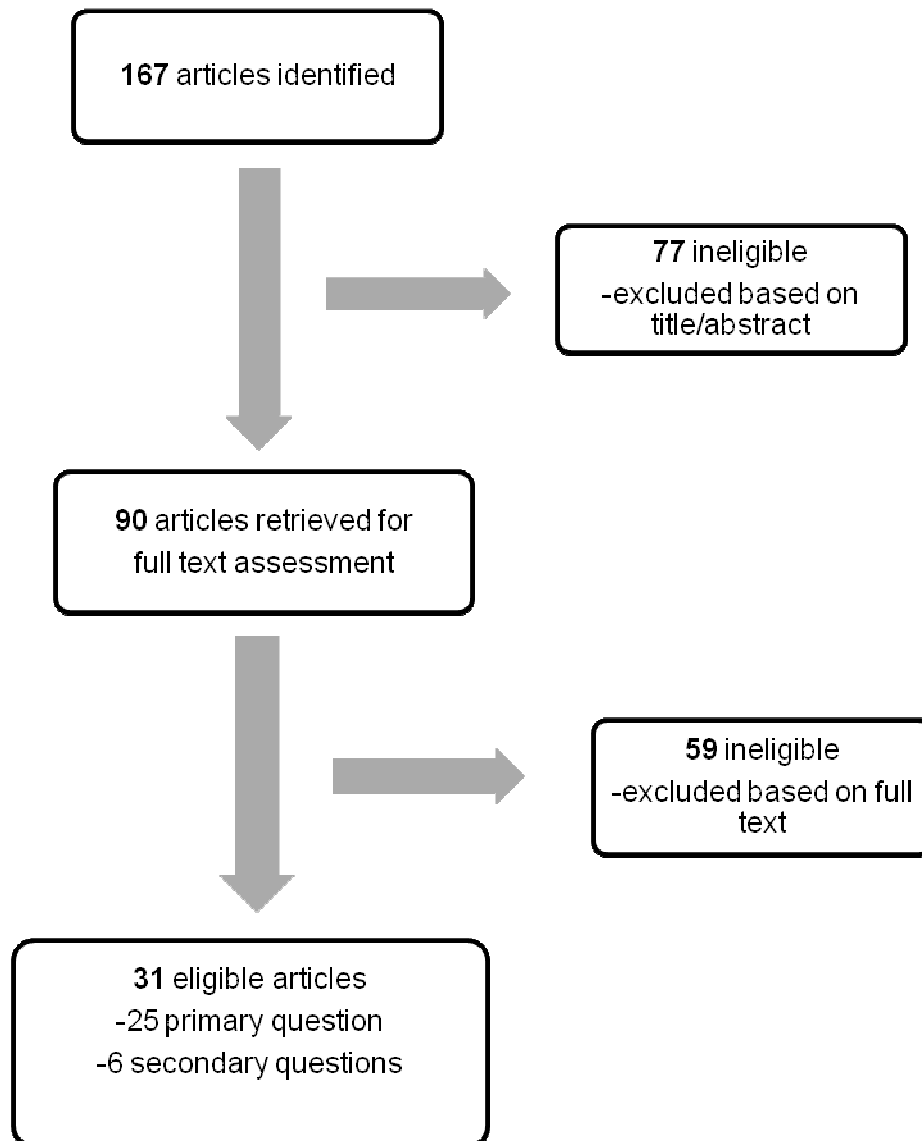
Terms used in search strategy

Key areas	Search Terms
Breast Cancer	(breast neoplasms/ or (breast and (cancer or carcinoma)))
Sentinel Node Biopsy	(Sentinel Lymph Node Biopsy/ or SLN\$ or SNB or (sentinel and (biopsy or dissection or lymphadenectomy)) or lymph\$ map\$)
Axillary dissection	((Axilla/ and Lymph Node Excision/) or ALND or CLND or (axilla\$ and (dissection or clearance or lymphadenectomy))
Randomised trials	(Randomized Controlled Trial/ or “randomized controlled trial” or “randomized controlled trials” or “randomised controlled trial\$” or “random\$” or “random allocation” or “controlled clinical trial” or “controlled trial” or “double blind method” or “single blind method” or (“meta-analysis/” or “meta-analysis” or “meta analysis”) or “systematic review” or “pooled analysis”)

* / indicates Mesh terms, \$ indicates truncated terms.

Appendix 4.

Flowchart of inclusion/exclusion process



Appendix 5.

Detailed lymphoedema data from randomised trials comparing SNB with ALND

Trial	Time after	SNB		ALND		p-value
		n	%	n	%	
Lymphoedema						
ALMANAC	1mth	14	3.2	50	12	
	3mth	20	5	61	15	
	6mth	19	4.5	71	17	
	12mth	20	5	53	13	<0.001
GIVOM	6mth		4		10	0.005
	12mth		4.5		9	0.03
	18mth		4.5		6	
	24mth		4.5		7	
Swelling						
ALMANAC	baseline		3.2		4.4	
	1mth		12		28	<0.001
	3mth		6.7		14.5	
	6mth		7.5		15.8	
	12mth		5.2		11.8	0.002
	18mth		7		14	
MILAN	6mth	11	11	69	69	
	24mths	7	7	75	75	
SNAC I (SSSS)	6mths and 12mths	3.4*		7.4*		<0.0001
Increased arm volume						
SNAC I			2.8		4.2	
Cambridge	1mth	8.1ml		49.6ml		0.001
	3mth	26.1ml		60ml		0.04
	6mth	22.1ml		45.5ml		0.2
	12mth	18.6ml		56.4ml		0.03
	Mean	17.7		53.1		0.004
	Maximum	78.4		113.7		0.02

*Scale 0-10, 10 being worst

Notes: ALND=axillary lymph node dissection, SNB=sentinel node biopsy, SSSS=SNAC study specific scale

Appendix 6.

Detailed morbidity data from randomised trials comparing SNB with ALND

Trial	Time after	SNB		ALND		p-value
		n	%	n	%	
Shoulder functioning						
ALMANAC (flexion degrees)	1mth	5.8		9.8		0.004
	3mth	2		3.7		0.33
	6mth	2		1.6		0.98
	12mth	2.7		0.1		0.054
Cambridge (flexion degrees)	12mth	6.7		13		0.04
GIVOM (movement restrictions)	6mth		7		15	0.005
	12mth		5		7	
	18mth		4		5	
	24mth		4		7	
Arm functioning						
ALMANAC (reporting poor range of movement)	Baseline		4.8		3.6	
	1mth		6.7		22	<0.001
	3mth		3.3		6.6	0.035
	6mth		4.4		6.6	
	12mth		6		8.8	
	18mth		6.2		8.4	
Milan (80%-100% mobility)	6mth	100	100	73	73	
	24mth		100		79	
Numbness						
ALMANAC (numbness in ipsilateral arm)	Baseline		1		2.6	
	1mth		9.3		29.7	<0.001
	3mth		7.3		26.6	
	6mth		9		26.5	
	12mth		6		20.4	
	18mth		8.7		19	
Milan (numbness in ipsilateral arm)	6mth	2	2	85	85	
	24mth	1	1	68	68	
Cambridge	12mths	68	48	115	65	
GIVOM	6mths		22		30	0.016
	12mths		12		20	0.004
	18mths		6		17	0.0002
	24mths		8		15	0.03

Sensory deficit		n	%	n	%	
ALMANAC (sensory loss)	1mth	74	18	252	62	
	3mth	81	20	209	54	
	6mth	69	16	178	43	
	12mth	46	11	124	31	
Cambridge	12mth	92	66	130	84	
Axillary pain		n	%	n	%	
Milan	6mth	16	16	91	91	
	24mth	8	8	39	39	
GIVOM	6mth		10		18	0.006
	12mth		9		11	
	18mth		7		9	
	24mth		8		10	

Notes: ALND=axillary lymph node dissection, SNB=sentinel node biopsy

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