Recommendations for use of Sentinel node biopsy

in early (operable) breast cancer

JUNE 2008 | Incorporates published evidence to July 2007

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY NATIONAL BREAST AND OVARIAN CANCER CENTRE (NBOCC)*

This document supplements guideline recommendation 9 about axillary node dissection (page 8) and information about *sentinel node biopsy* (page 57) contained in the National Breast Cancer Centre (NBCC)* *Clinical practice guidelines for the management of early breast cancer,* 2nd edition 2001.[1]

National Breast and Ovarian Cancer Centre (NBOCC)* has recommendations about staging and management of the *axilla* in *early breast cancer* to supplement chapter 4.4 (pages 55-59) of the NBCC *Clinical practice guidelines for the management of early breast cancer,* 2nd edition 2001.[1]

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Purpose

This guideline includes statements and recommendations based on available, high-level evidence about the use of *sentinel node biopsy* in women with early (operable) breast cancer. The guideline aims to provide health professionals with information to assist in making management recommendations for improved patient outcomes. NBOCC* also develops information specifically for consumers about *early breast cancer* diagnosis and treatment options.

Endorsed by:

Breast Cancer Network Australia

The Royal Australian and New Zealand College of Radiologists®
The Faculty of Radiation Oncology

RCPA
The Royal College of Pathologists of Australasia

The Royal Australasian College of Surgeons

* In February 2008, National Breast Cancer Centre (NBCC), incorporating the Ovarian Cancer Program, changed its name to National Breast and Ovarian Cancer Centre (NBOCC). In July 2011, NBOCC amalgamated with Cancer Australia to form a single national agency, Cancer Australia, to provide leadership in cancer control and improve outcomes for Australians affected by cancer.

Background

Early (operable) breast cancer is defined as tumours not more than five centimetres in diameter,** with either impalpable or palpable, but not fixed, *lymph nodes* and with no evidence of distant metastases.[1]

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) 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 significant number of the lymph nodes in the axilla. Axillary dissection has been associated with morbidity, particularly *lymphoedema*.[1] Only about 30% of women with early breast cancer will have positive axillary nodes, therefore around two thirds of women receive no benefit from axillary dissection and are at risk of morbidity associated with the procedure.[2]

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

Clinical practice recommendations

Recommendations to individuals should be based on their risks without sentinel node *biopsy*, the absolute benefits and harms of the procedure, and their preference. These factors should be discussed with the woman. Recommendations should also take account of any uncertainties about the long-term effects of sentinel node biopsy.

RECOMMENDATIONS	LEVEL OF EVIDENCE[19]	REFERENCE
In women with early (operable) breast cancer:		
Sentinel node biopsy should be offered as a suitable alternative to axillary dissection for women with: • unifocal tumours equal to or less than three centimetres in diameter and • clinically negative nodes Sentinel node biopsy is not recommended for women with clinically or pathologically positive nodes There are no randomised trial results to support the use of sentinel node biopsy in: • women with multicentric/multifocal tumours • pregnant or breastfeeding women • women with known allergies to radioisotopes or blue dye	II	Milan[4,5] ALMANAC[6] SNAC I[8] NSABP B-32[9] Cambridge[10] GIVOM[11,12]

RECOMMENDATIONS	LEVEL OF EVIDENCE[19]	REFERENCE
• women with previously treated breast cancer or axillary surgery on the affected side		
Information about procedures should be discussed with the patient. The patient should be adequately prepared for the procedure For sentinel node biopsy this includes: • a clear description of sentinel node biopsy • clear information about the objective of the procedure • the potential of an unsuccessful sentinel node biopsy or false negative result	I	NBCC* & NCCI[25]
If the sentinel node is identified at the time of sentinel node biopsy: • for a positive sentinel node—axillary dissection is recommended (with due consideration of the risks and benefits to the individual woman) • for a negative sentinel node—clinical follow-up of the *axilla* is recommended If the sentinel node is **not** identified at the time of sentinel node biopsy: • axillary dissection should be performed	II	Milan[4,5] ALMANAC[6] SNAC I[8] NSABP B-32[9] Cambridge[10] GIVOM[11,12]
Team, training and experience		
The outcome of women with breast cancer is better if they are treated by a clinician who has access to the full range of treatment options in a *multidisciplinary care* setting The team for performing sentinel node biopsy should comprise a surgeon, nuclear physician (where nuclear medicine facilities are available), *pathologist*, anaesthetist and appropriate nursing support throughout and following the procedure Ongoing data collection and audit of sentinel node biopsy performance by the team should be conducted	III	NBCC[1 *]
The surgeon performing sentinel node biopsy should be appropriately trained and experienced in the sentinel node biopsy techniques and have evidence of successful identification of sentinel node(s) The Australian SNAC I[22] protocol states the surgeon performing sentinel node biopsy should have completed sentinel node biopsy in at least 20 consecutive cases with a greater than 90% success rate in locating the sentinel node(s)		Milan[4,5] ALMANAC[6] SNAC I[8] NSABP B-32[9]
Technique		
Where possible, lymphatic mapping with pre-operative lymphoscintigraphy in combination with intraoperative use of the *gamma probe* and blue dye should be used to locate the sentinel node(s)	II	Radovanovic[13] Hung[14] Meyer-Rochow[15]

RECOMMENDATIONS	LEVEL OF EVIDENCE[19]	REFERENCE
Where combination technique is not available or suitable, use of blue dye or radioisotope alone is an appropriate option Blue dye alone could be used where no nuclear facilities are available; however, the individual surgeon's sentinel node biopsy technique and results should be audited	II	Radovanovic[13] Meyer-Rochow[15] Hung[14] Milan[4,5] GIVOM[11,12]
Trial results do not indicate that any site of injection (peritumoural, periareolar or intradermal) is superior in detecting the sentinel node(s) in the axilla		FRANSENODE[16] Povovski[17]
All identified sentinel nodes should be excised, including non-axillary sentinel nodes, if they can be accessed and excised without increased morbidity		SNAC I[22]
False negative rates		
To reduce false-negative rates, surgeons should aim to remove all identified sentinel and/or clinically suspicious nodes at the time of surgery However, removal of four or more nodes from the axilla can increase risk of morbidity, and does not lower the false negative rate significantly compared with removing up to three nodes	II	NSABP B-32(2007)[20]
Pathology		
Detailed, definitive histological assessment (including immunohistochemistry and serial sectioning) of the sentinel node is recommended for the detection of metastatic disease		NBOCC* & ACN[23]
Intraoperative assessment of the sentinel node may be performed, allowing those cases identified as positive for metastatic disease to proceed to immediate axillary dissection as a single procedure Intraoperative assessment should be confirmed with detailed, definitive histological assessment	II	NSABP B-32[9] GIVOM[11]
Adverse events		
Surgeons and anaesthetists should be aware of the possibility of adverse reactions (including allergies) in patients and, in the event of an adverse reaction, agreed protocols should be in place	IV	MSAC[24] TGA[26]
Clinical trials		
When sufficient evidence does not exist to guide definitive recommendations for the use of sentinel node biopsy, if possible, patients should be offered entry into properly conducted clinical trials where indicated and/or appropriate	III	NBCC[1*]

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Statements of evidence

STATEMENTS	LEVEL OF EVIDENCE[19]	REFERENCE
In women with early (operable) breast cancer with unifocal tumours equal to or less than three centimetres in diameter:		
Sentinel node *biopsy* is a suitable alternative to axillary dissection to determine if cancer cells have spread to the lymph nodes	II	Milan[4,5] ALMANAC[6] SNAC I[8] NSABP B-32[9] Cambridge[10] GIVOM[11,12]
Sentinel node biopsy is an accurate method of staging the axilla	II	Milan[4] SNAC I[8] NSABP B-32[9] GIVOM[11]
Sentinel node biopsy based management is associated with decreased arm morbidity, compared with axillary dissection	II	Milan[4,5] ALMANAC[6,7] SNAC I[8] Cambridge[10] GIVOM[12]
There are limited trial results to support recommendations for sentinel node biopsy in women with tumours greater than three centimetres in diameter		ALMANAC[6] NSABP B-32 (2007)[20]
Team, training and experience		
Three trials [6,8,9,21,22] that required surgeons to be trained and experienced in the sentinel node biopsy technique had lower false-negative rates and higher sensitivity and accuracy than the one trial[11] that did not require surgeons to have formal training or experience		ALMANAC[6] SNAC I[8,22] NSABP B-32[9,21] GIVOM[11]
Technique		
Lymphatic mapping using a combination of radioisotope and blue dye may be associated with a higher rate of sentinel node detection[14,15] than blue dye alone and may be associated with improved accuracy[13]	II	Hung[14] Meyer-Rochow[15] Radovanovic[13]
Using blue dye alone or radioisotope alone appears to provide good sentinel node detection and accuracy, however trial data for blue dye alone is limited		Milan[4,5] GIVOM[11,12]
Peritumoural, periareolar and intradermal injection sites have all been shown to be effective in detecting the sentinel node **in the axilla**		FRANSENODE[16] Povovski[17]
False negative rate		
The false negative rate of sentinel node biopsy decreases and morbidity is minimised if up to three sentinel nodes are removed.	II	NSABP B-32 (2007)[20]

STATEMENTS	LEVEL OF EVIDENCE[19]	REFERENCE
The removal of four or more nodes from the *axilla* does not lower the false negative rate significantly compared with removing up to three nodes		
Pathology		
Detailed, definitive histological assessment (including immunohistochemistry and serial sectioning) of the sentinel node increases the accuracy in the detection of metastatic disease		NBOCC* & ACN[23]
False-negative rates for intraoperative assessment (cytologic methods or frozen section) are up to 38.5%	II	NSABP B-32[9] GIVOM[11]
Where intraoperative assessment is used, cytologic methods conserve tissue for subsequent detailed histopathological assessment		NBOCC* & ACN[23]
Risk of recurrence		
The long term risk of axillary *recurrence* following sentinel node biopsy is not known		
The duration of follow-up in well-designed randomised control trials is currently limited to a maximum of six years and, to date, no increased risk of axillary recurrence has been identified		Milan[5] GIVOM[11] ALMANAC[6]
Adverse events		
Allergic reactions have been reported with the use of blue dye in sentinel node biopsy, however, these incidences are rare	II	NSABP B-32[9]
Trials did not report on adverse events relating to the dose of radiation to the patient from the use of radioisotope in sentinel node biopsy		Milan[4,5] ALMANAC[6,7] SNAC I[8] NSABP B-32[9] Cambridge[10] GIVOM[11,12]
Associated risks of radioisotope use in sentinel node biopsy are minimal and within acceptable limits for patients and staff		MSAC Review[24]

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Summary of evidence

The NBOCC* statements and recommendations for *sentinel node biopsy* in *early breast cancer* are based on a NBOCC* systematic review[3] of available evidence from randomised trials. It is recognised that there is a large body of non-randomised literature available regarding the use of sentinel node *biopsy* in early breast cancer management.

Recommendations have been confined to randomised trial data due to the strength of evidence in these trials. These trials are limited by their inclusion and exclusion criteria detailed below.

Six randomised trials were identified that assessed:

- The benefits and harms of using sentinel node biopsy compared to axillary *lymph* node dissection to detect cancer spread in early (operable) breast cancer.[4-12]

(see table 1 for trial details)

Six additional randomised trials were identified that assessed:

- the optimal technique for sentinel node biopsy in early (operable) breast cancer
  - different detection agents (blue dye, radioisotope)[13-15]
  - different injection sites (peritumoral, periareolar, intradermal) [16,17]
- different treatments after a positive sentinel node is detected (axillary lymph node dissection or no further surgery).[18]

(see table 2 for trial details)

Exclusion criteria across the trials included:

- women with clinically positive nodes
- women with multicentric/multifocal tumours
- pregnant or breastfeeding women
- women with known allergies to radioisotopes or blue dye
- women with previously treated breast cancer or axillary surgery on the affected breast (including those who had received *neoadjuvant* systemic treatment).

**** The statements and recommendations in this guideline are based on the populations and data included in the trials, i.e.:**

- women with clinically negative nodes and
- women with unifocal tumours equal to or less than **three** centimetres in diameter.

Tumour sizes varied across the trials. Tumours greater than three centimetres in diameter were not well represented in the trial populations. Median follow-up was from 12 months to five years.

Details of trials or studies

TRIAL	POPULATION	PATIENT NUMBERS SNB	ALND	SNB GROUP (METHOD OF SN DETECTION)	ALND GROUP	OUTCOMES MEASURED
MILAN[4,5]	Women aged 40–75 yrs with primary breast cancer ≤ 2 cm, and BCT performed	259	257	SNB isotope #ALND if SN positive	SNB #ALND	Axillary metastases, DFS, OS, detection rate

TRIAL	POPULATION	PATIENT NUMBERS SNB	ALND	SNB GROUP (METHOD OF SN DETECTION)	ALND GROUP	OUTCOMES MEASURED
	before SNB or ALND					
ALMANAC[6,7]	Female and male patients aged ≤80 yrs with clinically node negative invasive breast cancer	495 (478 ITT)	496 (476 ITT)	SNB (blue due and/or isotope)# ALND or axillary *radiotherapy* if SN positive	Standard axillary treatment (ALND or 4-node sampling)	Arm and shoulder morbidity, QoL, detection rate
SNAC I [8,22,27]	Women with histologically or cytologically confirmed *invasive breast cancer* ≤3 cm	544	544	SNB (blue dye and or/isotope) #ALND if SN positive	SNB#ALND	Arm volume, QoL, detection of SN
NSABP B-32 [9,20,21]	Women with operable invasive breast cancer and clinically negative nodes	2804	2807	SNB (blue dye and isotope) #ALND if SN positive	SNB#ALND	QoL, FN, detection rate
Cambridge[10]	Patients with ≤3 cm invasive breast cancer node negative breast cancer	143	155	SNB (blue dye and isotope) → ALND if SN positive	ALND	Physical and psychosocial morbidity
GIVOM [11,12]	Patients aged #80yrs with ≤3 cm 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 rate, ITT=intention to treat, OS=overall survival, QoL=quality of life, SN=sentinel node, SNB=sentinel node biopsy

TRIAL	POPULATION	TREATMENT	OUTCOMES MEASURED
Detection agent used			
Radovanovic[13]	Women clinically T1-2 N0 M0 breast cancer	i) Blue dye only n=50 ii) Blue dye and radioisotope n=100	Accuracy, FN rate, specificity, sensitivity
Hung[14]	Women ≤70 yrs *early breast cancer* ≤3 cm	i) Blue dye only n=57 ii) Blue dye and radioisotope n=61	Accuracy, FN rate, detection rate

TRIAL	POPULATION	TREATMENT	OUTCOMES MEASURED
Meyer-Rochow[15]	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[16]	T0-1 invasive breast cancer clinically negative axilla	i) Peritumoral injection of radioisotope and/or blue dye n=224 ii) Periareolar injection of radioisotope and/or blue dye n=225	Detection rate
Povoski[17]	Females >18 yrs T1-2 N0 M0 breast cancer (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
Treatment following a positive sentinel node			
ACOSOG Z0011[18]	Undergoing BCT clinical T1-2 N0 M0 breast cancer 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

Notes: ALND=axillary lymph node dissection, BCT=breast conserving therapy, DFS=disease free survival, FN=false negative rate, QoL=quality of life, SN=sentinel node, SNB=sentinel node biopsy

Summary of trial or study results

Sentinel node biopsy compared to axillary lymph node dissection

Tumour size

Tumour sizes varied across the trials. Three trials,[8,10-12,27] including the Australian SNAC I trial,[8,27] included patients with tumours equal to or less than three centimetres in diameter. The Milan trial[4,5] excluded patients with tumours

more than two centimetres in diameter. Two trials[6,20] did not exclude patients based on tumour size. However, up to 80% of patients in these two trials had patients with tumours equal to or less than two centimetres in diameter. Only 2% of patients in the NSABP B-32 trial[20] had tumours more than four centimetres in diameter and 2% of patients in the ALMANAC trial[6] had tumours more than five centimetres in diameter.

While the NBCC* definition of early (operable) breast cancer refers to tumours not more than five centimetres in diameter[1], there are limited trial results to support *sentinel node biopsy* in patients with tumours greater than three centimetres in diameter.

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Overall and disease-free survival

Three of the trials reported on overall and *disease-free survival*, with equivalent rates in both the *sentinel node biopsy* and the axillary dissection groups. Although reporting at five-year follow-up, the Milan[5] and GIVOM[11] trials are small trials and the ALMANAC trial[6] has only reported a median follow-up of 12 months, so it is difficult to draw firm conclusions based on these results. Further results from longer follow-up are needed to determine if sentinel node *biopsy* provides an overall survival and disease-free survival effect compared to axillary *lymph* node dissection.

Axillary recurrence

The current reported rates of axillary *recurrence* in the trials are low, with a relatively short (five year) follow-up. Further results from longer follow-up are needed to determine the effect of sentinel node biopsy on axillary recurrence rates compared to axillary lymph node dissection.

Accuracy of sentinel node biopsy

The trials[6,8,9,11] reported high success rates for localising the sentinel node for both the *sentinel node biopsy* and axillary dissection groups. Rates reported ranged from 93% to 98%, with slightly higher rates observed in the sentinel node *biopsy* arms. The accuracy (up to 97%) of sentinel node biopsy in the detection of the sentinel node could only be reported in trials that performed sentinel node biopsy followed by axillary dissection in the control arm.[4,9,11]

Arm morbidity

Sentinel node *biopsy* is associated with lower morbidity compared to axillary lymph node dissection, including lower rates of lymphoedema, arm morbidity and sensory deficit. The trials reported on a variety of physical morbidity outcomes, which were often measured differently. *Lymphoedema*, shoulder and arm functioning, numbness and pain were reported less often in the sentinel node biopsy groups than the axillary dissection groups.[4,6-8,10,12]

Team, training and experience

Three of the trials, ALMANAC,[6] SNAC I[22] and NSABP B32 [9,21] reported that prior to participation in the trial, surgeons must have been trained and accredited in the *sentinel node biopsy* technique to ensure optimal

performance. Training was measured differently, however, generally each surgeon had to perform a certain number of sentinel node biopsies and meet set criteria (for example localisation rates more than 90% and false negative rates less than 5%). The training requirements to achieve these criteria differed between the trials (from 1–40 completed procedures). The Milan[5] trial reported their surgeons were very experienced and expert *pathologists* were used. In the Australian setting, the SNAC I[22] trial protocol states: the surgeon should have completed sentinel node *biopsy* in at least 20 consecutive cases with a greater than 90% success rate in locating the sentinel node. The ongoing SNAC II[28] trial protocol states the surgeon should meet the criteria for SNAC I[22] or have equivalent evidence of their experience with the technique.

Axillary and non-axillary sentinel nodes

Most sentinel nodes will be located in the *axilla*. Results of the trials are based on the excision of all detected sentinel nodes (i.e. hot and blue nodes, or hot nodes where the *isotope* count is greater than ten times the background count, or blue nodes). There was a higher rate of detection of non-axillary sentinel nodes using a peritumoral injection site.[16] There are limited data from the trials to determine the utility of excision of non-axillary sentinel nodes. Identification of non-axillary sentinel nodes only occurred in up to 13.4% of cases.[16]

False negative rate

Sentinel node *biopsy* can produce false negative results. Although not explicitly tested, comparison of trial results suggests that experience of the surgeon performing the procedure may influence false negative rates.[4,8,9,11] The Milan[4] trial reported a false negative rate of 8.8%, similarly the SNAC I[8] and NSABP B-32[9] trials reported a false negative rate of 8.2% and 9.7% respectively. The GIVOM[11] trial, which did not require formal training for surgeons participating in the study, reported a higher false negative rate of 16.7%.

Pathology

The pathological methods used to examine the sentinel node differed for each trial. The Milan[4,5] and GIVOM[11] trials used frozen section intraoperative evaluation, and GIVOM[11] followed this by staining with haematoxylin-eosin (H&E) and cytokeratin antibody (immunohistochemistry) of serial sections for definitive histology. NSABP B32[9] undertook intraoperative cytology and H&E staining of serial sections. ALMANAC[6] examined the *lymph nodes* by H&E staining of serial sections only. The SNAC I[22] and Cambridge[10] trials used H&E staining of serial sections, followed by immunohistochemistry to detect smaller metastases.

A positive result on intraoperative assessment (cytological methods or frozen section) of the sentinel node may negate the need for second surgery, as axillary dissection may be performed immediately. There are two methods of intraoperative assessment for sentinel nodes; cytology and frozen section, both of which provide excellent specificity and acceptable rates of sensitivity. A moderate rate of false negative is inevitable with both techniques.[9, 11]

A potential disadvantage of the frozen section technique is that tissue is discarded during the preparation of the frozen section, and all care should be taken to keep this to a minimum.[23] Each pathology laboratory, in consultation with the surgical teams, should determine which procedure is most appropriate to be implemented depending on the resources and expertise available in the laboratory. Definitive histological assessment is needed to confirm intraoperative results.

Adverse events

Associated risks of radioisotope use in *sentinel node biopsy* are minimal and within acceptable limits for patients and staff.[24] Data relating to the use of radioisotope are available in trial protocols.

Allergic reactions

Most trials excluded patients with known allergies to blue dye or *isotope*. The NSABP B-32[9] trial is the only trial to report on adverse allergic reactions. Allergic reactions occurred in 0.7% of patients (0.2% *grade* 3 or 4 reactions). A review by the Australian Medical Services Advisory Committee (MSAC)[24] found case series reported small percentages of allergic reactions (0–1.6%) to blue dye. Up to August 2002, the Australian Drug Reactions Advisory Committee (ADRAC)[26] had received 42 reports of reactions to Patent Blue V. 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.[26]

Quality of life

Sentinel node *biopsy* appears to offer equivalent or improved quality of life for patients compared with axillary dissection, such as reduced arm morbidity (for example, reduced risk of lymphoedema).[4-8,10,12] Quality of life was assessed by various validated scales and questionnaires by four randomised control trials.[6-8,10,12] Significantly higher quality of life was reported by patients receiving sentinel node biopsy than those receiving axillary *lymph* node dissection in three trials,[6-8,10] however, one of the trials[10] reported no significant difference on some measures. One trial[12] reported no significant difference between patients receiving sentinel node biopsy or axillary lymph node dissection; however, quality of life information was available for only small number of patients in this trial. Most trials used validated questionnaires, such as the FACT or SF-36 (except Milan[4,5]), and the SNAC I[8] trial created its own validated scale. The ALMANAC[6,7] trial used a breast cancer specific questionnaire, FACT-B, which showed improved quality of life in the sentinel node biopsy arm compared to axillary dissection. Where trials used broad, general scales, differences in quality of life between patients receiving sentinel node biopsy and patients receiving axillary dissection were not reported.

Length of hospital stay

Patients receiving sentinel node biopsy reported shorter stays in hospital compared to patients receiving axillary dissection.[4,6]

Technique for sentinel node biopsy

Detection agents used

Three trials investigated differences in detection agents used to identify the sentinel node.[13-15] Comparisons were made between blue dye alone and a combination of blue dye and radioisotope. Two trials[14,15] reported that higher sentinel node detection rates were associated with combination methods for lymphatic mapping. Overall, accuracy in these trials was high and no difference was reported between combination methods and blue dye alone. One other trial[13] reported a possible association between combination methods and improved accuracy; however, accuracy rates in this trial were lower for both combination and blue dye alone groups than the two previous trials. Sensitivity, specificity and false negative rates appear to be similar between blue dye alone and combination methods, however each of these trials contained small numbers of patients. Further research is needed to determine optimal detection

agent(s) for *sentinel node biopsy*. Please refer to Table 1 for the detection methods used in the main trials and Table 2 for details of trials investigating technique of sentinel node *biopsy*.

Injection site

Two trials[16,17] reported on differences in the injection site used for *sentinel node biopsy* (i.e. peritumoral, periareolar, intradermal) and each investigated different routes. Further research is needed to determine the optimal injection site of blue dye/radioisotope for sentinel node *biopsy*. Non-axillary sentinel node sites were identified more commonly with peritumoral injection. For example, more internal mammary sentinel nodes were identified with peritumoral injection.[16]

Treatment following a positive sentinel node

One randomised trial[18] reported on treatment of patients with one or two positive sentinel nodes. Patients receiving *sentinel node biopsy* and axillary *lymph* node dissection reported more adverse surgical effects than patients receiving sentinel node *biopsy* alone. Two large ongoing randomised trials are investigating how to treat patients with micrometastases in the sentinel node.[29,30]

Additional references for sentinel node biopsy

Clinicians working in Australia may find the following resources useful:

- The pathology reporting of breast cancer. A guide for *pathologists*, surgeons, *radiologists* and oncologists (3rd edition)[23]
- SNAC I trial references[8,22,27,31]

Strengths and weaknesses of the evidence

The trials reporting on survival are not large enough to detect survival benefits. Longer follow-up and pooled analysis are needed.

Of the six randomised trials[4-12] comparing *sentinel node biopsy* to axillary dissection (Table 1) all were well designed and well conducted. However, the following should be noted:

- only one trial[9] is large enough in size to be able to detect a survival benefit
- overall and *disease-free survival* were reported by smaller trials or those with short-term follow-up
- morbidity and quality of life were measured differently between the trials.

Of the six randomised trials[13-18] investigating technique for sentinel node *biopsy*, those reporting detection agents were small trials,[13,15] those reporting injection sites[16,17] used different sites across the trials, and only one trial[18] reported on treatment following a positive sentinel node, while two more trials[29,30] investigating this topic are ongoing.

Future trials and reviews are needed to address important unanswered questions on sentinel node biopsy in *early breast cancer* (see sections on unanswered questions and ongoing trials).

Clinical practice recommendations developed by NBOCC* will be reviewed and revised as required as additional significant evidence becomes available.

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Unanswered questions

Important unanswered questions about the use of *sentinel node biopsy* in *early breast cancer* are outlined below. Some of these questions may be addressed in ongoing trials:

- accuracy of sentinel node *biopsy* in large and/or multifocal tumours
- accuracy of sentinel node biopsy following *neoadjuvant* treatment
- significance of micrometastases and isolated tumour cells
- optimal management of sentinel node-positive patients
- accuracy of sentinel node biopsy in recurrent breast cancer
- significance of the non-axillary sentinel node in prognosis
- optimal pathological methods for assessing sentinel node(s)
- role and method of intraoperative assessment
- overall and *disease-free survival* following sentinel node biopsy (meta analysis of randomised control trials with long-term follow-up).

Ongoing and additional trials or studies

A number of ongoing phase III trials are investigating the use of *sentinel node biopsy* for *early breast cancer*. Areas covered include:

- treatment following identification of a positive sentinel node and micrometastases from sentinel node *biopsy* (AMAROS[29] using radiotherapy; IBCSG-23-01[30] randomising to further surgery or no further surgery for micrometastases)
- accuracy of sentinel node biopsy in large and/or multifocal tumours (SNAC II[28])
- significance of micrometastases and isolated tumour cells (AMAROS,[29]IBCSG-23[30]).

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External review

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Full details of trial results are provided in the document *Sentinel node biopsy for early breast cancer; a systematic review 2007* which can be accessed via the NBOCC* website www.nbocc.org.au

Development process

Priority topic areas for NBOCC* guideline development are determined in consultation with key stakeholders including experts in relevant disciplines and consumer representatives. A specific multidisciplinary Working Group, including consumers, is established for each topic identified and is involved in all aspects of guideline development. A systematic evidence review is undertaken for each guideline. All members are asked to declare any conflicts of interest and these declarations are recorded. The content of the guideline is not influenced by any external funding body. The guideline is reviewed externally by key stakeholders and the wider community and endorsement is sought from relevant professional colleges and groups in Australia.

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