Sentinel Lymph Node Biopsy in Breast Cancer

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The Medical Services Advisory Committee (MSAC) is an independent committee established to provide advice to the Minister for Health and Ageing on the strength of evidence available on new and existing medical technologies and procedures in terms of their safety, effectiveness and cost-effectiveness. This advice will help to inform government decisions about which medical services should attract funding under Medicare.

MSAC recommendations do not necessarily reflect the views of all individuals who participated in the MSAC evaluation.

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Executive summary

The procedure

Sentinel lymph node biopsy (SLNB) for breast cancer uses radioisotopes and/or lymphotrophic blue dyes to identify sentinel lymph node(s) that, in theory, are the first node(s) to receive metastatic cells from the primary tumour. The sentinel nodes may be preoperatively identified by lymphoscintigraphy and can be surgically identified by either using a hand-held gamma probe or by visually identifying a blue stained lymph vessel and node, depending on the technique used to identify the sentinel nodes. The excised sentinel nodes are then pathologically examined and further treatment decisions are based on the metastatic status of the sentinel node(s). As only one or two nodes need be removed, SLNB has the potential to be a less invasive method of staging the axilla than axillary clearance (AC), in which many more axillary lymph nodes are removed for pathological testing, and could help to avoid the morbidities associated with axillary clearance.

Medical Services Advisory Committee – role and approach

The Australian Government established the Medical Services Advisory Committee (MSAC) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister for Health and Ageing on the evidence relating to the safety, effectiveness and cost-effectiveness of new and existing medical technologies and procedures, and under what circumstances public funding should be supported.

A rigorous assessment of evidence is thus the basis of decision making when funding is sought under Medicare. A team from the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) was engaged to conduct a systematic review of literature on SLNB in breast cancer. An advisory panel with expertise in this area then evaluated the evidence and provided advice to MSAC.

MSAC's assessment of sentinel lymph node biopsy in breast cancer

Clinical need

In 2000, approximately 11,314 Australian women and 86 men were diagnosed with invasive breast cancer and 1185 women were diagnosed with ductal carcinoma *in situ*. The incidence of breast cancer has been increasing by 1% to 2% per year for the past 10 years. In women the incidence increased from 93 per 100,000 in 1990 to 117 per 100,000 in 2000. Breast cancer is the most common cause of cancer-related death in women in Australia; 2521 women died from breast cancer in 2000. The 5-year survival rate for Australian women with breast cancer was 84% between 1992 and 1997.

In 2003–04 over 7500 patients received some form of lymph node excision in the private health system.[1] No relevant data from the public health system were readily available and this figure should be regarded as a low estimate of the number of axillary node dissections undertaken for breast cancer. A major source of morbidity associated with breast cancer is lymphoedema[2] secondary to surgery and/or adjuvant therapy, which has been shown to impact on quality of life and activities of daily living. Several Australian studies suggest that between 17% and 39% of women experienced lymphoedema between 6 months and 5 years after treatment for the primary tumour.

Diagnostic accuracy of sentinel lymph node biopsy

Localisation rates (192 studies; 228 sets of data) and false negative rates (130 studies; 136 sets of data)

Diagnostic accuracy was assessed by localisation rate (ability of SLNB to locate the sentinel node) and false negative rate (the number of sentinel nodes judged to be negative when they were, in fact, positive for axillary metastasis) compared to axillary clearance as the reference standard. The available evidence was of moderate quality, however, there was significant heterogeneity between included studies.

A random effects Bayesian meta-analysis found the pooled localisation rate to be 94.1% (95% posterior interval 93.3% to 95.0%) and the pooled false negative rate to be 4.7% (95% posterior interval 4.0% to 5.4%).

Impact of clinical team experience on diagnostic accuracy

The impact of clinical team experience on diagnostic accuracy could not be assessed directly from the included studies. However, two post-hoc sensitivity analyses were carried out which aimed to see whether localisation rates and false negative rates were affected by the cumulative world experience with the SLNB technique, or the number of procedures carried out by particular teams. Both of these are proxy measures of the impact of surgeon/team experience, since the first cannot control for publication lag, and the second cannot isolate the contribution of individuals or a SLNB volume effect for each individual surgeon/surgical team.

A cumulative meta-analysis based on year of publication showed that localisation rates have improved each year since 1998, although heterogeneity between sets remained consistently high throughout the study period. On the other hand, false negative rates have become worse, rising from a mean of 3.2% in 1998 to the overall mean of 4.7%, and appearing to plateau around 4.5 to 5.0% since 2000. When sets of data with fewer than 50 patients were excluded from the overall analysis, neither the mean localisation nor false negative rates changed significantly.

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[1] It is not possible to determine from the available data how many of these patients received axillary clearance for other types of cancer (e.g. axillary melanoma or squamous cell carcinoma), however, these conditions are quite rare and probably represent a very small proportion of the total cases.

[2] Lymphoedema is the abnormal swelling of the superficial body tissues, most often the limbs, caused by a failure of the lymphatic system to adequately collect or transport lymph.

Effect of test protocol variables on diagnostic accuracy

Localisation rates were higher and false negative rates were lower when a combination of dye and radioisotope were used as a tracer, compared to dye only. When either dye or radioisotope was injected at the subareolar or intradermal sites, localisation rates (but not false negative rates) were higher than for the peritumoural site, and when radioisotope was injected on the same day as surgery false negative rates (but not localisation rates) were lower than if injected the day before surgery. No clinically important differences were seen for type of dye or radioisotope injection. No difference in false negative rate was seen when permanent histology was used alone, or with immunohistochemistry, although immunohistochemistry had some impact on upstaging negative sentinel nodes.

Effect of patient/tumour variables on diagnostic accuracy

Tumour size or palpability did not show an influence on localisation or false negative rates. Clinically negative axillary nodes showed a higher localisation rate and a lower false negative rate than studies containing a mix of women with either clinically negative or clinically positive axillary nodes. However, SLNB is not currently indicated for patients with clinically positive axillary nodes. Women who had not received neoadjuvant chemotherapy showed a significantly lower false negative rate than those who did have neoadjuvant chemotherapy, but no difference was seen for localisation rate. There was a suggestion (not statistically significant) that excisional biopsy may result in lower localisation rates and higher false negative rates than other types of biopsy.

Safety

In one nonrandomised study, the SLNB complication rate was significantly lower than for axillary clearance and for SLNB followed by axillary clearance. There were statistically significantly fewer wound infections for SLNB than for axillary clearance in one out of two nonrandomised studies. Fourteen case series studies reported whether women reacted to the blue dye, ranging from 0% to 1.6% (median 0%). Complications arising from excision of extra-axillary lymph nodes were also occasionally reported in the SLNB case series.

Effectiveness

Although measured in different ways in nonrandomised comparative studies, significantly more axillary clearance patients experienced lymphoedema than did SLNB only patients; the median across six studies was 3.25% for SLNB and 27.05% for axillary clearance, a risk difference of 23.8%. However, this reduction in morbidity will only apply to 70% to 80% of patients undergoing SLNB, since the remaining 20% to 30% (with positive nodes) will subsequently need axillary clearance. Postoperative range of motion limitation, sensory morbidities and pain were also more common in patients receiving axillary clearance. Data regarding the impact of SLNB or axillary clearance on activities of daily living or quality of life were relatively sparse and inconsistent. No relevant studies regarding women's preferences for SLNB or axillary clearance could be located.

In one randomised controlled trial there were no axillary recurrences in either the SLNB group or the SLNB+AC group after a median follow-up of 46 months. In 29 case series of SLNB, the axillary recurrence rate did not exceed 1% in patients who were node negative at the time of SLNB (follow-up ranged from 8 months to 47 months). There was insufficient evidence to assess the relative effect on survival of SLNB. In one randomised controlled

trial, two patients in the SLNB group died (one from metastatic cancer) and six patients in the SLNB+AC group died (two from metastatic cancer), but the difference was not statistically significant. In a nonrandomised Level III-2 study, six SLNB patients and two SLNB+AC patients died from metastatic breast cancer. In 12 SLNB case series studies, survival after at least 24 months was greater than 98% in all but two of these studies.

Cost effectiveness

In a cost-minimisation analysis using recurrence and survival as effectiveness outcomes (SLNB and axillary clearance assumed to be of similar effectiveness) the cost per 100 procedures for SLNB (plus axillary clearance in the same surgery when required) ranged from $251,942 to $514,277 compared to a range of $325,185 to $499,600 for axillary clearance alone. The cost per 100 procedures for SLNB (plus axillary clearance in a subsequent surgery when required) ranged from $280,203 to $590,097 compared to a range of $325,185 to $499,600 for axillary clearance alone.

Using lymphoedema as the measure of effectiveness, in a cost-effectiveness analysis, SLNB both costs less and is more effective in the lower end of the costing range. At the high end of the costing range, SLNB (with axillary clearance in the same surgery when required) costs $8.63 for one case of lymphoedema avoided and $53.20 when axillary clearance (if required) is performed in a subsequent surgery.

Recommendation

Sentinel node biopsy appears to be safe and effective in identifying sentinel lymph nodes resulting in the reduction of complications due to axillary lymph node dissection, in particular lymphoedema. Longer-term outcomes are uncertain. MSAC recommends that interim funding for sentinel node biopsy should be provided pending the outcome of trials already in progress and should be reviewed in 5 years.

– The Minister for Health and Ageing endorsed this recommendation on 4 July 2005 –

1. Introduction

The Medical Services Advisory Committee (MSAC) has reviewed the use of SLNB as a diagnostic tool in breast cancer, specifically assessing its ability to determine which axillary lymph nodes are negative and which are positive for metastasis; and to use this information to avoid unnecessary removal of lymph nodes and reduce the consequent morbidity of axillary clearance without compromising survival. MSAC evaluates new and existing health technologies and procedures for which funding is sought under the Medicare Benefits Scheme in terms of their safety, effectiveness and cost-effectiveness, while taking into account other issues such as access and equity. MSAC adopts an evidence-based approach to its assessments, based on reviews of the scientific literature and other information sources, including clinical expertise.

MSAC's terms of reference and membership are detailed in Appendix A. MSAC is a multidisciplinary expert body, comprising members drawn from such disciplines as diagnostic imaging, pathology, surgery, internal medicine and general practice, clinical epidemiology, health economics, consumer health and health administration.

This report summarises the assessment of current evidence for using SLNB in breast cancer.

2. Background

Sentinel lymph node biopsy

SLNB is a surgical procedure used to stage breast cancer. The results of SLNB may determine whether disease has spread to the axillary lymph nodes (i.e. metastasised) in patients diagnosed with primary operable breast cancer. Staging of the primary tumour helps to determine whether axillary nodes should be removed and to plan future adjuvant therapy. It can also provide prognostic information about the patient's survival and tumour recurrence.

SLNB relies on the theory that cells detaching from the primary tumour are likely to arrive at, and be held by, the first node to receive lymph from the involved area (Veronesi et al. 1997). Either a lymphotropic dye or a radioisotope (^{99m}technetium (^{99m}Tc)-labelled radioisotope), or a combination of both, is injected into the breast and its drainage pattern traced. According to the theory, the first lymph node it reaches is the sentinel node. This node can then be removed and tested pathologically to determine whether it is negative or positive for metastatic disease (i.e. staging). SLNB for staging of breast cancer was introduced by Krag et al. (1993), using radiolabelled sulphur colloid for sentinel node identification, and by Giuliano et al. (1994) using a vital blue dye. The techniques were developed from those used for staging melanoma and penile cancer (Gould et al. 1960, Tanis et al. 2001a, Cabanas 1977, Morton & Chan 2000, Alex et al. 1993, van der Veen et al. 1994).

Although there is no fixed method for applying SLNB to the breast, the procedure has essential key elements (see Figure 1). The procedure is usually undertaken at the same time as surgery for removal of the primary tumour but may also be done as separate surgery. If radioisotope is used it is injected on the day before or the day of surgery. If dye is used it is injected during surgery, usually after induction of anaesthesia and 5 to 10 minutes before axillary incision. Nonpalpable tumours may also require the use of ultrasonography or stereotaxy to guide placement of the injection. The procedure may vary according to the type of radioisotope or dye used and the site of the injection. If radioisotope is used dose and timing of injection may also vary. Sometimes, after injection, the breast is massaged as this is thought to improve uptake of the tracer fluid. If radioisotope is used the sentinel node is identified using an intraoperative hand-held gamma probe. If dye is used, the node can be located by visually identifying a blue stained lymph vessel and node. Preoperative lymphoscintigraphy may be performed to assess whether there is drainage to lymph nodes in the ipsilateral axilla and also drainage to internal mammary nodes, supra- and infraclavicular, contralateral axilla.

Once the sentinel node(s) has been identified it is surgically excised and subjected to pathological analysis. Pathology may be done intraoperatively, via frozen section or imprint cytology, and, if positive, immediate removal of axillary nodes is usually indicated. However, for some patients this occurs in a second surgery giving the patient and surgeon time to discuss treatment options and management of the disease. Permanent histology usually includes examination of fixed and embedded slices of sentinel nodes using haematoxylin and eosin (H&E) staining, although serial sectioning may also be used. Immunohistochemistry (IHC) against cytokeratin may be performed in addition to H&E staining, usually in order to detect micrometastases.

Treatment for positive sentinel nodes is axillary clearance – surgical removal of lymph nodes in the affected axilla[3] – performed at the same time as the SLNB or in a separate surgery at another time.

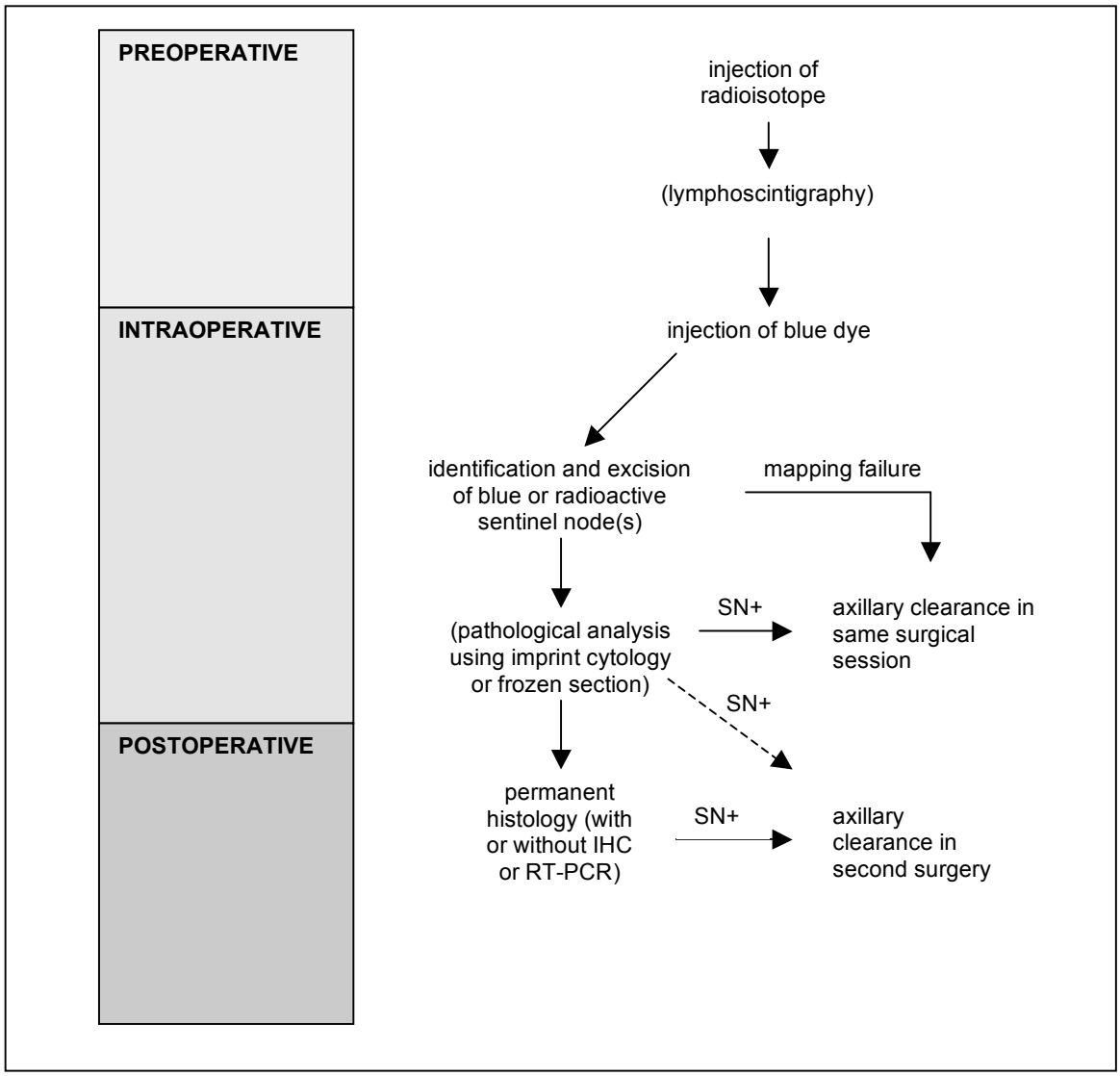


Figure 1 Flow diagram of sentinel lymph node biopsy

Radioisotopes

In Australia, ^{99m}Tc-labelled antimony sulphide colloid ('Lympho-Flo', produced by the Royal Adelaide Hospital Radiopharmacy, South Australia, Australia) is used to detect the sentinel lymph node. The type of radioisotope used differs between countries, with sulphur colloids typically used in the United States and albumin colloids used in Europe (Clarke & Mansel 2001). Other radioisotopes used included rhenium and antimony sulphides, tin, phytate, dextran and MIBI (2-methoxy isobutyl isonitrile).

[3] The extent of axillary dissection can be defined with reference to the pectoralis minor muscle: Level I – lower axilla up to the lower border of pectoralis minor; Level II – axillary contents up to the upper border of pectoralis minor; Level III – axillary contents extending to the apex of the axilla (NHMRC 2001).

The size of the radioisotope colloid particles may affect uptake and deposition in the lymph nodes and the amount of radioactivity accumulating at the site of injection. Particle size needs to be small enough to facilitate rapid uptake into the lymphatics and to flow within the lymphatics, but must be large enough so that the particles do not leak from the lymphatics and pass though blood capillary membranes (Styblo et al. 2001). Filtered radioisotopes have a smaller particle size than unfiltered radioisotopes, and are therefore thought to be superior (Bass et al. 1999a). However, if the radioisotope particle is too small (<100 nm), there is the possibility of migration to second-tier lymph nodes, beyond the sentinel lymph node (Hung et al. 2002). If the particle size is too large, (as with unfiltered radioisotope) there is the potential for 'shine-through', where large amounts of the radioactive radioisotope are left at the tumour site hindering sentinel node detection, although appropriate surgical or shielding techniques may help to alleviate this problem.

In terms of patient safety, radioisotope use is believed to be safe, with no reactions and no known side effects apart from some pain during injection and exposure to a small amount of radiation (Kumar et al. 2003). During the course of SLNB using radioisotopes, surgeons, operating theatre staff and pathologists will also be exposed to radiation. Although associated risks have been shown to be minimal and radiation exposure within acceptable limits, exposure should be minimised to reduce the anxiety felt by staff working with the radioactive substances and tissues (Stratmann et al. 1999, Creager & Geisinger 2002, Zavagno et al. 2000, Morton et al. 2003).

Dyes

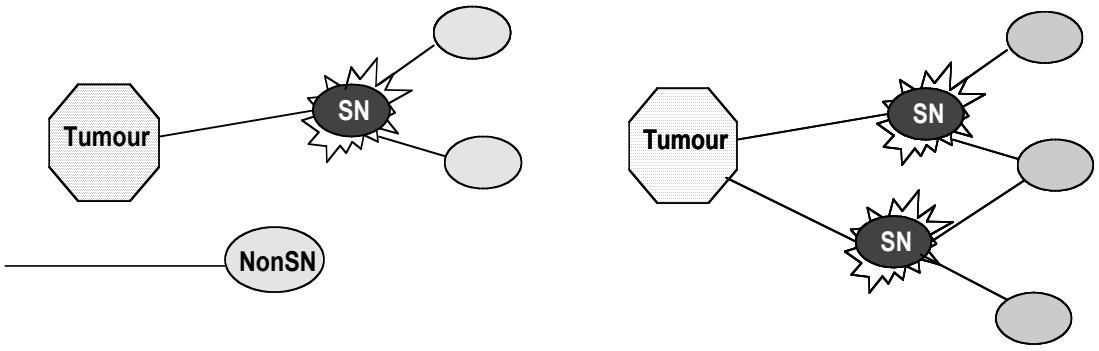
There are a variety of blue dyes in use throughout the world for SLNB localisation. Patent blue dye (as distinct from patent blue V dye) is the only dye used for colorimetric localisation of the sentinel lymph node in Australia, with isosulphan blue used in the United States and patent blue V in Europe. Isosulphan blue is not often available in Asia, where dyes such as indigocarmine, activated charcoal (CH40) or India ink are more common (Imoto & Hasebe 1999). The technical characteristics of these different dye types may influence their suitability for sentinel node biopsy. Isosulphan blue dye is thought to permeate the lymphatic vessels more easily than indigocarmine (Imoto & Hasebe 1999), and the smaller particle size of CH40 blackens the lymph nodes faster, and more clearly, than India ink (Kataoka et al. 2000). Another alternative is methylene blue, however, concerns about complications, such as fat necrosis being mistaken for recurrent disease in the conserved breast (Clarke & Mansel 2001), have led some to believe that patent blue dye is a better option (Jianjun et al. 2001). On the other hand, methylene blue is widely available and has been shown to cost substantially less than isosulphan blue (Winchester 2003, Simmons et al. 2003).

The Australian Therapeutic Goods Administration (TGA) has published an adverse drug reaction bulletin on patent blue dye, stating that surgeons and anaesthetists should be aware of the potential for severe allergic reactions and the product information recommends testing for hypersensitivity (TGA 2002).

Technical considerations for sentinel lymph node biopsy

Definition of a sentinel lymph node

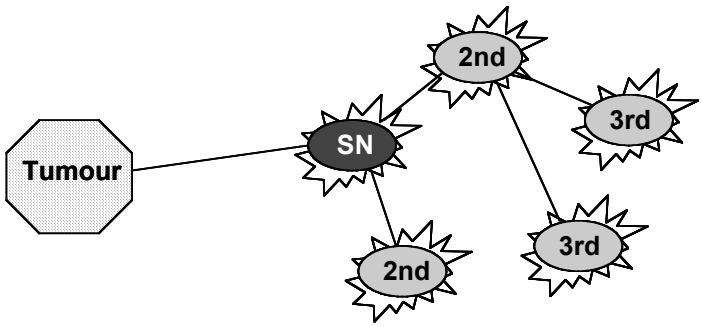
For SLNB to be effective the procedure must identify the true sentinel node. However, a number of technical characteristics of the procedure mean that this can be problematic. Although axillary nodes with breast cancer have a relatively low rate of involvement of Level II or Level III nodes in the absence of involved Level I nodes (called skip metastases) (Veronesi et al. 1987), it is not always clear which is the true sentinel node. For a lymph node to be designated as the sentinel node, it must receive direct drainage from the tumour, and this may not always be the node closest to the tumour. Usually the sentinel node is located in the ipsilateral axilla; however, drainage from the tumour to internal mammary nodes, supra- and infraclavicular nodes, or the contralateral axilla can occur. It is also possible that two lymphatic channels originate from the same tumour region and this may result in identification of more than one sentinel node (Nieweg et al. 2001) (see Figure 2). Following injection of radioisotope, these multiple sentinel nodes may appear at different times during lymphoscintigraphy, making identification of the sentinel node difficult for the operator, who is likely to regard the 'hottest' node as the sentinel node.



Adapted from Nieweg et al. 2001

Figure 2 In A the lymph node closest to the tumour is not necessarily the sentinel node, whereas in B multiple lymphatic channels originate from the same tumour, resulting in identification of more than one true sentinel lymph node

The radioactivity of the lymph nodes may also impact on the identification of the sentinel node. The amount of tracer that is accumulated can depend on not only the position of the node, but the number of lymphatic channels that enter the node and the lymph flow rate. Radioactive tracer will flow to the sentinel node within 20 to 30 minutes and be confined to that node, but, after several hours, the radioactivity will spread to other non-sentinel nodes (Morton & Chan 2000) (see Figure 3). Preoperative dynamic lymphoscintigraphy should identify the first draining node, if performed soon after injection, but this node may be missed if an intraoperative gamma probe is used to identify the sentinel node. A node may also receive less tracer if its activity as a lymph node is hampered by metastatic tumour cells. Furthermore, the brightness of the lymph node, on the lymphoscintigram, not only depends on the amount of radioactivity within the node but also the distance from the gamma probe (Nieweg et al. 2001).



Adapted from Nieweg et al. 2001

Figure 3 Radioactivity spreads over time to second and third tier nodes that are not sentinel nodes

When using a hand-held gamma probe, some operators define the sentinel node as any node that is radioactive, which can result in removal of many nodes, a procedure that may be nearly as invasive as a standard axillary clearance (Nieweg et al. 2001). However, in Australia between one and three nodes are typically removed. Radioactive tracer and blue dye should identify the same lymphatic route, and identify the same sentinel node. However, approximately 8% of blue nodes are not also identified using radioisotope, and some of these nodes are the only site of metastases (Morton & Chan 2000, Rahusen et al. 2000b, Chu & Giuliano 2000).

Site of injection

Peritumoural injection

The peritumoural lymphatics should connect to the axillary sentinel lymph nodes draining that particular region of the breast and thus peritumoural injection is probably the most logical site for SLNB (Tuttle et al. 2002). However, the lymphatic network deep in the breast parenchyma is not as developed as that in the skin of the breast, and only a small amount of radioisotope may reach the sentinel node, making identification difficult (Tuttle et al. 2002). Injection of the radioisotope around tumours in the upper outer quadrant may result in 'shine-through' that may obscure detection (by lymphoscintigraphy or hand-held gamma probe) of the sentinel lymph node in the axilla.

Dermal or subdermal injection

The breast parenchyma and the skin of the breast arise together from embryonic ectoderm and therefore are most likely to have a common lymphatic system (Tanis et al. 2001b). Contrasting to the less developed lymphatic system of the deep breast parenchyma, there is a rich lymphatic network present in the skin of the breast and therefore more tracer is likely to reach the sentinel lymph node (Tuttle et al. 2002, Borgstein et al. 1997, Cox et al. 1998c). Advantages of intradermal radioisotope injections include less pain at the injection site, less operator expertise (as ultrasonography or stereotaxy are not required), and a smaller dose of radioisotope, which may prevent shine-through (Weerts et al. 2002). However, permanent tattooing of the skin may occur (Allweis et al. 2003) and nonaxillary sentinel lymph nodes, such as internal mammary nodes, may not be identified (Tuttle et al. 2002).

Subareolar injection

Subareolar injections have a number of benefits in comparison with other injection sites. They may be more accurate, especially for nonpalpable or multiple tumours, and less subject

to operator variability (Smith et al. 2000, Klimberg et al. 1999, Kern et al. 1999, Layeeque et al. 2003, Bauer et al. 2002). For lesions close to the axilla the problem of radioisotope shine-through may be avoided and visualisation of potential internal mammary nodes is possible (Smith et al. 2000, Bauer et al. 2002), though some have found internal mammary nodes cannot be visualised using this injection site (Beitsch et al. 2001, Jakub et al. 2002). However, the prognostic value of internal mammary metastases is unknown at present (Beitsch et al. 2001). As a precaution, some radioisotope could be injected peritumourally in order to identify extra-axillary nodes (Celliers & Mann 2003). If blue dye is injected via the subareolar site, ultrasound guidance for nonpalpable lesions or excisional biopsy cavities is not required, the entire breast can be mapped with a single injection (important if the tumour is multifocal or multicentric) and the operator is not required to work in a field of blue dye (Bauer et al. 2002).

Method of histologic analysis

Haematoxylin and eosin staining

The standard examination for axillary lymph nodes is a single section stained with H&E stain, however, it has been suggested that detection of micro- and macro-metastatic deposits by this method is inadequate, and that serial sectioning and immunohistochemical analysis can increase the detection rate by 9% to 33% (Dowlatshahi et al. 1997). However, the prognostic significance of micrometastases is not yet clear (Hansen et al. 2001, Turner et al. 2000, McGuckin et al. 1996, Nasser et al. 1993, International (Ludwig) Breast Cancer Study Group 1990). While examination of the entire axillary contents by serial sectioning and/or IHC would be an exhausting and expensive process, SLNB gives the opportunity for analysis of the node most likely to contain metastases, and therefore methods such as serial sectioning and/or IHC could be performed routinely on the sentinel node(s) (Ollila & Stitzenberg 2001).

Immunohistochemical staining

Immunohistochemical (IHC) analysis, using markers for cytokeratin, exploits the fact that breast cancer cells are epithelial in origin and cytokeratin proteins are found on epithelial cells but not in lymph tissue (Ollila et al. 2001). Proponents of cytokeratin IHC (e.g. Turner et al. 2001) advocate its use over multiple H&E sections, as it is more sensitive, less time-consuming and therefore less expensive. Intensive histopathologic techniques, such as serial sectioning and IHC, have been shown to detect occult micrometastases in 10% to 25% of lymph nodes that were determined to be negative by H&E (Ollila et al. 2001).

Intraoperative pathologic examination

Intraoperative pathological examination can be done by frozen section or imprint cytology. Pathological analysis done at the time of the surgery would allow for synchronous SLNB and axillary clearance if the sentinel node were positive. This would generally avoid the need for a second operative procedure with associated anaesthetic risks, increased surgical risk due to distortion of the anatomy of the axilla from the previous biopsy, and additional time away from work or personal commitments and prolonged anxiety for the patient (Kane et al. 2001). Unfortunately, there are concerns with the use of intraoperative pathologic methods, as false negative rates can be high and there is a potential for loss of diagnostic tissue (Turner et al. 2001, Usman et al. 1999, Kane et al. 2001). For this reason, imprint cytology or touch-prep analysis, performed by pressing the cut face of the node to a slide, may have

advantages over frozen section. However, it is not clear whether this would further compromise diagnostic accuracy (Noguchi et al. 1999, Motomura et al. 2000, van Diest et al. 1999, Menes et al. 2003, Beach et al. 2003).

Reverse transcriptase – polymerase chain reaction

Reverse transcriptase – polymerase chain reaction (RT-PCR) has potential to be the most sensitive method of detecting lymph node metastases in breast cancer (Manzotti et al. 2001). However, it may be less accurate than an extensive histological work-up if multiple mRNA markers are used individually, as it is unlikely that one single mRNA marker would be consistently expressed in the metastatic sentinel node, and a multimarker panel would be preferred (Manzotti et al. 2001). At this stage, RT-PCR is not appropriate for analysis of sentinel nodes, but may be a viable alternative in the future.

How does SLNB fit into breast cancer practice?

The expert panel has developed a clinical algorithm for SLNB (see Figure 4). The algorithm illustrates the place of SLNB in the clinical pathway for managing early breast cancer and allows comparison with the standard current practice, axillary clearance.

Clinical indications for sentinel lymph node biopsy

SLNB is used in female and male breast cancer patients with operable invasive breast cancer. In Australia it is usually offered to patients with smaller (T1 and T2) tumours that are clinically node negative. It may be offered to patients with larger tumour sizes (T3 or T4) or clinically positive nodes, however, results would be expected to be poorer in these patients. Results would also be expected to differ for patients with ductal carcinoma *in situ* or multicentric breast cancer and those who have received neoadjuvant therapy (radiotherapy, chemotherapy, hormone therapy).

Patients undergo SLNB after a diagnosis of primary operable breast cancer has been established by any means (including clinical examination, mammography and usually biopsy) The SLNB procedure is usually performed at the same time or after the primary tumour has been treated (using breast conserving surgery or mastectomy).

Reference standard

The reference standard for assessing the diagnostic accuracy of SLNB is staging by axillary clearance (see description below).

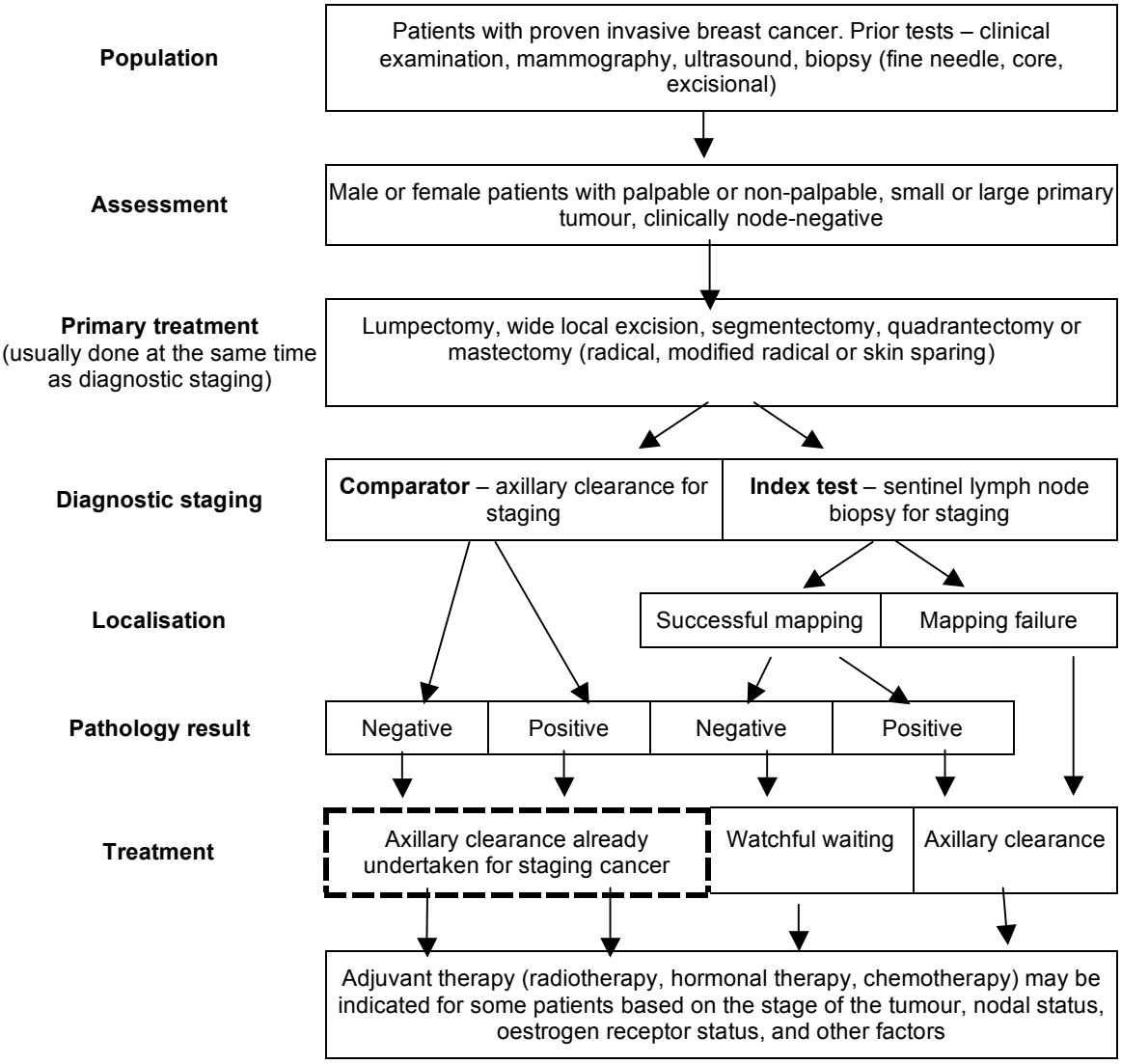


Figure 4 Clinical algorithm for sentinel lymph node biopsy in breast cancer

Existing test strategies for staging breast cancer

Axillary clearance

Axillary clearance is removal of the lymph nodes in the axilla of the side affected by breast cancer. During surgery for breast cancer the clearance of Level I and II, and occasionally Level III, lymph nodes, gives local control of axillary disease (Sosa et al. 1998, Hayward & Caleffi 1987, Atkins et al. 1972, Kjaergaard et al. 1985, Cabanes et al. 1992). Axillary clearance also allows pathologic examination of the nodes, to determine whether lymph node metastases are present and how many lymph nodes are affected. The status of these axillary nodes remains the single most important independent variable predicting prognosis for breast cancer patients (Moffat et al. 1992); the presence of nodal metastases decreases 5-year survival by approximately 40%, compared to patients who are free of nodal disease (Carter et al. 1989, Nemoto et al. 1980). Prognosis is related to the number of positive axillary nodes (Fisher et al. 1983) and postoperative treatment, for example chemotherapy

and/or radiation therapy, may be given, depending on the presence and number of affected nodes.

Axillary clearance is the standard method for staging the tumour and for planning treatment of disease that has spread to the axilla. Axillary clearance is also the method used to treat metastatic disease that has spread to the lymph nodes. The United States National Institutes of Health Consensus Conference in 1990 recommended that Level I and II axillary clearance be routine for staging and regional control for patients with early breast cancer (National Institutes of Health 1990). Since the pathological analysis of excised axilla is done after surgery, axillary clearance proves to be unnecessary in some women, with up to 70% of women with small tumours (i.e. T1 or T2) found to have negative lymph nodes after axillary clearance (Pijpers et al. 1997). Furthermore, around 50% of patients staged by axillary clearance develop morbidities (Lin et al. 1993), including pain, paraesthesias, damage to sensory and motor nerves, seroma formation, wound infection, drain complications, limitation of shoulder movement and acute and chronic lymphoedema (Hack et al. 1999, Tasmuth et al. 1995, Tasmuth et al. 1996, Kissin et al. 1986).

Thus, the routine use of axillary clearance has been questioned, since many women (with node-negative tumours) may be needlessly exposed to the risk of significant morbidities through having unnecessary axillary clearance (Cady et al. 1996).

Axillary sampling and other less invasive methods

There have been attempts to stage the axilla using less invasive measures, but unfortunately the methods have tended to be unreliable and have high error rates. For example, palpation for diseased lymph nodes is unreliable for staging of the axilla (Wallace & Champton 1972, Sacre 1986). Radiation of the axilla, although less invasive, results in similar morbidities to axillary clearance. There are less invasive procedures that remove fewer nodes than a Level I or II axillary clearance including triple-node biopsy (Du Toit et al. 1990), where the internal mammary, axillary and apical lymph nodes are sampled; and axillary node sampling, where a small number of Level I nodes are removed. A recurrence rate of 21% has been found with triple-node biopsy (Locker et al. 1989) and although axillary node sampling is associated with fewer complications (Steele et al. 1985; Dixon 1998, Chetty et al. 2000, Lambah et al. 2000) and no increase in recurrence (Chetty et al. 2000, Lambah et al. 2000), it has been shown to have a high error rate (24%) (Kissin et al. 1982).

How would sentinel lymph node biopsy change standard treatment for breast cancer?

The diagnostic accuracy of axillary clearance primarily depends on the diagnostic accuracy of the histopathological methods used to test the removed axillary nodes. A 2% to 3% false negative rate for axillary clearance is currently accepted, and there is a 2% to 4% rate of skip metastases above axillary Levels I and II (Boova et al. 1982, Rosen et al. 1983, van Lancker et al. 1995). However, since 70% to 80% of breast cancer patients are found to have negative nodes, a large number of axillary clearance procedures turn out to be unnecessary.

SLNB aims to identify for pathological analysis only the nodes most likely to show metastatic status (i.e. only the positive nodes). Once the metastatic status of the sentinel nodes is established patients requiring full axillary clearance as a treatment for lymph node involvement can be identified and treated (Pendlebury et al. 2001, Tobin et al. 1993). It is

also possible that SLNB may result in increased sensitivity as a diagnostic procedure, since focused pathologic attention is paid to the lymph nodes(s) that are most likely to harbour metastases, compared to brief pathologic analysis of all excised lymph nodes in an axillary dissection.

Marketing status of the device

There are several hand-held gamma probes (used for intraoperative mapping with radioisotope) registered for use in Australia. The Navigator GPS (Tyco Healthcare, Lane Cove, NSW, Australia) and Gammasonics Gamma Surgical Radiation Probe, Model SRP MK II (Gammasonics, Five Dock, NSW, Australia) are available. The TGA listing/registration numbers for the probes are listed in Table 1.

Table 1 TGA listing/registration for Navigator and Gammasonics hand-held gamma probes

Description	TGA listing/registration
Navigator Power Probe System	AUST L 81397
Navigator GPS System, Navigator Gamma Probes – Various	AUST L 63025
Navigator GPS Co pilot	AUST L 71204
Navigator Gamma Probe Drape	AUST L 72449
Gammasonics Surgical Radiation Probe (SRP) MK II	AUST L 65154

Current reimbursement arrangement

Table 2 shows the Medicare Benefits Scheme (MBS) schedule fees for the 2003–04 financial year and Table 3 the number of services provided. SLNB in breast cancer is currently funded under an interim arrangement, under item number 30332, which is the existing item number for axillary node sampling. However, some women who undergo SLNB may require a further procedure to remove the rest of the Level I and II lymph nodes, i.e. item numbers 30335 and 30336.

There is no appropriate item descriptor for a sentinel node found in the internal mammary chain as this is quite a different procedure to a biopsy within the axilla. Although the sentinel node is not within the breast, the internal mammary procedure does require preoperative localisation as well as intraoperative localisation and then confirmation of removal during and after the procedure with the use of a hand-held gamma probe, and so item number 31506 could be considered.

Table 2 2004 MBS Schedule of Fees for axillary sampling, excision to Level I, II or II and breast biopsy

Category	Item number	Fee
Lymph nodes of axilla, limited excision of (sampling) (Anaes) (Assist.)	30332	$288.20
Lymph nodes of axilla, complete excision of, to Level I (Anaes) (Assist.)	30335	$720.40
Lymph nodes of axilla, complete excision of, to Level II or Level III (Anaes.) (Assist.)	30336	$864.55
Breast, abnormality detected by mammography or ultrasound where guidewire or other localisation procedure is performed, excision biopsy of (Anaes.) (Assist.)	31506 (previously 30343)	$324.20

Source: MBS Book 1 November 2003 and 1 May Supplement

Table 3 Number of services by Australia states and territories, July 2003 to June 2004 (MBS)

Item	NSW	Vic.	Qld	SA	WA	Tas.	ACT	NT	Total
30332	931	209	176	87	237	96	62	11	1809
30335	412	371	368	56	101	47	7	5	1367
30336	1541	1082	871	497	373	55	87	25	4531
31506	1217	376	603	140	208	89	21	14	2668

Source: http://www.hic.gov.au/statistics/dyn_mbs/forms/mbs_tab4.shtml

Clinical need/burden of disease

Incidence and prevalence rates for breast cancer

In Australia in 2000, 11,314 women and 86 men were diagnosed with breast cancer. Figure 5 gives age-specific rates (per 100,000 of population) in 2000. Burden of disease was highest in the 60–64 year age group for women (AIHW 2000).

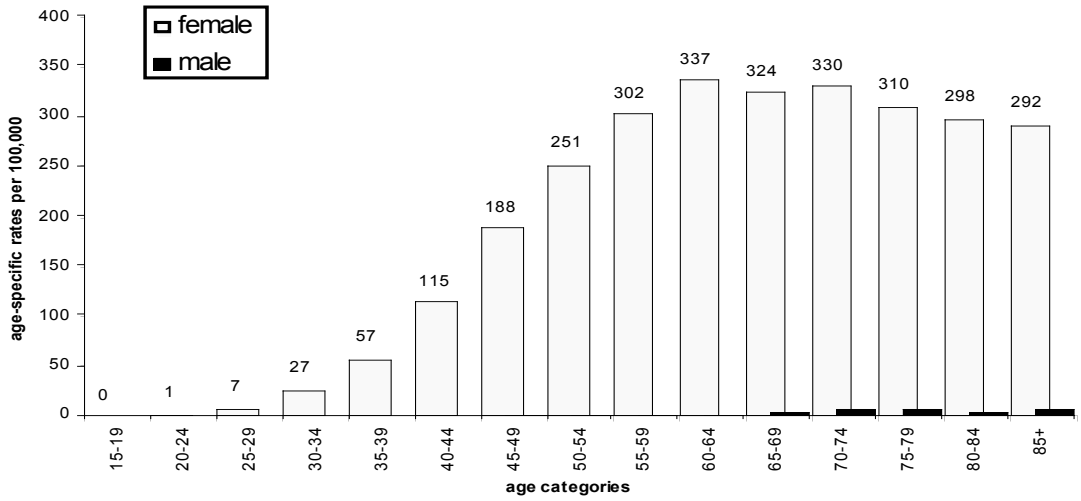


Figure 5 Age-specific rates of breast cancer in Australian women and men for 2000

The incidence of breast cancer increases with age, and has been increasing by 1% to 2% per year for the past decade (NHMRC 2001). Figure 6 shows the crude rates of breast cancer per 100,000 population. The incidence of breast cancer in women rose from 93 cases per 100,000 population in 1990 to 117 cases per 100,000 population in 2000 (AIHW 2000).

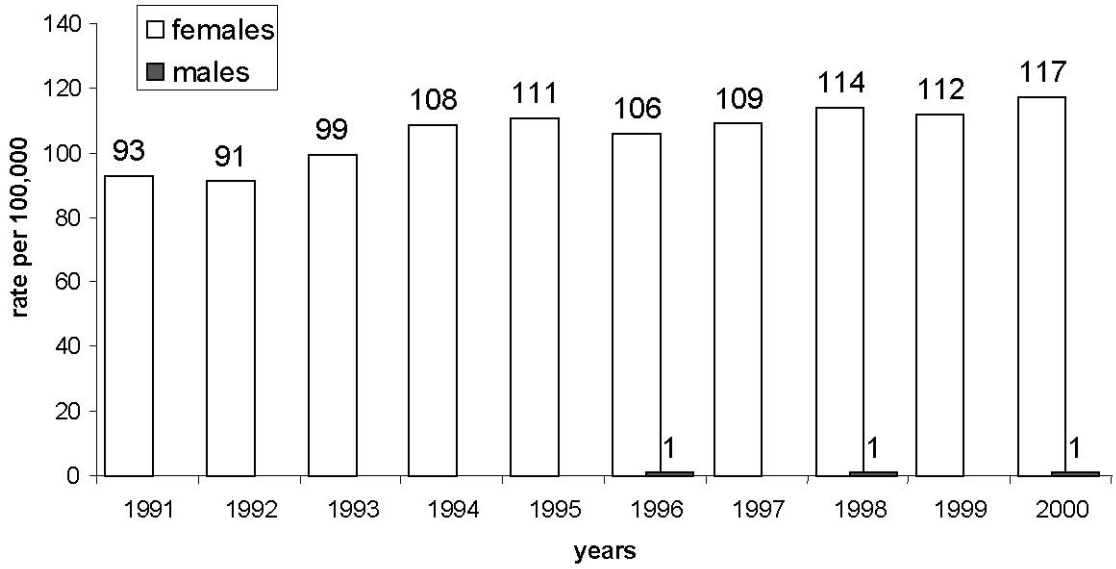


Figure 6 Incidence (rates per 100,000 of population) of breast cancer in Australian 1991–2000

In 1998, in Australia, 1185 women were diagnosed with ductal carcinoma *in situ* (AIHW 2000a). The number being diagnosed increased by two-thirds in the 1993 to 1998 period, mainly due to the increase in women undergoing mammographic screening and improved data collection, although the number diagnosed per year was relatively stable between 1995 and 1998 (AIHW 2000b).

Morbidity and mortality associated with breast cancer

Survival after breast cancer

Breast cancer is the most common cause of cancer-related death in women in Australia, resulting in 2521 deaths from breast cancer in 2000. The 5-year relative survival rate (i.e. excluding all other causes of death) for Australian women with breast cancer between 1992 and 1997 was 84%. The death rate from breast cancer reduced by around 2% per year between 1990 and 2000 (AIHW 2000).

Secondary lymphoedema

A major source of morbidity associated with breast cancer is lymphoedema[4] secondary to surgery and/or adjuvant therapy. A recent MSAC review[5] considered lymphoedema in Australia including that associated with breast cancer. The MSAC review estimated age-specific prevalence rates for lymphoedema from all causes (based on United Kingdom prevalence data applied to Australian census figures for 2001) at 25,188, but advised that this

[4] Lymphoedema is the abnormal swelling of the superficial body tissues, most often the limbs, caused by a failure of the lymphatic system to adequately collect or transport lymph.

[5] *The review of current practices and future directions in the diagnosis, prevention and treatment of lymphoedema in Australia* (February 2004).

estimate should be treated with extreme caution due to methodological differences in reporting and collecting of data, and is highly likely to be an underestimate. Axillary dissection to treat breast cancer is the most common cause of secondary lymphoedema in Australia. In 2003–04 over 10,000 patients received some form of lymph node excision or SLNB in the private health system (see Table 3). The MSAC review noted that accurate estimates of the prevalence of secondary lymphoedema in Australian women with breast cancer are not readily available. However, several Australian studies suggest that between 17% and 39% of women experienced lymphoedema between 6 months and 5 years after treatment for the primary tumour (Edwards 2000, McCredie et al. 2001, Zissiadis et al. 1997). As prevalence is known to increase over time this may explain some of the variation in these estimates. Lymphoedema has been shown to impact on quality of life and activities of daily living, however, at this time there are no Australian data published, although there are a number of ongoing studies.

Research questions

The primary question to be answered by this review is whether SLNB for breast cancer can identify patients for whom axillary clearance is not indicated (i.e. those who are lymph node negative), without increasing axillary recurrence rates or decreasing long-term survival.

A number of subsidiary questions arise from this primary question, and these form the basis of the systematic review. The methodology developed to answer these questions is described in Section 3, Approach to Assessment.

Diagnostic accuracy

1. How good is SLNB at finding the sentinel node (what are the localisation or mapping failure rates)?

2. What is the impact of surgeon and team experience/skill on localisation rates?

3. How does SLNB compare to axillary clearance in detecting the presence of axillary lymph node metastases (what are the false negative rates)?

4. What is the impact on diagnostic accuracy of variations in testing protocol (such the types and combinations of tracer fluid used and location and method of injection) and patient/tumour characteristics (such as tumour size and invasivity, multifocality/ multicentricity, clinical axillary status)?

Safety and effectiveness

5. What morbidities are associated with SLNB and how do these compare to morbidities associated with axillary clearance for staging breast cancer?

6. How do SLNB and axillary clearance compare in terms of avoidance of lymphoedema, and impact on quality of life and activities of daily living?

7. What are the cancer recurrence and survival outcomes for patients receiving SLNB compared with those receiving axillary clearance for the staging of their cancer?

8. Which techniques are women likely to prefer?

Cost effectiveness

9. Is SLNB more cost effective than axillary clearance?

3. Approach to assessment

Review of literature

Databases listed in Table 4 were searched from inception to December 2003 using search terms given in Table 5. The Cochrane Library and other trials databases were searched again in June 2004 to update the ongoing trials list in Appendix K.

Table 4 Databases searched

Database	Platform	Edition
MEDLINE	Ovid	1966 to December 2003
EMBASE	Ovid	1980 to Week 52 2003
Current Contents	ISI Current Contents	1993 to December 2003
Cochrane Library	www.update-software.com/cochrane	Issue 4, 2003
Clinical Trials Database (US)	http://www.clinicaltrials.gov/	Searched 1 Dec 2003
NHS Centre for Research and Dissemination (UK)	http://nhscrd.york.ac.uk	Searched 1 Dec 2003
NHS Health Technology Assessment (UK)	HTA on CD	Searched 1 Dec 2003
National Research Register (UK)	http://www.update-software.com/national	Searched 1 Dec 2003
EORTC Protocols Database	http://www.eortc.be/protoc/	Searched 1 Dec 2003
CancerLit (US)	http://cancer.gov/clinical_trials/	Searched 1 Dec 2003

Note: NHS – National Health Service; EORTC – European Organisation for Research and Treatment of Cancer; ISI – Institute of Scientific Information; HTA – Health Technology Assessment.

Table 5 Search terms

Database	Sentinel lymph node biopsy	Axillary clearance
MEDLINE	{Sentinel lymph node biopsy [MESH] or (SLN* or SNB or (sentinel and (biopsy or dissection or lymphadenectomy)) or lymph* map*)} and {Breast neoplasms [MESH] or (breast and (cancer or carcinoma)}	{Axilla [MESH] and Lymph node excision [MESH]) or (ALND or CLND or (axilla* and (dissection or clearance or lymphadenectomy))} and {breast neoplasms [MESH] or (breast and (cancer or carcinoma)}
EMBASE	{Lymph node biopsy [MESH] or Lymphoscintigraphy [MESH] or (SLN* or SNB or (sentinel and (biopsy or dissection or lymphadenectomy)) or lymph* map*)} and {Breast tumour [MESH] or (breast and (cancer or carcinoma)}	{Axilla [MESH] and (Lymph node dissection [MESH] or Lymphadenectomy [MESH]) or (ALND or CLND or (axilla* and (dissection or clearance or lymphadenectomy))} and {Breast tumour [MESH] or (breast and (cancer or carcinoma)}
Current Contents	(SLN* or SNB or (sentinel and (biopsy or dissection or lymphadenectomy)) or lymph* map*)} and {breast and (cancer or carcinoma)}	{(ALND or CLND or (axilla* and (dissection or clearance or lymphadenectomy))} and {breast and (cancer or carcinoma)}
Cochrane Library	Breast and sentinel Breast and axill* and sentinel	

Note: * is a truncation character that retrieves all possible suffix variations of the root word, e.g. surg* retrieves surgery, surgical, surgeon, etc. In databases accessed via the Ovid platform the truncation character is $.

Criteria for selecting studies

Participants

Female and male breast cancer patients with operable invasive breast cancer, however diagnosed, were included. Patients were included irrespective of tumour size, diagnosis of ductal carcinoma *in situ*, clinical nodal status, neoadjuvant therapy (such as chemotherapy or hormone therapy) or presence of multicentric breast cancer. Studies of patients with previous axillary dissection or current pregnancy were excluded.

Sentinel lymph node biopsy (Index test)

Included studies reported on the surgical removal of sentinel lymph nodes as indicated by the presence of dye or radioisotope or dye and radioisotope together. For assessing the false negative rate of SLNB all patients in the study must have received a confirmatory axillary clearance. Studies were included in which only patients with positive sentinel lymph node had confirmatory axillary clearance if they were reported in conjunction with the results for patients who did receive a confirmatory axillary clearance. Studies in which the sentinel node was identified by lymphoscintigraphy only were excluded, as were studies that used endoscopic sentinel lymph node detection.

Axillary clearance (Comparator)

Included studies reported on the clearance of the axilla to Levels I, II or III (described as total axillary dissection, axillary clearance, formal axillary dissection, total lymphadenectomy or it was apparent that the axilla was cleared). Studies that used endoscopic axillary clearance were excluded.

Outcomes

All included studies contained the primary outcome. Primary outcomes were defined according to the question being addressed.

Localisation rates

Primary outcome

- Intraoperative localisation rate.

Secondary outcomes

- Concordance of lymphoscintigraphic and surgical localisation.
- Concordance of dye and radioisotope.

False negative rates

Primary outcome

- The number of true and false positive patients and true and false negative patients for all patients localised.

Safety and effectiveness

A primary outcome was not defined. Each included study contained information on at least one of the following outcomes of SLNB compared to axillary clearance, or contained safety outcomes for SLNB:

- Perioperative and postoperative mortality of patients (short- and long-term).
- Perioperative and postoperative morbidity of patients, including, but not limited to pain, paraesthesias, seroma formation, wound infection, drain placement and complications, limitation of shoulder movement and acute and chronic lymphoedema.
- Regional recurrence rates.
- Length of hospital stay.
- Quality of life.

Cost-effectiveness

Any study that reported an evaluation of the costs incurred in using SLNB compared with axillary clearance was considered for inclusion.

Types of studies

Diagnostic accuracy

Consecutive and non-consecutive case series in which patients received SLNB were included. For assessment of false negative rates, patients must also have received a confirmatory axillary clearance. Depending on how data were reported in individual studies, it was sometimes possible to calculate both a localisation rate and a false negative rate from the same study, and so the study was included for both analyses.

Safety and effectiveness

Randomised controlled trials or non-randomised comparative studies using concurrent or historical controls comparing lumpectomy, wide local excision, segmentectomy, quadrantectomy or mastectomy (radical, modified radical or skin sparing) and axillary clearance with sentinel node biopsy (with or without axillary clearance, depending on nodal status) prior to lumpectomy, wide local excision, segmentectomy, quadrantectomy or mastectomy (radical, modified radical or skin sparing), were included for review. Case series were included for safety outcomes and recurrence, and case reports for adverse events.

Where appropriate, additional relevant published material in the form of letters, conference material, commentary, editorials and abstracts were included as background information.

Language restriction

Searches were conducted without language restriction. Non-English language studies were included for assessing safety and effectiveness, but excluded for assessing diagnostic accuracy, as many patients appeared to be reported in other English language publications.

Disclaimer

Although every attempt was made to identify studies that met the inclusion criteria some studies may have been missed due to the multitude of publications on SLNB in breast cancer. In addition, patients may have been included in more than one study from the same centre. Attempts were made to include the most appropriate patient set for extraction of localisation rates and false negative rates.

Methods of the review

Literature database

Articles were retrieved when judged by their abstract to possibly meet the selection criteria. Two reviewers independently applied the selection criteria to these retrieved papers and any differences were resolved by discussion. In some cases, when the full text of the article was retrieved, closer examination revealed that it did not meet the inclusion criteria specified by the review protocol. Consequently, these papers were not used to formulate the evidence base for the systematic review (See Appendix D). However, relevant information contained in these excluded studies was used to inform and expand the review discussion. The bibliographies of all publications retrieved were manually searched for relevant references that may have been missed in the database search (pearling). The results of this process are shown in Figure 7.

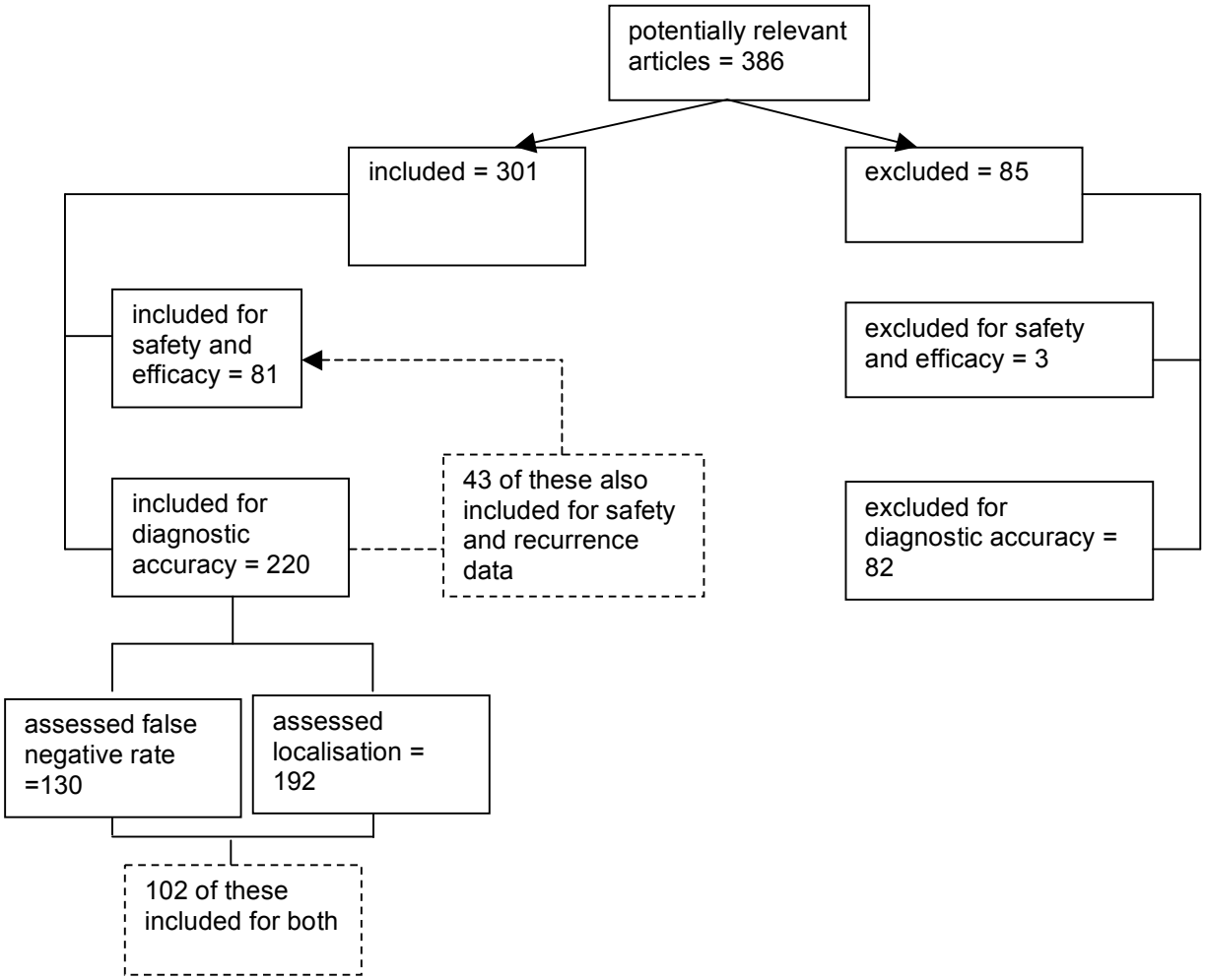


Figure 7 Flowchart for inclusion of studies in the review

Data extraction

Data were extracted onto data extraction sheets designed for this review by one reviewer and checked by a second. Data were only reported if stated in the text, tables, graphs or figures of the article, or if they could be accurately extrapolated from the data presented. If no data were reported for a particular outcome then no value was tabulated. This was done to avoid the bias caused by incorrectly assigning a zero value to missing data. For example if no localisation rate was reported, the result was not assumed to be zero. All results are tabulated in Appendices H, I and J.

Calculation of localisation and false negative rates

For each study included to assess diagnostic accuracy, it was necessary to calculate a localisation rate and false negative rate, where data available in the study allowed such calculations to be made.

Localisation rate

Localisation rate refers to the number of times the sentinel node was located using the SLNB method. In some studies, a proportion of patients had bilateral breast cancer and had sentinel lymph node mapping performed in each axilla, therefore localisation rates were based on the number of mappings rather than the number of patients undergoing sentinel lymph node mapping.

Localisation rates were calculated according to the following formula:

$$\text{Localisation rate} = \left[\frac{\text{successful mappings}}{\text{total number of mappings}} \right] \text{X } 100$$

False negative rate

The false negative rate represents the proportion of patients whose sentinel nodes were negative, but positive node(s) were found elsewhere in the axilla, either during surgery (i.e. a palpable nonradioactive and/or blue node) or during pathologic analysis of the axillary contents. False negative rates were calculated from the raw data, using the following formula, which represents the number of negative tests that were incorrect and equates to one minus the negative predictive value.

$$\text{False negative rate} = \left[\frac{\text{false negatives}}{\text{false negatives + true negatives}} \right] \text{X } 100$$

McMasters et al. (1998) proposed an alternative method for calculating false negative rates. By this method the false negative rate represents the number of diseased patients that the test missed and equates to one minus the sensitivity. However, this method was considered to be less clinically relevant to the analysis as all patients receiving SLNB are known to have breast cancer.

$$\text{False negative rate} = \left[\frac{\text{false negatives}}{\text{false negatives + true positives}} \right] \text{X } 100$$

For the purposes of comparison we have reported the overall false negative rates using both the formulas but the first is considered the primary analysis and all subgroup analyses are based on that formula.

Data analysis

Diagnostic accuracy

Meta-analysis (SAS Version 8, SAS Institute Inc., Cary, NC, US) was used to calculate weighted mean localisation rates and false negative rates with 95% confidence intervals for each applicable study. These results were combined using random effects meta-analysis (WinBUGS Version 1.2, Spiegelhalter et al. 1999). Random effects meta-analysis using a Bayesian framework was chosen because it was expected there would be significant heterogeneity between studies. Since random-effects meta-analysis allows study rates to vary around the mean overall rate, it is more realistic when there is a large variation in the rates (Higgins & Thompson 2002, Normand 1999).

To investigate factors influencing localisation rate and false negative rate a number of planned subgroup analyses were undertaken. Subgroups were defined according to categories listed in Appendix F. Random effects meta-analysis was used to calculate estimated means for each category with 95% posterior intervals.[6] To compare means within each subgroup, estimated mean differences and 95% posterior intervals were calculated. The probability that the groups were equal given the data was tested using a Bayesian p-value for each difference. The Bayesian p-value can be interpreted in a similar way to standard p-values (Gelman et al. 1995). Statistical significance was set at $p \leq 0.05$.

Subgroups tested were: type and combination of injectate, method of injection, timing of injection, tumour size, invasiveness, clinical axillary status, tumour biopsy method, multifocality/multicentricity and neoadjuvant chemotherapy use. Estimated mean differences were only calculated for those comparisons thought to be clinically relevant.

Safety and effectiveness

There were no included studies suitable for meta-analysis.

Cost effectiveness

A cost minimisation and cost effectiveness analysis of SLNB and axillary clearance was undertaken. The ideal measure of effectiveness would be relative long-term survival with SLNB compared to axillary clearance. Since this information will not be available until completion of several large ongoing randomised controlled trials (see p. 59 and Appendix K), the analyses in this review assume similar recurrence and survival outcomes in a cost-minimisation analysis and also use avoidance of lymphoedema in a cost-effectiveness analysis.

Description and methodological quality of included studies

The evidence presented in the included studies was assessed and classified using the dimensions of evidence defined by the National Health and Medical Research Council (NHMRC, 2000) (see Table 6). These dimensions consider important aspects of the evidence supporting a particular intervention and include three main domains: strength of the evidence, size of the effect and relevance of the evidence. The first domain is derived directly from the literature identified as informing a particular intervention. The last two require expert clinical input as part of their determination.

[6] A posterior interval may be interpreted as the range of values within which there is a high probability that the true estimate lies.

Table 6 Dimensions of evidence

Type of evidence	Definition
Strength of the evidence	
Level	The study design used, as an indicator of the degree to which bias has been eliminated by design.*
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The *p*-value or, alternatively, the precision of the estimate of the effect. It reflects the degree of certainty about the existence of a true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance of evidence	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

*See Table 7.

The three sub-domains (level, quality and statistical precision) are collectively a measure of the strength of the evidence. The designations of the levels of evidence are shown in Table 7.

Table 7 Designations of levels of evidence

Level of evidence	Study design
I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudorandomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies (including systematic reviews of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pre-test/post-test.

Source: Modified from NHMRC, 2000.

Expert advice

An advisory panel with expertise in breast surgery was established to evaluate the evidence and provide advice to MSAC from a clinical perspective. In selecting members for advisory panels, MSAC's practice is to approach the appropriate medical colleges, specialist societies and associations and consumer bodies for nominees. Membership of the advisory panel is provided in Appendix B.

4. Diagnostic accuracy of sentinel lymph node biopsy

Included studies

Comparative studies (randomised and non-randomised)

There were no comparative studies assessing diagnostic accuracy. One randomised controlled trial (Veronesi et al. 2003), included to assess safety and effectiveness, reported false negative rates and was treated as a case series and counted below.

Case series

A total of 220 studies were included for the review of diagnostic accuracy. Fifty-two (23.6%) of the included studies stated that patients were consecutively selected.

The location of studies was fairly evenly split between the Americas (90/220) and Europe (87/220), with 43/220 conducted elsewhere. However, 36% of all included studies were conducted in the United States (80/220), 13% in Italy (29/220) and 8% in Japan (17/220).

Localisation rates and false negative rates were not available for all included studies. Localisation rates were addressed in 192 studies and false negative rates were addressed in 130 studies. In 102/220 (46.4%) studies both localisation rates and false negative rates were addressed, and these studies were included in both analyses. Details are in Appendix C; and study profiles are in Appendix F.

Results

Data for analysis

Of the 192 studies assessing localisation rates, 24 reported rates for more than one patient group. As a result, 228 sets of values were available for the localisation rate analysis. Of the 130 studies assessing false negative rates, six reported rates for more than one patient group, and therefore 136 sets of values were available for the false negative rates analysis. Localisation and false negative rates, together with other results for each included study, are listed in Appendix H.

In seven studies the sentinel node was mapped to a location other than the axilla (usually the internal mammary chain) in some patients, and reported as a mapping failure (Blessing et al. 2002, Feggi et al. 2000, Fernandez et al. 2002, Gucciardo et al. 2000, Molland et al. 2000, Rink et al. 2001, Ugur et al. 2003). As this was not considered to be a mapping failure of the axillary region according to the review protocol, these patients were not included in calculation of the localisation rate.

Distribution of localisation rates and false negative rates in included studies

Localisation rate

In Figure 8 the 228 sets included in the analysis have been categorised into 5% bands for localisation rate. The localisation rate was greater than 95% in 96/228 (42.1%) sets, with 33/228 (14.5%) having no localisation failures. The vast majority of sets (215/228, 94.3%) had a localisation rate above 80%.

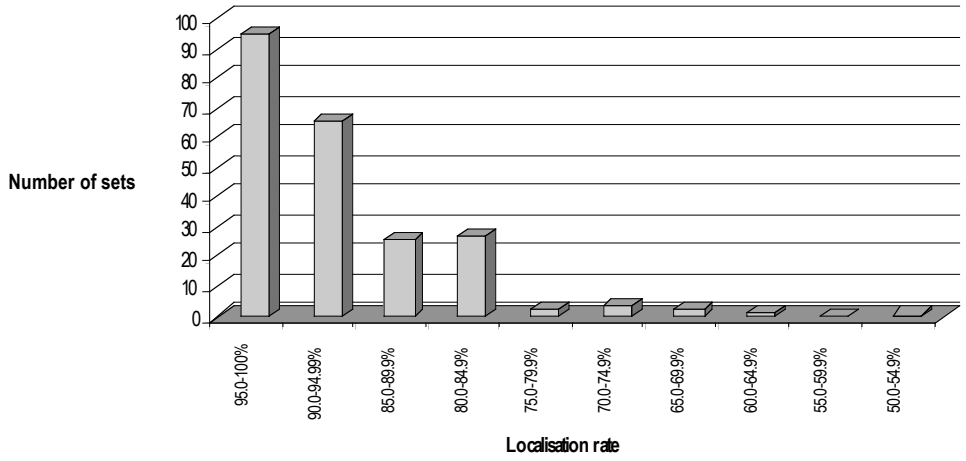


Figure 8 Distribution of localisation rates in 228 sets of data

False negative rates

Most sets of patients (108/136, 79.4%) had false negative rates below 15%, 39/136 (36.0%) had a false negative rate below 5%, with 28/136 (20.6%) having a false negative rate of 0% (see Figure 9).

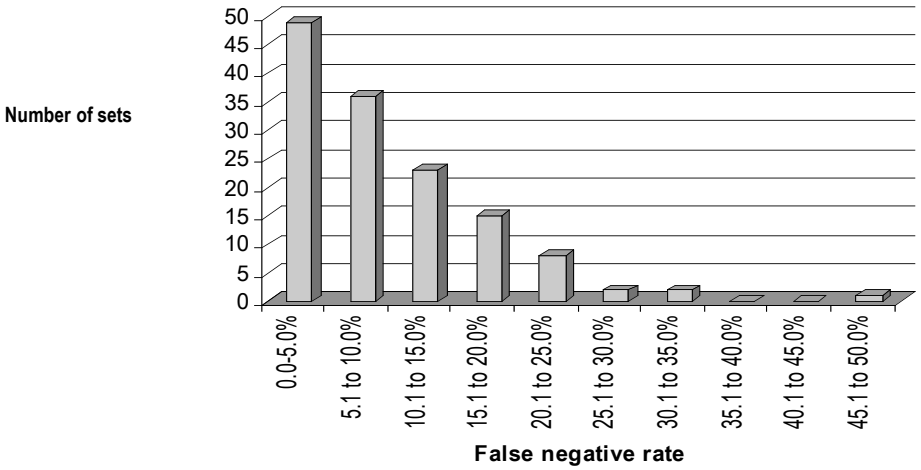


Figure 9 Distribution of false negative rates in 136 sets of data

Mean localisation and false negative rates

Localisation rate

In 228 sets of data, the mean set size was 143, the median 68, and the range 6 (Feezor et al. 2002) to 3324 (Wong et al. 2002a).

The mean localisation rate was 94.1% (95% PI: 93.3% to 95.0%)

The meta-analysis showed strong evidence of between-patient variation and heterogeneity between sets (test of heterogeneity, I^2=89.3%, *p*-value=<0.0001[7]). This is illustrated in Figure 10 that shows the weighted mean localisation rate with 95% confidence interval for each included set and the overall pooled mean.

False negative rate

In 136 sets of data, the mean set size was 69, the median 37, and the range 14 (Brady 2002, Kitapci et al. 2001) to 2117 patients (Wong et al. 2002a). The distribution of set sizes was skewed by the largest set (i.e. Wong et al. 2002a), with the next largest set having 286 patients (Bergkvist et al. 2001).

The mean false negative rate was 4.7% (95% PI: 4.0% to 5.4%).

There was evidence of a moderate amount of between-patient variation and heterogeneity between sets (I^2=34.0%, *p*-value=<0.0002). This is illustrated in Figure 11 that shows the weighted mean false negative rate with 95% confidence interval for each included set and the overall pooled mean.

Alternative calculation of false negative rate (using McMasters et al. 1998 formula):

The mean false negative rate was 7.4% (95% PI: 6.5 to 8.5%)

[7] I^2 is interpretable as the proportion of total variation in the false negative rates that is due to heterogeneity between studies.

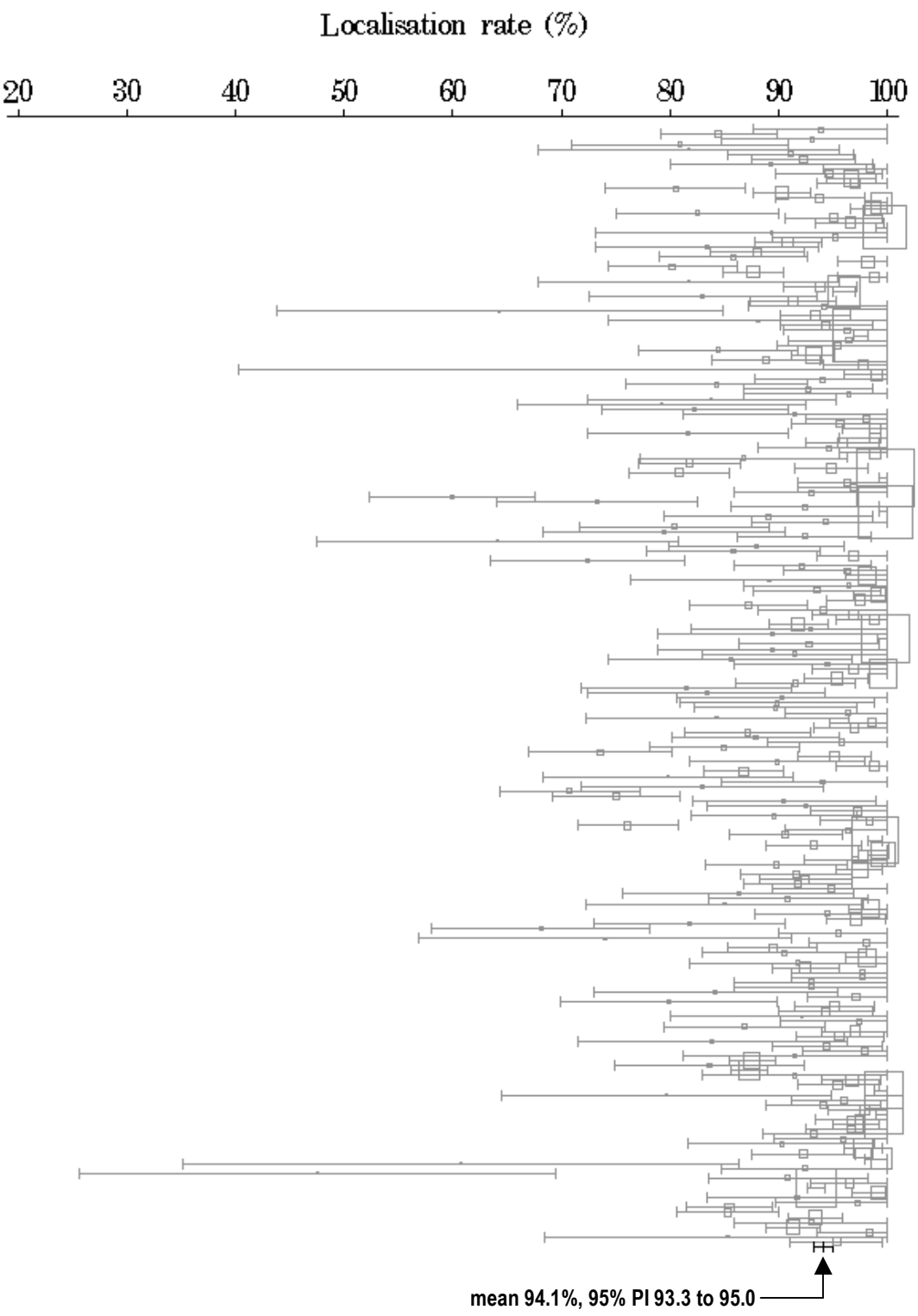


Figure 10 There was a large amount of heterogeneity between and within sets of data as illustrated by the variability in mean localisation rates weighted for sample size (horizontal lines)

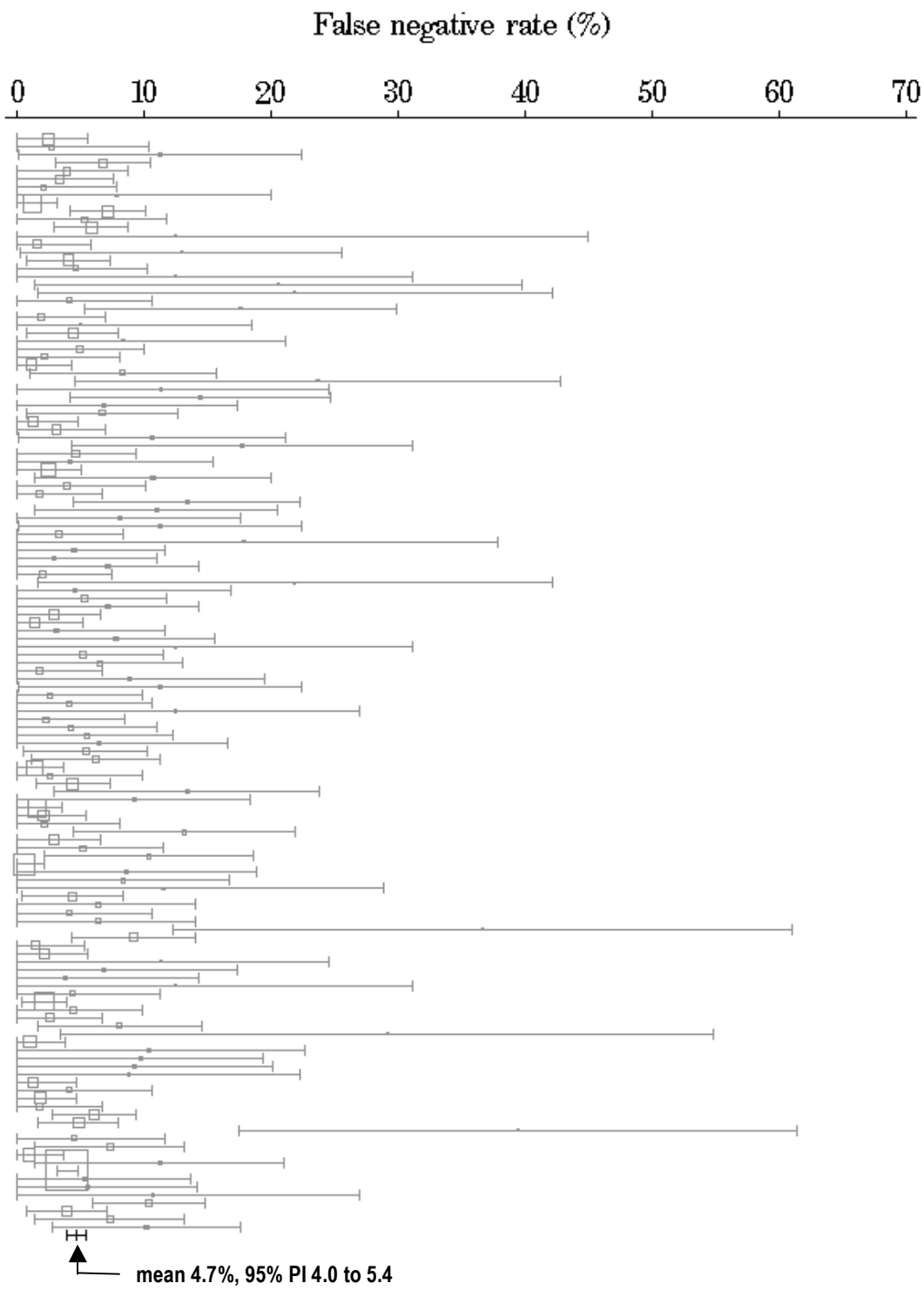


Figure 11 There was less heterogeneity among sets of data for false negative rates than for localisation rates but some sets had very wide confidence intervals and high mean false negative rates (weighted for sample size)

Impact of clinical team experience on diagnostic accuracy

There were no included studies that directly assessed the impact of the experience of the clinical team[8] on diagnostic accuracy. However, two post-hoc sensitivity analyses were carried out which attempted to assess the possible contribution of learning curve issues and refinement of the SLNB technique since it was first used in breast cancer. The first was a cumulative meta-analysis based on year of publication, and the second excluded sets with fewer than 50 patients and compared this with the overall mean localisation and false negative rates. The aim of these analyses was to see whether localisation rates and false negative rates were affected by the cumulative world experience with the SLNB technique, or the number of procedures carried out by particular teams. Both of these are proxy measures of the impact of surgeon/team experience, since the first cannot control for publication lag, and the second cannot isolate the contribution of individuals or a SLNB volume effect for each individual surgeon/surgical team.

Cumulative meta-analysis

Localisation rates

Heterogeneity (disagreement between study results) was high and remained constant with time, as shown by the I^2 values in Table 8. The cumulative localisation rate increased in a linear fashion from 1998 to 2003 (see Table 8 and Figure 12). The overall pooled mean (year 2003 in Table 8) was statistically significantly better than the pooled mean for the years 1999, 2000 and 2001.

Table 8 Cumulative meta-analyses by year of publication for localisation rates

Year	Number of sets	I^2 (%)	Mean localisation rate (%)	95%PI	*p*-value*
1998	11	81.9	89.2	81.7, 94.9	0.10
1999	32	91.3	90.2	86.0, 93.6	0.021
2000	74	89.8	91.7	90.0, 93.5	0.005
2001	113	88.5	92.6	91.1, 94.1	0.043
2002	175	89.5	93.3	92.2, 94.3	0.11
2003	228	89.3	94.1	93.3, 95.0	–

Note: PI – posterior interval; * test of cumulative localisation rate compared to overall rate.

False negative rates

There is a clear increase in heterogeneity (disagreement between study results) over time evident in Table 9 as an increase in I-squared between 1998 and 2003. The false negative rate increased marginally from 1998 to 2000, and remained relatively stable from there on (Table 9 and Figure 13). No significant difference between the overall false negative rate (year 2003 in Table 9) and the rate for each year could be detected.

[8] The clinical team is typically made up of surgical, radiological, nursing, pathology and nuclear medicine staff.

Table 9 Cumulative meta-analyses by year of publication for false negative rates

Year	Number of sets	I^2 (%)	Mean false negative rate (%)	95%PI	*p*-value*
1998	14	0.0	3.2	1.8, 4.9	0.072
1999	29	0.0	3.9	2.8, 5.1	0.15
2000	56	19.5	4.7	3.6, 5.7	0.95
2001	85	19.2	4.8	4.0, 5.6	0.84
2002	112	29.7	4.4	3.7, 5.1	0.37
2003	136	34.0	4.7	4.0, 5.4	-

Note: PI – posterior interval; * test of cumulative false negative rate compared to overall rate.

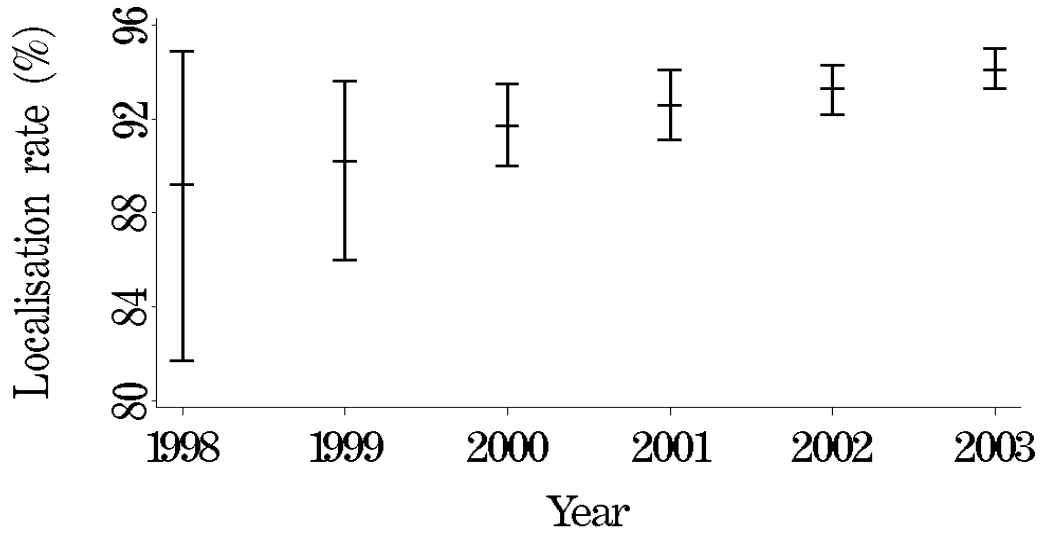


Figure 12 Cumulative random effects meta-analyses by year of publication for localisation rates

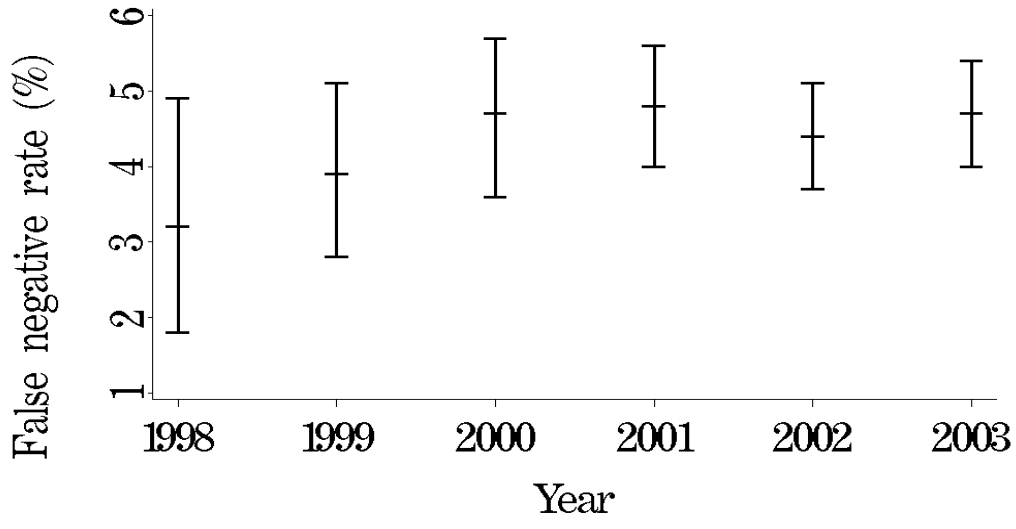


Figure 13 Cumulative random effects meta-analyses by year of publication for false negative rates

Study size sensitivity analysis

Localisation rate

No difference was seen between the overall pooled mean localisation rate when sets with fewer than 50 patients were excluded (see Table 10). However, heterogeneity was slightly higher when the smaller sets were excluded.

Table 10 Sensitivity analysis for localisation rate, by study size

Study size	Number of sets	I^2 (%)	Mean localisation rate (%)	95%PI
Large (*n*>=50)	150	92.3	94.1	93.0, 95.0
All	228	89.3	94.1	93.3, 95.0

Note: PI – posterior interval

False negative rate

There was little difference between the overall pooled mean false negative rate when sets with fewer than 50 patients were excluded (see Table 11). However, heterogeneity was higher when the smaller sets were excluded.

Table 11 Sensitivity analysis for false negative rate by study size

Study size	Number of sets	I^2 (%)	Mean false negative rate (%)	95%PI
Large (*n*>=50)	46	51.3	4.2	3.4, 5.0
All	136	34.0	4.7	4.0, 5.4

Note: PI – posterior interval

Summary of sensitivity analyses

Overall, localisation rates appear to have improved each year since 1998 suggesting that, as experience with the SLNB technique has grown, the procedure has become more refined. However, heterogeneity between sets was consistently high throughout the study period. No clear explanations for this heterogeneity were apparent. On the other hand, false negative rates have become worse than the mean false negative rate of 3.2% in 1998, appearing to plateau around 4.5 to 5.0% since 2000. Excluding sets with fewer than 50 patients did not appear to affect either the mean localisation rate or the mean false negative rate.

Effect of test protocol variables on diagnostic accuracy

Results of subgroup analyses for the following variables are shown in Table 12:

- type of tracer used (radioisotope and/or dye)
- type of radioisotope used
- location of radioisotope injection
- timing of radioisotope injection
- type of dye used

- location of dye injection
- histological analysis (false negative rates only).

Type of tracer used

Localisation rate

Localisation rate was significantly higher when a combination of radioisotope and dye was used compared to dye only (estimated mean difference 8.5%, 95%PI: 5.1 to 12.2, p<0.0001), or radioisotope only was used compared to dye only (estimated mean difference 6.9%, 95%PI: 3.2 to 10.8, p<0.0001). The difference between radioisotope only and a combination of radioisotope and dye approached significance, however, the estimated mean difference was small (estimated mean difference 1.6%, 95%PI:-0.2 to 3.5, p=0.08) (see Figure 14).

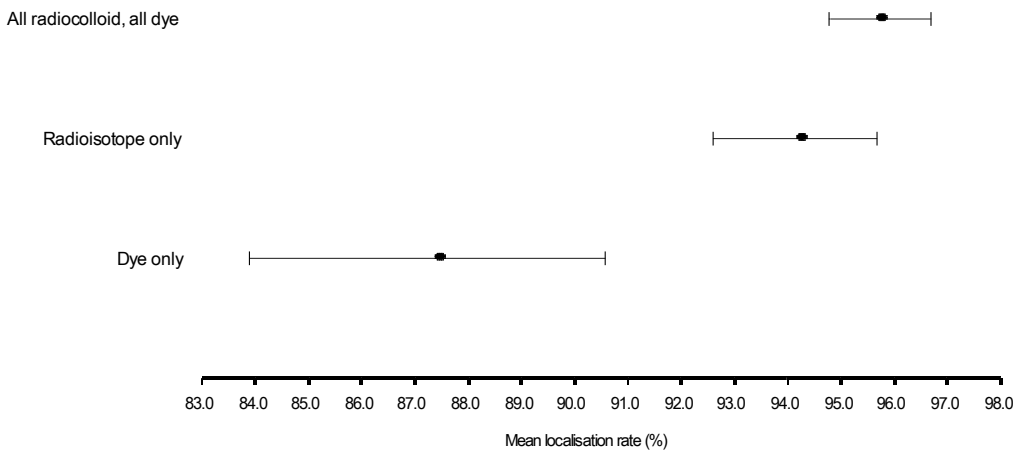


Figure 14 Estimated mean localisation rate and 95%PI for type of tracer used

False negative rate

The false negative rate was significantly lower when both radioisotope and dye were used compared to dye only (estimated mean difference 2.9%, 95%PI: 0.8 to 5.3, p=0.005). The difference between radioisotope only and a combination of radioisotope and dye approached significance, and the estimated mean difference and posterior intervals may have included clinically important values (estimated mean difference -1.6%, 95%PI: 0.2 to -3.5, p=0.084) (see Figure 15).

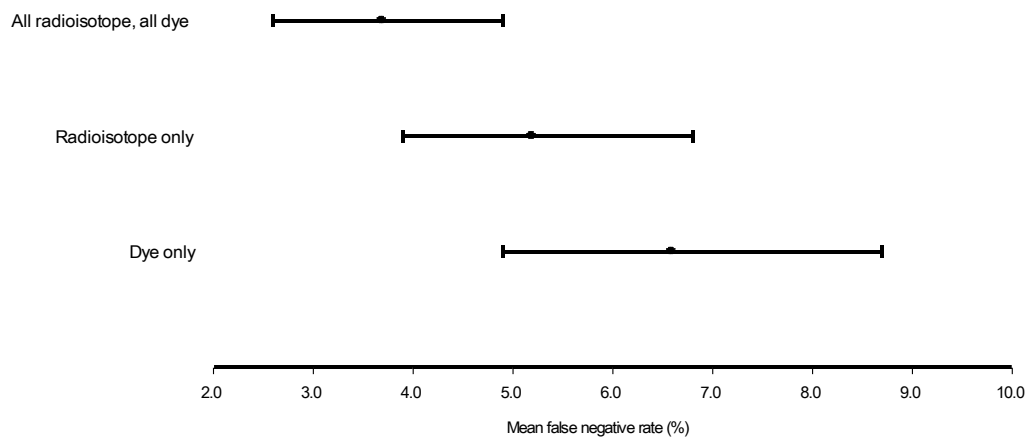


Figure 15 Estimated mean false negative and 95%PI rate for type of tracer used

These results were consistent with results in those included studies where internal comparisons of type of tracer were undertaken (Ahrendt et al. 2002, Canavese et al. 2001, Mahajna et al. 2003, McMasters et al. 2000a, Noguchi et al. 2000a, Motomura et al. 2001). Some studies also found that fewer sentinel nodes were located using blue dye than radioisotope (Patel et al. 2003, McMasters et al. 2000a).

Concordance between radioisotope and dye

Concordance is the percentage of identical axillary nodes localised simultaneously by two markers (Borgstein et al. 2000). The concordance between dye and radioisotope was reported in 33 sets of data and ranged from 21.1% to 97.6%. Concordance of 100% was not reported in any study. Difference in concordance rates between sets could be due to the effect of the learning curve (Kumar et al. 2003) (see Appendix E).

Type of radioisotope used

Little difference was seen in the localisation rates regardless of the type of radioisotope used. Although the false negative rate using sulphur colloid was lower (3.5%) than using albumin colloid (4.8%), this difference was not thought to be clinically important, and multiple comparison tests were not performed.

Table 12 Random effects subgroup analysis: effect of test protocol variables on diagnostic accuracy

Subgroup	Category		Localisation rates			False negative rates	
		Number of sets	Mean	95%PI	N	Mean	95%PI
Type of tracer	All radioisotope, all dye	94	95.8	94.8, 96.7	37	3.7	2.6, 4.9
(see Figures 14 and 15)	Radioisotope only	50	94.3	92.6, 95.7	36	5.2	3.9, 6.8
	Dye only	39	87.5	83.9, 90.6	33	6.6	4.9, 8.7
	Other*	45	93.3	91.2, 95.0	30	3.9	2.8, 5.3
Type of radioisotope	Sulphur colloid	70	94.5	93.1, 95.8	36	3.5	2.5, 4.7
	Albumin colloid	53	95.2	93.6, 96.5	33	4.8	3.5, 6.3
	Other radioisotope	36	95.1	93.0, 96.7	19	4.8	3.1, 6.8
	Other†	69	91.7	89.7, 93.5	48	5.8	4.4, 7.3
Location of radioisotope injection	Peritumoural	101	93.8	92.4, 95.0	58	3.6	2.8, 4.7
(see Figure 16)	Subareolar or periareolar	10	98.1	96.0, 99.3	4	4.9	1.5, 11.1
	Intradermal or subdermal or subcutaneous	30	96.2	94.4, 97.5	15	5.3	3.2, 8.1
	Intralesional	4	94.2	86.1, 98.3	2	3.0	0.5, 9.0
	Other‡	83	92.8	91.1, 94.3	57	5.6	4.5, 7.0
Time of radioisotope injection	Day before	59	95.1	93.6, 96.3	31	5.7	4.0, 7.6
(see Figure 17)	Same day	53	94.3	92.5, 95.8	31	3.5	2.4, 4.8
	Combination	42	95.2	93.4, 96.7	21	4.6	3.1, 6.4
	Not applicable/not stated/not clear	74	91.9	89.8, 93.7	53	5.1	3.9, 6.3
Type of dye	Patent blue dye	56	93.6	91.6, 95.2	37	4.9	3.6, 6.5
	Isosulfan blue dye	75	95.0	93.6, 96.1	38	3.5	2.5, 4.8
	Methylene blue dye	8	94.3	88.9, 97.7	3	5.6	1.7, 12.9
	Other dye	18	92.4	87.9, 95.7	10	5.2	3.0, 8.4
	Two or more different types of dye used	71	93.9	92.2, 95.3	48	5.3	4.1, 6.7
Location of dye injection	Peritumoural	103	93.2	91.8, 94.5	60	4.4	3.4, 5.6
(see Figure 18)	Subareolar or periareolar	14	96.5	94.0, 98.2	5	3.1	0.6, 8.3
	Intradermal or subdermal or subcutaneous	25	95.1	92.8, 96.9	14	5.2	3.2, 7.8
	Intralesional	5	91.1	81.9, 96.5	2	3.5	0.6, 10.7
	Other‡	81	94.5	93.1, 95.7	55	5.0	3.9, 6.2
Histology	Permanent histology	-	-	-	51	4.8	3.6, 6.1
	Permanent histology + IHC in all localised patients	-	-	-	31	4.5	3.1, 6.1
	Permanent histology + IHC in some localised patients	-	-	-	39	4.3	3.2, 5.6
	Frozen section or IHC only or Not stated/Not clear	-	-	-	15	6.2	3.9, 9.3
All sets		228	94.1	93.3, 95.0	136	4.7	4.0, 5.4

Note: * Some radioisotope only, some dye only, some radioisotope + dye or variation or Not stated/Not clear; †Two or more types of radioisotope used within a study. Unspecified radioisotope or not stated/not clear/unsure/Not applicable (radioisotope not used within the study); ‡ Two or more methods within a patient or a study, Not stated/Not clear/Not applicable (radioisotope or dye not used within the study); IHC – immunohistochemistry staining; PI – posterior interval.

Location of radioisotope injection

Localisation rate

Both subareolar and intradermal injection sites were associated with significantly higher localisation rates than peritumoural injection sites (estimated mean difference subareolar versus peritumoural: -4.4%, 95%PI: -6.2 to -2.3, p<0.0001; and estimated mean difference intradermal versus peritumoural: -2.4%, 95%PI: -4.3 to -0.5, p=0.02). The difference between subareolar and intradermal approached significance (estimated mean difference 2.0%, 95%PI: -0.3 to 4.0, p=0.07) but, as there were only 10 sets where the subareolar injection site was used, the statistical analysis may be underpowered. These results are consistent with internal comparisons in five included studies (Jastrzebski et al. 2002, McMasters et al. 2001a, Rettenbacher et al. 2000, Fleming et al. 2003, Martin et al. 2001a, Motomura et al. 2003). However, it is difficult to estimate the clinical importance of this finding given that the majority of included sets used the peritumoural injection site, reflecting what is probably more typical in clinical practice. As there were only five sets in which the intralesional injection site was used, the mean localisation rate and 95% posterior intervals are wide, and it was not possible to compare these results statistically with the other injection sites (see Figure 16).

False negative rate

No significant differences were seen in false negative rates regardless of the location of the radioisotope injection (see Appendix E for estimated mean difference statistics).

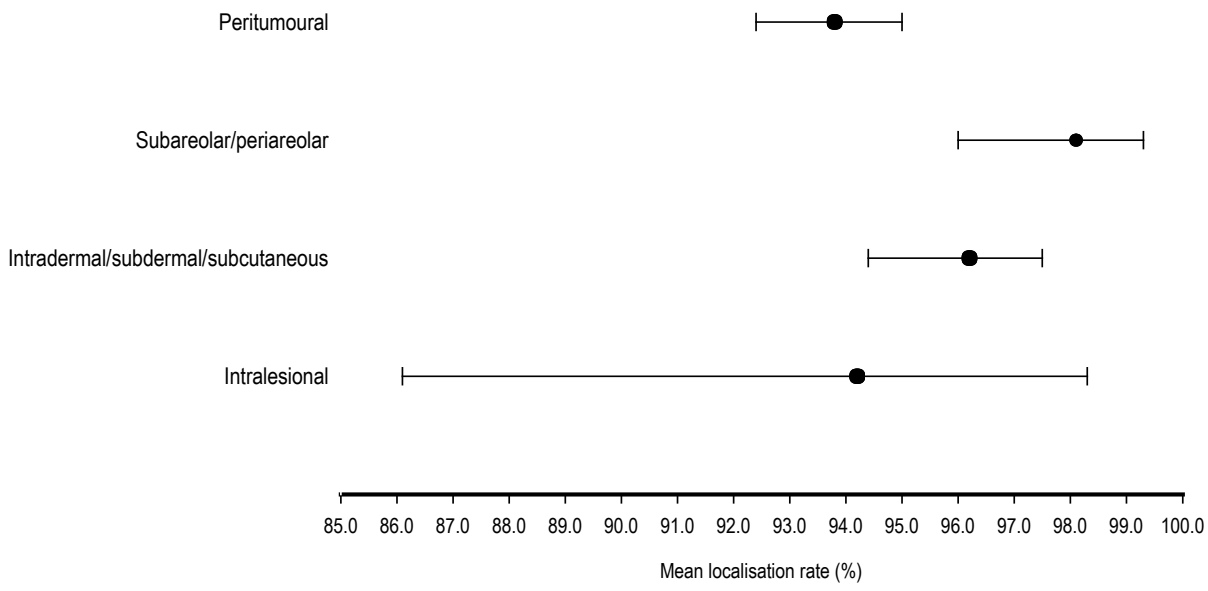


Figure 16 Estimated mean localisation rate and 95%PI rate for location of radioisotope injection

Time of radioisotope injection

Localisation rate

No statistically significant difference was seen in the localisation rates regardless of whether the radioisotope was injected on the day before surgery or on the same day as surgery (estimated mean difference 0.7%, 95%PI: -1.3 to 2.7, p=0.46). These results were supported by two studies in which internal comparisons of injection timing were made (Krag et al. 2001, Sutton et al. 2002), but one study found localisation rates were higher when radioisotope was injected on the day of surgery (Bergkvist et al. 2001).

False negative rate

The false negative rate when the radioisotope was injected the same day was significantly lower (3.5%) than when it was injected the day before (5.7%) (estimated mean difference 2.0%, 95%PI: -0.0 to 4.1, p=0.046) (see Figure 17).

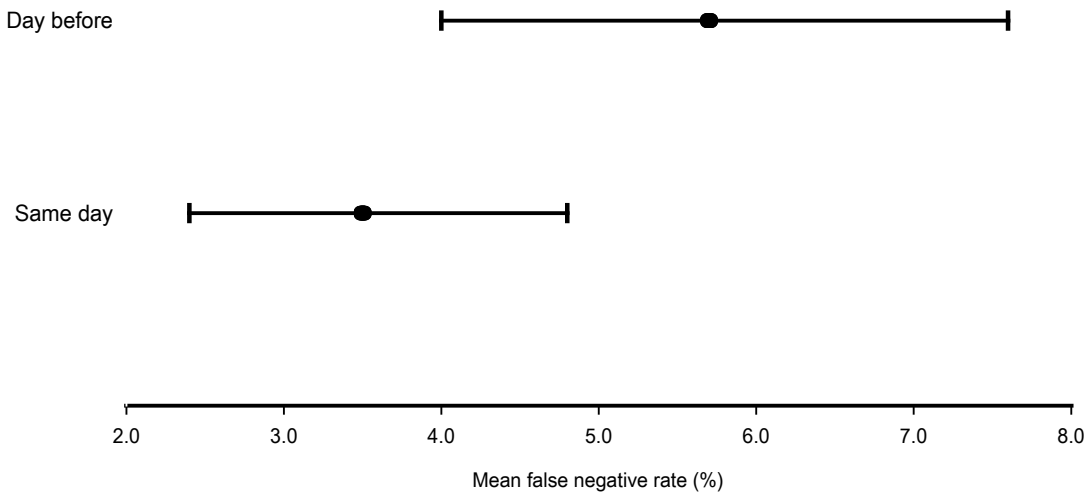


Figure 17 Estimated mean false negative rate and 95%PI rate for timing of radioisotope injection

Type of dye used

No significant differences were seen in localisation rates or false negative rates regardless of which type of dye was used (see Appendix E for estimated mean difference statistics). Since methylene blue was only used in eight sets included in the analysis of localisation rates and three in the analysis of false negative rates, the analysis may have been underpowered, however, the estimated mean differences are small and are probably not clinically important. These results were consistent with results in those included studies where internal comparisons of type of dye were undertaken (Blessing et al. 2002, Koller et al. 1998).

Location of dye injection

Localisation rate

Localisation rate was significantly higher for subareolar injection than for peritumoural injection (estimated mean difference 3.4%, 95%PI: 0.6 to 5.6, p=0.026). No significant differences were seen between peritumoural and intradermal (estimated mean difference 2.0%, 95%PI: -4.2 to 0.5, p=0.11), or subareolar and intradermal (estimated mean difference 1.4%, 95%PI: -1.7 to 4.4, p=0.34). There were too few studies to compare intralesional injection site (see Figure 18).

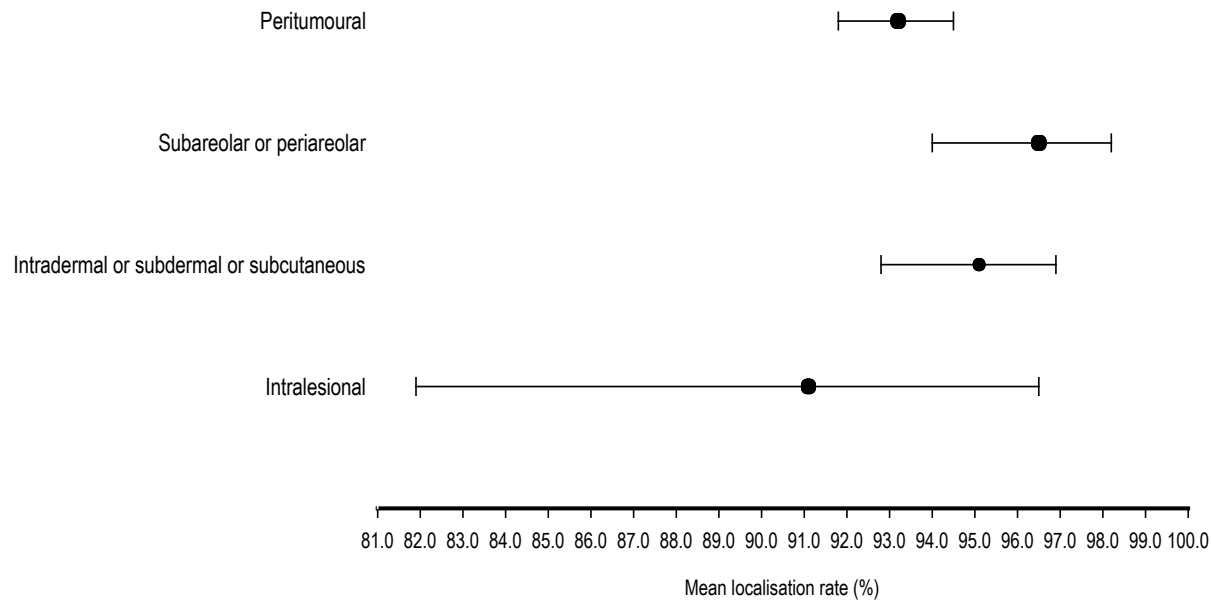


Figure 18 Estimated mean and 95%PI localisation rate for location of dye injection

False negative rate

No significant differences were seen in false negative rates regardless of the location of the dye injection (see Appendix E for estimated mean difference statistics).

Effect of histology method on false negative rate

The false negative rate was not significantly different regardless of whether IHC was used together with permanent histology, or whether permanent histology was used alone (estimated mean difference 0.4%, 95%PI: -1.3 to 2.2, p=0.61). No other statistical comparisons were made since the included sets reported that IHC was only used in a proportion of patients, and this was not thought to provide any additional clinically relevant information.

However, there was sufficient information in 31/130 (23.8%) studies to calculate a conversion rate, that is, the rate at which patients found to be sentinel node negative by

H&E were upstaged to sentinel node positive by IHC. Conversion rates varied widely, ranging from 0% to 52.2% (see Table 13).

Table 13 Conversion rates

Study	Negative by H&E	Positive by IHC	Conversion rate	(%)
Allen et al. 2001	19	2	2/19	10.5
Altinyollar et al. 2000	27	1	1/27	3.7
Baitchev et al. 2002	62	4	4/62	6.5
Bergkvist et al. 2001	304	18	18/304	5.9
Bobin et al. 1999	46	2	2/46	4.3
Cohen et al. 2000	20	4	4/20	20.0
Czerniecki et al. 1999	29	3	3/29	10.3
de Kanter et al. 2000	127	8	8/127	6.3
Dowlatshahi et al. 1999	46	24	24/46	6.3
Haid et al. 2001	14	3	3/14	21.4
Haigh et al. 2000	151	14	14/151	9.3
Hung et al. 2002	19	0	10/19	0
Ilum et al. 2000	63	15	15/63	23.8
Ishida et al. 2002	18	1	1/18	5.6
Mahajna et al. 2003	54	4	4/54	7.4
Miller et al. 2002	24	3	3/24	12.5
Noguchi et al. 1999	37	1	1/37	2.7
Nos et al. 2001	167	60	60/167	35.9
Offodile et al. 1998	25	3	3/25	12.0
Peley et al. 2001	47	7	7/47	14.9
Pizzocaro et al. 2000	61	9	9/61	14.8
Sachdev et al. 2002	132	9	9/132	6.8
Sardi et al. 2002	40	6	6/40	15.0
Shimazu et al. 2002	33	1	1/33	3.0
Smillie et al. 2001	57	3	3/57	5.3
Stitzenberg et al. 2002	7	55	7/55	12.7
Tsugawa et al. 2000	24	0	0/24	0
Ugur et al 2003	17	2	2/17	11.8
Vaggelli et al. 2000	22	5	5/22	22.7
Xavier et al. 2001	33	7	7/33	21.2
Xu et al. 2002	25	4	4/25	16.0

Note: H&E – haematoxylin and eosin staining; IHC – immunohistochemistry staining.

False negative rates for frozen section and imprint cytology

False negative rates were calculated for frozen section or imprint cytology from 17/130 of the included studies (see Table 14). The range of values is wide (from 0% to 54%) and this may call into question the reliability of intraoperative histology for staging the axilla. However, there were few studies on which to base this analysis and there may be a number of operator-related factors contributing to this variability.

Table 14 False negative rates using intraoperative histologic methods

Data set	TP	TN	FP	FN	False negative rate
Frozen section					
Altinyollar et al. 2000	18	30	0	1	1/(18+1) = 5.3%
Canavese et al. 2001	61	134	0	11	11/(61+11) = 15.3%
Hung et al. 2002	8	19	0	4	4/(8+4) =33.3%
Koizumi et al. 2003	14	46	0	0	0/(0+14) = 0%
Lauridsen et al. 2000	30	35	0	13	13/(13+30) = 30.2%
Noguchi et al. 1999	19	34	0	9	9/(9+19) = 32.1%
Ozmen et al. 2002	48	32	0	5	5/(5+48) = 9.4%
Stearns et al. 2002		21*	2	5	Cannot calculate
Vaggelli et al. 2000	14	22	0	5	5/(14+5) = 26.3%
Veronesi et al. 1999**	55	111	0	26	26/(55+26) = 32.1%
Veronesi et al. 1999†	52	64	0	3	3/(52+3) = 5.5%
Zavagno et al. 2000	25	44	0	12	12/(25+12) = 32.4%
Imprint cytology					
Baitchev et al. 2002	24	58	0	5	5/(24+5) = 17.2%
Llatjos et al. 2002	21	45	0	10	10/(21+10) = 32.3%
Noguchi et al. 1999	6	25	0	7	7/(6+7) = 53.8%
Ratanawichitrasin et al. 1999	14	40	0	1	1/(14+1) = 6.7%
Yu et al. 2002	21	55	1	1‡	1/(21+1) = 4.5%

Note: TP – true positive; TN – true negative; FP – false positive; FN – false negative; * number of true positive and true negative patients was not stated; ** frozen section; † exhaustive frozen section ‡The paraffin section was negative by H&E but a microfocus of cytokeratin positive carcinoma was found on staining of the paraffin sections.

Noguchi et al. (1999) used imprint cytology, frozen section and permanent section. Separate false negative rates for frozen section and imprint cytology are given in Table 14 above. When the two methods were combined, there were 10 true positives, 25 true negative and 3 false negatives, for a combined false negative rate for intraoperative evaluation, of 3/(10+3) = 21.1%, compared to permanent section (H&E and cytokeratin IHC).

If using frozen section or imprint cytology intraoperatively, a false positive pathology result may lead to the patient unnecessarily receiving axillary clearance. Only one false positive was reported (Yu et al. 2002) in all of the included studies assessing false negative rates.

Effect of patient/tumour variables on diagnostic accuracy

Results of subgroup analyses for the following variables are shown in Table 15:

- biopsy method
- tumour size
- tumour histology
- tumour palpability
- clinical axillary status
- whether patients had multicentric and/or multifocal tumours
- whether patients had neoadjuvant chemotherapy.

For many of these comparisons, data were not reported in the included studies in such a way that clinically useful comparisons could be made. In general this was because data could only be grouped into categories that were not mutually exclusive, so some of the categories include patients with and without the variable of interest; where this occurred, it has been noted.

Biopsy method

The mean localisation rate was higher and the mean false negative rate lower for patients who did not receive excisional biopsy than for patients receiving excisional biopsy, and this difference approached statistical significance (estimated mean difference in localisation rate 5.8%, 95%PI: -1.4 to 17.0, p=0.18 and estimated mean difference in false negative rate -8.1, 95%PI: -20.9 to 1.1, p=0.094). However, the statistical analysis is likely to have been underpowered, as there were only five sets for localisation and four sets for false negative rates in which patients received excisional biopsy exclusively. The 95% posterior intervals for the estimated mean differences are wide, reflecting the variability in these sets, but may include clinically important values; however, it is very difficult to estimate the true effect from these data. These results are illustrated in Figures 19 and 20.

In those included studies in which internal comparisons of biopsy method were undertaken no significant differences were found in localisation rate or false negative rate (Birdwell et al. 2001, Brenot-Rossi et al. 2003, Chua et al. 2003, Euhus et al. 2002, Haigh et al. 2000, Kollias et al. 2000, Krag et al. 2001, McMasters et al. 2000a, Motomura et al. 2002a, Noguchi et al. 2000a, Nason et al. 2000, Nwariaku et al. 1998, Ozmen et al. 2002, Patel et al. 2003, Rubio et al. 1998b, Tsugawa et al. 2000, Yong et al. 2003, Guenther 1999).

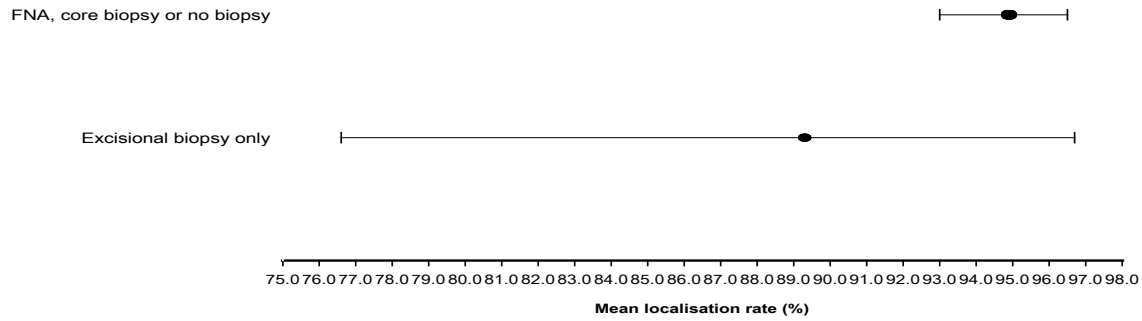


Figure 19 Estimated mean localisation rate and 95%PI for biopsy method

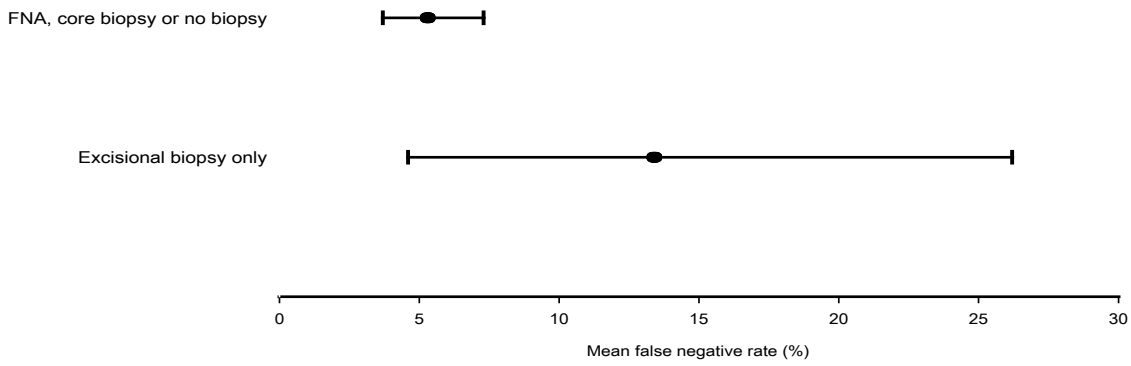


Figure 20 Estimated mean false negative rate and 95%PI for biopsy method

Table 15 Random-effects subgroup analysis: effect of patient/tumour variables on diagnostic accuracy

Subgroup	Category	Localisation rate			False negative rate		
		Number of sets	Mean	95%PI	N	Mean	95%PI
Biopsy method	Varied	100	93.5	92.1, 94.7	55	4.0	3.1, 5.0
(see Figures 19 and 20)	FNA, CB or no biopsy	42	94.9	93.0, 96.5	29	5.3	3.7, 7.3
	Excisional biopsy only	5	89.3	76.6, 96.7	4	13.4	4.6, 26.2
	Not stated/ Not clear	81	94.6	93.1, 95.8	48	5.1	3.9, 6.4
Tumour size	T0 and/or Tx and/or Tis, T1-T2	117	94.8	93.7, 95.9	67	4.6	3.6, 5.6
	T0 and/or Tx and/or Tis, T1-T2, T3-T4 or T3-T4 only	82	93.6	91.9, 95.0	60	5.0	3.9, 6.3
	Not stated/Not clear	29	92.6	89.5, 95.1	9	3.8	1.9, 6.3
Invasivity	Invasive tumours only	136	93.9	92.8, 95.0	102	5.0	4.1, 5.9
	Invasive and in situ	71	94.6	93.3, 95.9	26	3.9	2.6, 5.3
	In situ	1	100.0	99.8, 100	–	–	–
	Not stated/not clear	20	92.3	88.3, 95.2	8	4.2	2.1, 7.3
Tumour palpability	Palpable only	17	92.4	88.0, 95.6	16	6.5	4.1, 9.6
	Palpable and impalpable	79	94.7	93.3, 95.8	43	4.0	3.1, 5.2
	Impalpable only	6	96.1	91.0, 98.8	2	2.5	0.1, 10.2
	Not stated/Not clear	126	93.8	92.5, 94.9	75	4.9	3.9, 5.9
Clinical axillary status	Negative	137	94.9	93.9, 95.8	76	4.6	3.8, 5.6
(see Figures 21 and 22)	Negative and positive	39	90.1	86.8, 92.8	27	6.9	4.9, 9.3
	Not stated/Not clear	52	94.3	92.6, 95.8	33	3.6	2.5, 4.9
Multifocality/multicentricity	Unifocal tumours	59	93.9	92.0, 95.5	44	5.2	4.0, 6.6
	Some multifocal tumours	20	94.4	91.2, 96.7	10	7.6	4.5, 11.9
	All multifocal tumours	2	97.6	90.3, 99.8	3	5.2	1.2, 13.0
	Not stated/Not clear	147	94.1	93.0, 95.1	79	4.1	3.2, 5.0
Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	36	92.8	90.1, 95.0	25	5.3	3.7, 7.2
(see Figure 23)	Some neoadjuvant chemotherapy	10	91.3	84.7, 95.6	7	5.8	3.0, 9.7
	All neoadjuvant chemotherapy	10	90.1	82.2, 95.3	9	14.3	8.0, 23.2
	Not stated/not clear	172	94.6	93.7, 95.5	95	4.3	3.6, 5.1
All sets		**228**	**94.1**	**93.3, 95.0**	**136**	**4.7**	**4.0, 5.4**

Note: FNA – fine needle aspiration; CB – core biopsy; PI – posterior interval

Tumour size

Data regarding tumour size in the included studies were not reported in such a way that they could be sensibly compared statistically. In many studies (82) localisation rates and false negative rates were given for patients with tumours of all sizes, whereas in some studies only patients with smaller tumours were included. Since smaller and larger tumour groups could not be separated, comparison of the available data is not clinically informative (see Table 15).

However, a number of included studies reported internal comparisons of patients with different tumour sizes. Tumour size was not found to significantly affect localisation rates (Guenther 1999, McMasters et al. 2000a, Wong et al. 2001a, Motomura et al. 1999a, Motomura et al. 2002a, Noguchi et al. 1999, Patel et al. 2003, Tanis et al. 2002b, Tsugawa et al. 2000, Euhus et al. 2002, Yong et al. 2003, Nason et al. 2000, Brenot-Rossi et al. 2003, Chua et al. 2003, Haigh et al. 2000, Krag et al. 2001, Morrow et al. 1999, Vargas et al. 2003, Noguchi et al. 2000a); however, the effect of tumour size on false negative rates was less clear with five studies reporting no significant effect (McMasters et al. 2000a, Wong et al. 2001a, Noguchi et al. 1999, Tsugawa et al. 2000, Yong et al. 2003) and three studies reporting higher false negative rates for larger tumours (Nason et al. 2000, Noguchi et al. 2000a, Ozmen et al. 2002).

Tumour histology

Data regarding tumour histology in the included studies were not reported in such a way that they could be sensibly statistically compared. In many studies (71) results were reported for patients with invasive and *in situ* tumours together. Only one study reported localisation rates for *in situ* tumours separately and no studies reported false negative rates for this group. Clinically relevant conclusions could not be made regarding invasiveness from the data available for subgroup analysis.

Internal comparisons of tumour histology in the included studies found no significant effect on localisation rates (Brenot-Rossi et al. 2003, Chua et al. 2003, Guenther 1999, Euhus et al. 2002, Krag et al. 2001, Motomura et al. 1999a, Motomura et al. 2002a, Vargas et al. 2003). Only one study compared false negative rates in patients with differing tumour histology and no difference in false negative rate could be detected (Yong et al. 2003).

Tumour palpability

No significant difference in localisation rates or false negative rates between palpable and nonpalpable tumours was detected (estimated mean difference in localisation rate -3.8%, 95%PI: -9.4 to 1.5, p=0.15, and estimated mean difference in false negative rate 4.0%, 95%PI: -4.4 to 8.5, p=0.19). However, there were relatively few sets of data available for this comparison, particularly for nonpalpable tumours, and the analysis may have been underpowered to detect a significant difference. Internal comparison of tumour palpability in the included studies suggests that palpable tumours are associated with better localisation rates (Chao et al. 2003, Chua et al. 2003, Kollias et al. 2000, Morrow et al. 1999, Wong et al. 2001a, Tanis et al. 2002b).

Clinical axillary status

Localisation rate was significantly higher and false negative rate significantly lower in sets of data where all the patients had clinically negative axillary lymph nodes than in sets of

data where patients were either clinically node negative or clinically node positive (estimated mean difference in localisation rate 4.7%, 95%PI: 2.0 to 8.0, p=0.001, and estimated mean difference in false negative rate -2.3%, 95%PI: -4.8 to -0.0, p=0.046). However, these results cannot be interpreted to mean that sets of data in which all patients were clinically node positive would also have a poorer localisation rate than node negative patients, since the data were not reported separately for node positive patients (see Figures 21 and 22).

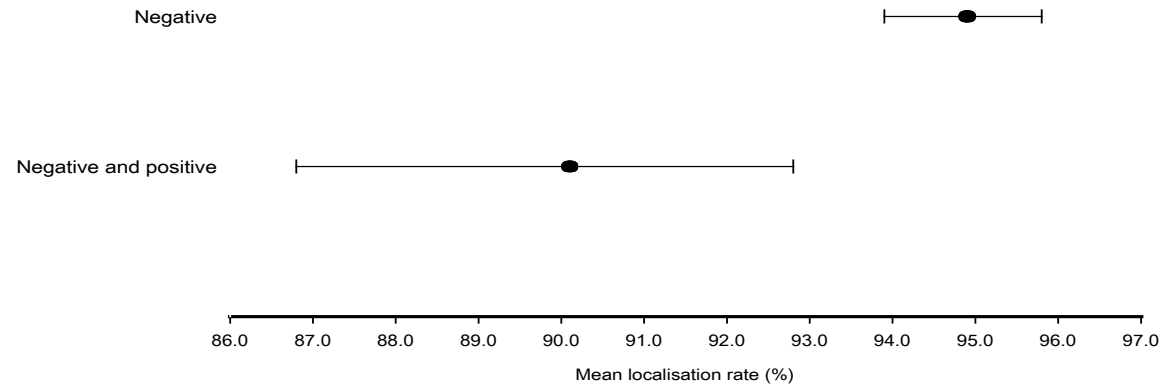


Figure 21 Estimated mean localisation rate and 95%PI for clinical axillary status

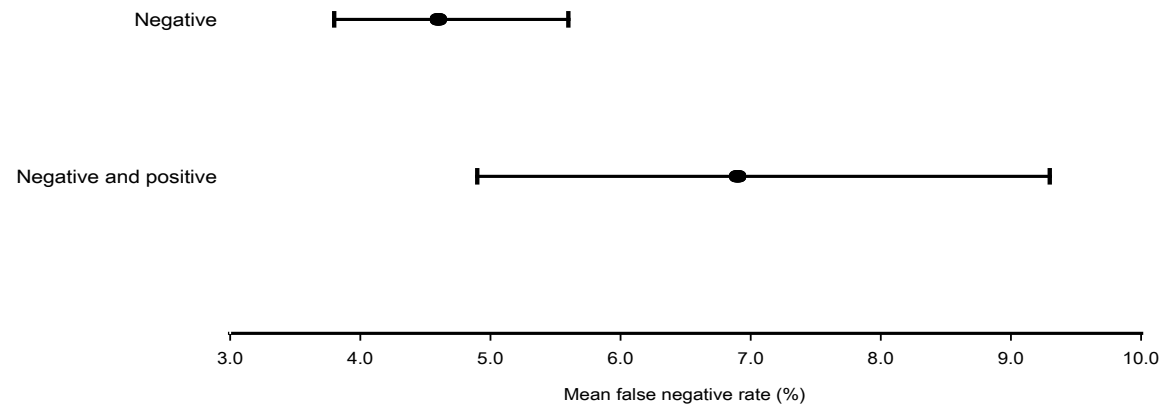


Figure 22 Estimated mean false negative rate and 95%PI for clinical axillary status

Few studies in which internal comparisons of localisation rate and false negative rate were undertaken showed any significant differences according to clinically axillary status. Localisation rates were not found to differ between node positive and node negative patients in four studies (Choi et al. 2003, Chua et al. 2003, Noguchi et al. 1999, Tsugawa et al. 2000) but Noguchi et al. (2000a) demonstrated a significantly better localisation rate in node negative than node positive patients. Two studies (Noguchi et al. 1999, Tsugawa et al. 2000) reported no significant difference in false negative rates.

Multifocality/multicentricity

There were only two sets of data for localisation rates and three sets of data for false negative rates in which all patients had multifocal tumours. In many studies (20) there was a mixture of patients with unifocal and multifocal tumours. As a result, a clinically relevant comparison of diagnostic accuracy could not be made between unifocal and multifocal tumours (see Table 15).

Neoadjuvant chemotherapy

Localisation rates

No significant difference between sets of data in which no patients received neoadjuvant chemotherapy and those where all patients received neoadjuvant chemotherapy was found (estimated mean difference 3.1%, 95%PI: -3.0 to 11.2, p=0.42). However, as there were relatively few sets of data where all patients received chemotherapy (10) the analysis may be underpowered to detect a significant difference.

False negative rates

The mean false negative rate for sets of data in which patients received no adjuvant chemotherapy was significantly lower than in sets of data in which all patients received chemotherapy (estimated mean difference -9.0%, 95%PI: -17.9 to -2.2, p=0.026) (see Figure 23). Although the difference is likely to be clinically important, the 95% posterior interval is wide, suggesting a lack of precision in the point estimate, a result of only nine sets of data where all patients received chemotherapy being available for analysis.

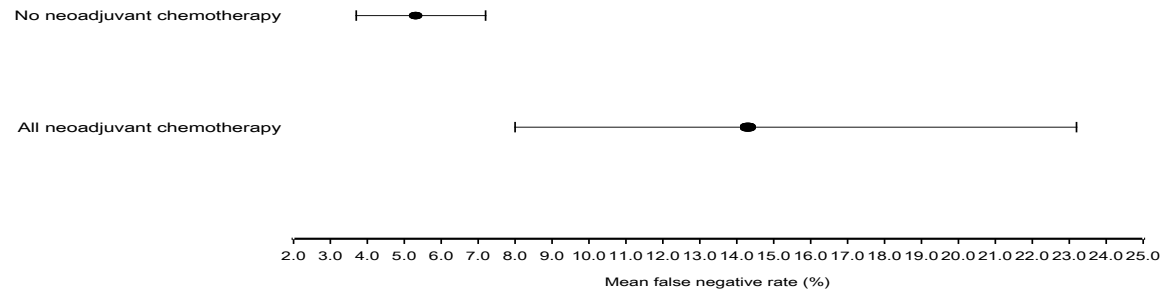


Figure 23 Estimated mean false negative rate and 95%PI for neoadjuvant chemotherapy

Summary of results

The results of the review of diagnostic accuracy of SLNB are shown in Table 16.

Table 16 Summary of results of diagnostic accuracy of SLNB review

Result	Localisation rate	False negative rate
Included studies	n=228 sets (median set size 68)	n=136 sets (median set size 37)
Distribution of study values	94% of sets above 80%	80% of sets below 15%
Pooled weighted mean	94.1% (95%PI: 93.3 – 95.0)	4.7% (95%PI: 4.0 – 5.4)
Subgroup analysis		
Type of tracer used	Significantly higher for radioisotope + dye or dye alone than for radioisotope alone	Significantly lower for radioisotope alone or radioisotope + dye than for dye alone
Type of radioisotope used	Little difference between types	Some difference between sulphur and albumin colloid but questionable clinical significance
Location of radioisotope injection	Significantly higher for subareolar or intradermal than for peritumoural	No significant differences
Timing of radioisotope injection	No significant differences	Significantly lower for same day than for day before SLNB
Type of dye used	No significant differences	No significant differences
Location of dye injection	Significantly higher for subareolar than peritumoural – no other significant differences	No significant differences
Effect of histology method	NA	No significant difference between permanent histology alone and permanent histology + IHC
Biopsy method	Higher for excisional biopsy than no excisional biopsy but not statistically significant*	Lower for excisional biopsy than no excisional biopsy but not statistically significant*
Tumour size	Could not undertake statistical comparison of subgroups but internal comparisons found no significant difference	Could not undertake statistical comparison of subgroups and internal comparisons found inconsistent results
Tumour histology	Could not undertake statistical comparison of subgroups but internal comparisons found no significant difference	Could not undertake statistical comparison of subgroups and insufficient evidence in internal comparisons (only one study)
Tumour palpability	No significant difference between palpable and nonpalpable tumours*	No significant difference between palpable and nonpalpable tumours*
Clinical axillary status	Significantly higher for node negative only compared to node negative + node positive	Significantly lower for node negative only compared to node negative + node positive
Multifocality/multicentricity	Insufficient data for statistical comparison	Insufficient data for statistical comparison
Neoadjuvant chemotherapy	No significant difference between no chemotherapy and all chemotherapy*	No chemotherapy significantly lower than all chemotherapy

Note: * analysis may have been underpowered to detect a significant difference; PI – posterior interval; NA – not applicable; SLNB – sentinel lymph node biopsy; IHC – immunohistochemistry.

5. Safety and effectiveness of sentinel lymph node biopsy

Included studies

Comparative studies (Randomised and non-randomised)

Eighteen comparative studies were included in the assessment of safety and efficacy. There was one randomised controlled trial (Level II) and 17 non-randomised comparative studies; 14 studies used concurrent controls (Level III-2), two used historical controls (Level III-3) and one used concurrent and historical controls (Level III-2/3 study) (see Table 17). Study profiles are given in Appendix I.

In 8/14 Level III-2 studies patients who received axillary clearance – the comparator – were selected from the group of patients who had already received SLNB (Baron et al. 2002, Blanchard et al. 2003, Burak et al. 2002, Giuliano et al. 2000, Leidenius et al. 2003a, Rietman et al. 2003, Temple et al. 2002, Swenson et al. 2002). Reasons for axillary clearance after SLNB are shown in Table 13.

The quality of the single randomised controlled trial (Veronesi et al. 2003) was difficult to assess as key indicators, such as methods of randomisation, allocation concealment and blinding, and losses to follow-up were not reported. The two groups were well balanced with regard to prognostic (baseline) factors; however, effectiveness outcomes such as axillary pain, numbness and paraesthesias, arm mobility, aesthetics of the scar and arm swelling were only reported for patients who received SLNB alone, and not for those who went on to have axillary clearance. As a result the effectiveness outcomes were reported on a 'convenience sample' rather than a truly randomised population. Only the recurrence and survival outcomes can be considered as Level II evidence, with all of the effectiveness outcomes considered Level III-2 non-randomised comparative evidence.

Two key features limited the Level III-2 concurrently controlled comparative studies. In seven studies (as detailed above) patients in the axillary clearance arm had already undergone SLNB and safety and efficacy outcomes may have been confounded as a result of an additive effect. This may also have been the case in the one Level III-2/3 study (Sener et al. 2001). In most studies there was little information regarding selection of patients to each treatment arm. Six studies stated that patients were consecutively selected (Blanchard et al. 2003, Giuliano et al. 2000, Peintinger et al. 2003, Rietman et al. 2003, Swenson et al. 2002; Temple et al. 2002). However, in four studies (Blanchard et al. 2003, Swenson et al. 2002, Schijven et al. 2003, Haid et al. 2002b) there were significant baseline differences between the two groups, and only one (Swenson et al. 2002) attempted to adjust for these in the analysis.

Table 17 Included comparative studies

Study	Intervention	N	Follow-up	Reason for AC*
Level II				
Veronesi et al. 2003 for recurrence only	SLNB (+ AC) SLNB + AC	259 257	46 months	Sentinel node positive For verification of SLNB
Level III-2				
Gemignani et al. 2000	SLNB AC	50 50	NR	NA
Golshan et al. 2003	SLNB AC	77 48	NR	NA
Haid et al. 2002b†	SLNB AC	66 85	2 months	NA
Peintinger et al. 2003	SLNB AC	25 31	9 to 12 months	NA
Schijven et al. 2003	SLNB AC	180 213	NR	NA
Schrenk et al. 2000	SLNB AC	35 35	15 months 17 months	NA
Blanchard et al. 2003	SLNB SLNB + AC	730 164	28 months	Sentinel node positive or required by training protocol
Burak et al. 2002	SLNB SLNB + AC	48 48	15 months	NR
Giuliano et al. 2000	SLNB SLNB + AC	67 58	39 months	Sentinel node positive or mapping failure
Leidenius et al. 2003a	SLNB SLNB + AC	49 36	3 months	Sentinel node positive or multifocal tumour identified
Swenson et al. 2002	SLNB SLNB + AC	169 78	12 months	Sentinel node positive or mapping failure or surgeon in training
Baron et al. 2002**	SLNB SLNB + AC	187 96	6 months	Sentinel node positive
Temple et al. 2002**	SLNB SLNB + AC	171 62	12 months	Sentinel node positive
Veronesi et al. 2003 (for effectiveness only)	SLNB SLNB + AC	100 100	24 months	For verification of SLNB
Rietman et al. 2003	SLNB SLNB + AC/ AC	66 138	1.5 months	Sentinel node positive
Level III-2/3				
Sener et al. 2001	SLNB SLNB + AC	303 117	19 months 24 months	NR
Level III-3				
Chirikos et al. 2001	SLNB non-SLNB	555 256	44 months	NA
Haid et al. 2002a†	SLNB AC	57 140	18 months 25 months	NA

Notes: SLNB – sentinel lymph node biopsy; AC – axillary clearance; NA – not applicable; NR – not reported; * for those studies where AC followed SLNB; ** same patient set but different follow-up periods – in Temple only patients with data for all follow-up points were included; † – SLNB patients probably the same but AC comparator group different. Different outcomes reported in each study therefore both included separately.

One Level III-3 historically controlled comparative study (Haid et al. 2000a) may have been subject to recall bias as patients in the axillary clearance group were administered the study questionnaire between 2 years and 5 years after undergoing the procedure. In this study the SLNB group is likely to include the same patients that Haid et al. (2000b) reported, where they were compared to a concurrent, randomly selected cohort of

patients who had axillary clearance. Both studies have been reported here as they detail different outcomes.

Losses to follow-up were not reported in most of the comparative studies, except for those that used a questionnaire. These studies generally stated which patients were included in the analysis and gave reasons for omission (Blanchard et al. 2003, Baron et al. 2002, Temple et al. 2002, Schijven et al. 2003, Rietman et al. 2003, Swenson et al. 2002, Burak et al. 2002). Blinding of outcomes assessors was only stated in one of the comparative studies (Burak et al. 2002) where hand swelling was measured subjectively by a blinded observer. All studies were possibly subjected to performance bias as few controlled for differences in care between the SLNB and axillary clearance groups. The only exceptions may have been Sener et al. (2001) where standard lymphoedema precautions and range-of-motion exercises were taught regardless of which surgery the patients had undergone; and Leidenius et al. (2003a) in which patients received light exercises to maintain range of shoulder motion, regardless of the type of surgery they received.

Patient-relevant outcomes were measured with a variety of assessment tools, some of which were well validated and some of which were not. Table 18 lists the assessment tools used in the included studies and their validation status.

Table 18 Patient-relevant outcome assessment tools and validation

Included studies	Tool	Authors	Validated?
Baron et al. 2002 Temple et al. 2002	Breast Sensation Assessment Scale©	Baron et al. 2000	yes
Blanchard et al. 2003	Not described	NR	NR
Haid et al. 2002a	Compiled by the investigators based on the literature and their own clinical experience with regard to possible problems that occur after axillary surgery	NA	no
Peintinger et al. 2003	EORTC QoL questionnaires C30 and B23	Aaronson et al. 1993	yes
	McGill Pain Questionnaire	Mezlack 1975, Stein & Mendel 1988	yes
	Karnofsky Performance Scale Status	NR	yes
Rietman et al. 2003	Shoulder Disability Questionnaire	van der Heijden et al. 2000	yes
	Groningen Activity Restriction Scale	Kempen et al. 1996	yes
Schijven et al. 2003	Treatment-specific QoL questionnaire	Tilburg University Department of Clinical Health Psychology	yes
Swenson et al. 2002	Measure of Arm Symptom Survey	Swenson et al. 2002	no

Notes: NR – not reported; EORTC - European Organisation for Research and Treatment of Cancer; QoL – quality of life; NA – not applicable.

Case series and case reports

Fifty-one case series and 12 case reports were included. Consecutive selection was stated in 14/51 (27.5%) of included case series.

Is it safe?

Wound infection, seroma and haematoma

Concurrently controlled comparative studies (Level III-2)

Fewer wound infections for SLNB, compared with axillary clearance, were reported in two studies (Blanchard et al. 2003; Swenson et al. 2002) and the difference was statistically significant in one (Blanchard et al. 2003). More axillary clearance than SLNB patients experienced wound inflammation requiring antibiotic treatment in one study (Rietman et al. 2003) but the difference did not reach statistical significance.

Seromas occurred in more patients who underwent axillary clearance than in patients receiving SLNB (Blanchard et al. 2003, Giuliano et al. 2000, Leidenius et al. 2003a, Rietman et al. 2003, Swenson et al. 2002). This reached statistical significance in one study (Blanchard et al. 2003) and bordered on statistical significance in a second (Rietman et al. 2003). More patients who underwent axillary clearance had seroma requiring aspiration (Swenson et al. 2002) or aspiration of fluid collection (as distinct from seromas) (Leidenius et al. 2003a).

Giuliano et al. (2000) reported an overall complication rate of 3% for SLNB and 35% for axillary clearance ($p=0.001$), and that complications were significantly increased when SLNB was followed by axillary clearance. In the 58 patients who received SLNB+AC, wound infections were reported in 3/58 (5%) and haematoma in the axilla in 4/58 (7%). No patient who underwent SLNB suffered paraesthesias or numbness over the intercostobrachial nerve distribution. One SLNB patient (1/67, 1.5%) had superficial cellulitis (Giuliano et al. 2000).

Case series

Seromas were reported in three studies (Hansen et al. 2002, Choi et al. 2003, Schrenk et al. 2001). Hansen et al. (2002) reported five cases (2%) of seroma requiring aspiration, one of which also required temporary placement of a drain. Choi et al. (2003) reported 6/81 (7.4%) patients with seroma at the 1-week follow-up, one requiring needle aspiration. One patient (1.2%) had erythema at the wound, and received antibiotics. It was unclear whether these patients had SLNB alone or SLNB followed by axillary clearance. Schrenk et al. (2001a) reported 1/83 (1.2%) patients with seroma.

Axillary lymphocoele was reported in 22/200 (11%) patients in one study (Classe et al. 2003) and 8/100 (8%) in another (Meijer et al. 2002). No patient required reoperation. Axillary abscess was reported in 4/200 (2%) patients (Classe et al. 2003). It was unclear whether these patients had SLNB alone or SLNB followed by axillary clearance.

Wound infections were reported in 1/83 (1.2%) patients in one study (Schrenk et al. 2001), and no patients in another (Rodier et al. 2000). Haematoma requiring reoperation was reported in 1/290 (0.3%) patients in a third study (van Berlo et al. 2003). In a fourth study one patient (0.4%) suffered cellulitis, which was resolved with antibiotics (Hansen et al. 2002).

Eight studies (Acosta et al. 2003, Balch et al. 2003, Dale & Williams 1998, Giuliano et al. 1997, Kapteijn et al. 1998, Miner et al. 1999, Sabel et al. 2003, Yong et al. 2003) reported no complications (see Appendix J, Tables J1 and J2).

Anaphylactic and allergic reactions to blue dye

Concurrently controlled comparative studies (Level III-2)

Swenson et al. (2002) reported that 15/247 (6%) patients experienced a reaction to isosulphan blue dye. The study compared patients who had SLNB only, and SLNB and/or axillary clearance. It was reported that there was no difference in the proportion of patients in each group reporting a dye reaction (Swenson et al. 2002) (see Appendix J, Table J3).

Case series

Thirteen studies specifically reported reactions to blue dye, ranging from 0% to 1.6% of patients, median 0% (Albo et al. 2001, Altinyollar et al. 2000, Cox et al. 2000a, Ilum et al. 2000, Koller et al. 1998, Montgomery et al. 2002, Mostafa & Carpenter 2001, Rodier et al. 2000, Tsugawa et al. 2000, Ugur et al. 2003, Walker et al. 2002, Yong et al. 2003, Yu et al. 2002). Reactions generally occurred between 15 and 49 minutes after injection of the dye. In one study (Albo et al. 2001), the length of hospital stay was prolonged by a mean 1.6 days in the seven patients who experienced anaphylactic reaction. No deaths were reported after injection of blue dye. Profound hypotension was reported in 7/639 (Albo et al. 2001), 3/1700 (Cox et al. 2000a) and 9/2392 (Montgomery et al. 2002) patients. Other reactions included skin reactions such as erythema, urticaria, rashes, hives, and pruritus, and wheezing, tachycardia and/or minor hypotension (see Table 19).

Table 19 Anaphylactic and allergic reactions to blue dye in included case series

Study	n/N	%	Dye	Reaction
Albo et al. 2001	7/639	1.1	Isosulphan blue	Skin, respiratory/cardiac (profound hypotension in 7/7 patients)
Cox et al. 2000a	>1700	1	Isosulphan blue	Skin, respiratory/cardiac (profound hypotension in 3 patients)
Montgomery et al. 2002	39/2392	1.6	Isosulphan blue	Skin, respiratory/cardiac (profound hypotension in 9/39 patients)
Ugur et al. 2003	0/28	0	Isosulphan blue	NR
Ilum et al. 2000	1/159*	0.6	Patent blue	Skin, respiratory/cardiac
Koller et al. 1998	1/98	1	Patent blue	Skin
Walker et al. 2002	1/122	0.8	Patent blue	Skin
Altinyollar et al. 2000	0/60	0	Patent blue	NR
Rodier et al. 2000	0/73	0	Patent blue	NR
Tsugawa et al. 2000	0/48	0	Patent blue	NR
Yong et al. 2003	0/312	0	Patent blue	NR
Mostafa & Carpenter 2001	0/80	0	Methylene blue	NR
Yu et al. 2002	0/218	0	Methylene blue	NR

Note: *This reaction was reported as universal exanthema, which is typically a skin reaction associated with certain infectious diseases, rather than an anaphylactic or allergic reaction. No allergic testing was performed so it is unknown whether the reaction was drug related; NR – not reported.

Case reports

Twenty-four case reports of anaphylactic reactions were reported in 15 studies (Cimmino et al. 2001, Efron et al. 2002, Giménez et al. 2001, Kuerer et al. 2001a, Kuerer et al. 2001b, Laurie et al. 2002, Lyew et al. 2000, Sadiq et al. 2001, Sprung et al. 2003, Stefanutto et al. 2002 Crivellaro et al. 2003, Galatius et al. 2003, Mullan et al. 2001, Quiney et al. 2003, Salvat et al. 1999). Isosulphan blue was used in 10 studies and patent blue in five. There were no case reports of anaphylactic reactions after injection of methylene blue dye. Reactions occurred between 5 and 45 minutes after injection of dye, most commonly at 5 minutes and 30 to 40 minutes after injection. The most common symptoms were urticaria, rashes or hives in 18/24 (75%) patients, hypotension in 16/24 (66.7%) patients, oedema in 6/24 (25%) patients, bradycardia in 4/24 (16.7%) patients, tachycardia or pallor in 2/24 (8.3%) patients and wheezing and dyspnea in 1/24 (4.2%) patients each. Reactions experienced and type of dye used are shown in Table 20.

Table 20 Anaphylactic and allergic reactions to blue dye in included case reports

Study	Dye	Reaction
Cimmino et al. 2001	Isosulphan blue	Rash or hives, hypotension, brachycardia
Efron et al. 2002	Isosulphan blue	Rash or hives, hypotension, oedema
Giménez et al. 2001	Isosulphan blue	Rash or hives, hypotension, pallor
Kuerer et al. 2001a	Isosulphan blue	Rash or hives, hypotension
Kuerer et al. 2001b	Isosulphan blue	Rash or hives, hypotension, oedema
Laurie et al. 2002	Isosulphan blue	Rash or hives, hypotension, tachycardia, wheezing
Lyew et al. 2000	Isosulphan blue	Hypotension, oedema, tachycardia
Sadiq et al. 2001	Isosulphan blue	Rash or hives
Sprung et al. 2003	Isosulphan blue	Rash or hives, brachycardia
Stefanutto et al. 2002	Isosulphan blue	Oedema
Crivellaro et al. 2003	Patent blue	Rash or hives, hypotension, brachycardia, dyspnea
Galatius et al. 2003	Patent blue	Rash or hives, hypotension
Mullan et al. 2001	Patent blue	Rash or hives, hypotension, brachycardia
Quiney et al. 2003	Patent blue	Rash or hives, hypotension, brachycardia
Salvat et al. 1999	Patent blue	Rash or hives, hypotension

In some studies it was found that previous exposure or sensitisation to blue dye or its derivatives may have contributed to the anaphylactic event (Galatius et al. 2003, Laurie et al. 2002, Mullan et al. 2001, Quiney et al. 2003, Giménez et al. 2001, Lyew et al. 2000, Sprung et al. 2003). Patients suffered no reactions to other drugs, such as antibiotics, anaesthetics and sedatives, used as part of the SLNB surgery. For further details of treatment of the anaphylactic reactions and the outcome of the intended surgery, see Appendix J, Table J4.

Effect on pulse oximetry readings

Hypoxia (hypoxemia or oxygen desaturation) was reported after injection of blue dye in 7/24 (29.2%) patients (Laurie et al. 2002, Lyew et al. 2000, Mullan et al. 2001, Sadiq et al. 2001, Sprung et al. 2003, Stefanutto et al. 2002). However, this appears to be an artefact rather that a true decrease in pulse oxygen as injection of blue dye appears to interfere with pulse oximetry readings (Guenther et al. 1997, Koivusalo et al. 2002, Rizzi et al. 2000). Pulse oximetry uses spectromorphic analysis and plethysmography to calculate

oxygen saturation of haemoglobin (Kelleher 1989). The presence of any substance in blood that absorbs light in the red or infrared spectrum can alter the oxygen saturation readings (Rizzi et al. 2000). Normal oxygenation can be verified with arterial blood gas analysis (Hoskin & Granger 2001).

Skin discolouration or necrosis from blue dye

Discolouration from blue dye was reported in 359/712 (50%) patients in one study (Blanchard et al. 2003). Patients were surveyed at 2 years post-SLNB (median 24 months, range 15–53); 314/712 (44.1%) reported that the discolouration had faded (median time to fade: 1 month, range 0–32), and 45/712 (6.3%) reported that injection site had not faded. In a second study, 86/247 (35%) patients experienced blue staining on the breast, chest wall or underarm (Swenson et al. 2002). A faint blue haze or skin discoloration was reported in four studies (Borgstein et al. 2000, Giuliano et al. 1997, Ratanawichitrasin et al. 1998, Yong et al. 2003), and stained faeces and/or urine in four (Ratanawichitrasin et al. 1998, Giuliano et al. 1997, Imoto & Hasebe 1999, Kapteijn et al. 1998). Although these effects are of no clinical significance, patients should be made aware that these side effects might occur.

Wear et al. (2003) reported an unusual complication; on extubation, the endotracheal tube was found to be stained with concentrated isosulphan blue dye. The patient maintained good oxygen and breath sound, and chest radiographs ruled out pneumothorax or pleural effusion. The patient was admitted overnight but discharged the next day without incident.

Skin necrosis or lesions after the injection of methylene blue dye were reported in 5/24 (21%) patients in one study (Stradling et al. 2002) and 0/35 (0%) in another study (Mokbel & Mostafa 2001) (for details see Appendix J, Tables J5 and J6).

Complications arising from excision of extra-axillary lymph nodes

Internal mammary artery injury

Injury to the internal mammary vasculature was reported in 10 case series (Carcoforo et al. 2002, Dupont et al. 2001, Estourgie et al. 2003a, Galimberti et al. 2002, Jansen et al. 2000, Johnson et al. 2000, Paganelli et al. 2002b, Sacchini et al. 2001, Tanis et al. 2002a, van der Ent et al. 2001). Internal mammary artery damage was reported in 3/150 (2.0%) patients in one study (Estourgie et al. 2003a), 1/142 patients (0.7%) in a second (Sacchini et al. 2001), and 'occasionally' in a third study (Tanis et al. 2002a). Traumatic bleeding of the internal mammary vein was reported in 1/142 (0.7%) patients in one study (Sacchini et al. 2001) and bleeding related to attempted removal was reported in one of two patients with parasternal nodes in another study (de Kanter et al. 2000).

Pleural injuries and pneumothorax

Ten studies detailed pleural injuries (Carcoforo et al. 2002, Estourgie et al. 2003a, Feggi et al. 2001, Galimberti et al. 2002, Johnson et al. 2000, Paganelli et al. 2002b, Rönka et al. 2002, Sacchini et al. 2001, Tanis et al. 2002a, van der Ent et al. 2001). Recovery (when reported) was uneventful. Pneumothorax was reported in two studies (Dupont et al. 2001, Johnson et al. 2000). In one study, 3/36 (8%) patients were treated with intraoperative aspiration, and did not require a chest tube or prolonged hospital stay

(Dupont et al. 2001). In the second study 1/80 (1.25%) patients had pneumothorax secondary to violation of the pleura, but the pneumothorax was easily evacuated and the patient had no postoperative consequences (Johnson et al. 2000). One case of serous accumulation, which resolved after aspiration, was reported (Galimberti et al. 2002). Estourgie et al. (2003a) reported no long-term morbidity after occurrences of internal mammary artery damage and pleural injuries. Complications were also reported arising from excision of nodes detected under ribs (Feggi et al. 2001), parasternal nodes (de Kanter et al. 2000) or nodes detected outside axillary Levels I or II (Rönka et al. 2002). For details see Appendix J, Table J7.

Is it effective?

Perioperative outcomes

Length of hospital stay

Length of hospital stay[9] was significantly shorter for SLNB patients (mean 7.5 days, range 3–13) than for axillary clearance patients (mean 11.9 days, range 5–31; p=0.0001) in one study (Haid et al. 2002a) and was also shorter in a second (SLNB mean 2.1 days, AC mean 4.3 days) but was not compared statistically (Veronesi et al. 2003).

Placement of drains

Postoperative drain placement was required by more axillary clearance patients than SLNB patients, or was required for a longer period in axillary clearance patients (Burak et al. 2002, Haid et al. 2002a, Leidenius et al. 2003a, Swenson et al. 2002). The number of SLNB patients requiring drains ranged from none (Haid et al. 2002a) to 16% (Burak et al. 2002, Swenson et al. 2002). In one study although almost all patients (SLNB and AC) required placement of a drain, SLNB patients were usually discharged on the first day after surgery without axillary drains, whereas axillary clearance patients were usually discharged on the second postoperative day with drains *in situ*, which were removed on the fifth or sixth postoperative day (Leidenius et al. 2003a) (see Appendix J, Tables J8 and J9).

Postoperative outcomes

Avoidance of lymphoedema

Lymphoedema was measured in a variety of different ways in the included studies in which it was reported. Four studies reported numbers of patients experiencing lymphoedema in the two groups, two studies reported a number of patients experiencing swelling, though in one of these studies this was expressed as a function of the difference between the ipsilateral and contralateral arms. Four studies reported arm circumference, either the mean change pre to postoperatively, or the difference between the ipsilateral

[9] Length of stay after lumpectomy, mastectomy, quadrandectomy or wide resection with SLNB and/or axillary clearance. Length of stay may differ between countries due to differences in hospital protocols and can change over time as procedures evolve. The data here may not reflect current Australian experience.

and contralateral arms expressed as a ratio or a difference score. These results are shown in Table 21.

The differences in reporting of this outcome make it difficult to draw firm conclusions. However, it is apparent that significantly more patients who received axillary clearance, whether alone or after SLNB, experienced lymphoedema, compared to patients who received SLNB alone. The median rate of lymphoedema (percentage of patients reporting lymphoedema or arm swelling) across six studies was 3.25% for SLNB and 27.05% for axillary clearance, a 23.8% risk reduction (Blanchard et al. 2003, Golshan et al. 2003, Sener et al. 2001, Schijven et al. 2003, Veronesi et al. 2003, Haid et al. 2002a). One other study (not included in the table as results were not quantified) found that SLNB patients reported significantly less arm swelling (p=0.0005) and axillary clearance patients were more likely to report that swelling interfered with daily life (p=0.012) (Swenson et al. 2002).

Table 21 Lymphoedema in the included comparative studies

Study		SLNB		SLNB + AC/AC	p-value
patients reporting lymphoedema	**n/N**	**%**	**n/N**	**%**	
Blanchard et al. 2003	39/683	5.7	31/91	34.1	p<0.001
Golshan et al. 2003	2/77	2.6	13/48	27.1	RR: 0.09 (95%CI:0.02 to 0.39)
Schijven et al. 2003	2/180	1.1	15/213	7.1	p<0.01
Sener et al. 2001	9/303	3.0	20/117	17.1	p<0.0001
patients reporting arm swelling	**n/N**	**%**	**n/N**	**%**	
Veronesi et al. 2003					
I:C no difference	93/100	93	25/100	25	NR
I:C <1 cm	6/100	6	38/100	38	NR
I:C 1–2 cm	1/100	1	25/100	25	NR
I:C >2 cm	0/100	0	12/100	12	NR
Haid et al. 2002a					
overall	2/57	3.5	38/140	27	p<0.001
arm	2/57	3.5	29/140	21	p=0.002
forearm	1/57	1.8	21/140	15	p=0.007
arm circumference (cm)					
Rietman et al. 2003	mean change	SD	mean change	SD	
upper arm	0.9	4.2	0.1	4.3	not significant
forearm	0.4	3.1	0.0	2.9	not significant
Temple et al. 2002					
upper arm	0.03	1.6	0.3	1.3	not significant
forearm	-0.05	0.8	0.4	1.1	not significant
Burak et al. 2002	ratio I:C	SD	ratio I:C	SD	
upper arm	1.0	0.04	1.1	0.04	p=0.001
forearm	1.0	0.07	1.0	0.06	not significant
Schrenk et al. 2000	difference I:C	SD	difference I:C	SD	
upper arm	1.14	0.15	1.5	0.75	p=0.0001
forearm	0.16	0.86	0.95	0.80	p=0.0001

Notes: SLNB – sentinel lymph node biopsy; AC – axillary clearance; CI – confidence interval; SD – standard deviation; I:C – ipsilateral to contralateral arm; NR – not reported.

In one study significantly more axillary clearance patients experienced swelling of the arm than SLNB patients (Haid et al. 2002a), and a similar trend was apparent in a second study, though not tested statistically (Veronesi et al. 2003). However, when lymphoedema

was measured as a function of arm circumference few significant differences were found, either in the change in circumference pre and postoperatively (Rietman et al. 2003, Temple et al. 2002), or in the ratio of ipsilateral to contralateral arm circumference (Burak et al. 2002). One study did find a significant difference between SLNB and axillary clearance in objective arm volume (Schrenk et al. 2000).

Sener et al. (2001) found that tumour locations in the upper outer quadrant were significantly associated with lymphoedema in SLNB patients (p=0.012), but not for axillary clearance patients. No differences were seen in the number of sentinel nodes removed or the median tumour size between the SLNB patients who developed lymphoedema – 9/303 (3%) – and the patients who did not.

Lymphoedema is a morbidity that may occur in the immediate postoperative period (acute lymphoedema), but can also be a longer-term morbidity (chronic lymphoedema). The length of follow-up in all of the included comparative studies was too short to determine whether there was a significant long-term difference between SLNB and axillary clearance.

For details of reports of lymphoedema or arm swelling, see Appendix J, Tables J8 and J10.

Range of motion limitation and arm strength

In eight studies postoperative range of motion limitation was found to be significantly worse in axillary clearance patients than in SLNB patients, or was reported in more axillary clearance patients than SLNB patients (Veronesi et al. 2003, Haid et al. 2002a, Haid et al. 2002b, Leidenius et al. 2003a, Peintinger et al. 2003, Schijven et al. 2003, Schrenk et al. 2000, Swenson et al. 2002). In one study no significant difference between SLNB and axillary clearance patients was reported (Rietman et al. 2003). No significant difference in abduction was found in another study (Haid 2002b).

Range of motion limitation was more common in patients who received mastectomy compared to breast-conserving surgery (Swenson et al. 2002), and more common in patients having higher level axillary nodes excised than in patients having Level I and II axillary clearance, regardless of whether the patient had received SLNB or SLNB and axillary clearance (Leidenius et al. 2003a). Axillary web syndrome[10] was also found to be more common in axillary clearance patients than in SLNB patients (Leidenius et al. 2003a)

Postoperative arm strength was found to be significantly better in SLNB patients than in axillary clearance patients in two studies (Haid et al. 2002b, Schijven et al. 2003) but no significant difference was detected in two other studies (Schrenk et al. 2000, Rietman et al. 2003) (see Appendix J, Table J11).

Sensory morbidities

Sensory morbidities include pain and discomfort, numbness and paraesthesia, tightness, stiffness, and tingling. They may be measured objectively (e.g. by measuring skin

[10] Axillary web syndrome is a self-limiting cause of early postoperative morbidity. The proposed pathogenesis in lymphovenous injury, stasis and hypercoagulability as a consequence of superficial venous stasis, lymphatic disruption and tissue injury, caused by AC (Moskovitz et al. 2001).

sensitivity) or subjectively using a variety of scales. Some of these focus on individual aspects of sensory morbidity, such as use of visual analogue scales for pain, whereas others provide a global assessment, such as the Breast Sensation Assessment Scale© (see Table 18).

Global assessments

Using the Breast Sensation Assessment Scale©, two studies found that sensory morbidities were significantly more prevalent in patients receiving axillary clearance than in patients receiving SLNB at 6 months postoperatively, although some may be the same patients in both studies (Baron et al. 2002, Temple et al. 2002). Axillary clearance patients were more likely to report that these sensations were severe and distressing than SLNB patients (Baron et al. 2002). SLNB patients who later received axillary clearance also reported more sensory morbidities than patients who only received SLNB (Temple et al. 2002). Another study used the McGill Pain Questionnaire to measure sensory morbidities, and found significantly more sensory problems in the affected arm of the axillary clearance group than the SLNB group at 9 months to 12 months after surgery (Peintinger et al. 2003).

Numbness/paraesthesia

More axillary clearance patients experienced numbness or paraesthesia than SLNB patients in six studies (Haid et al. 2002a, Haid et al. 2002b, Schijven et al. 2003, Schrenk et al. 2000, Swenson et al. 2002, Veronesi et al. 2003) but in one study no significant difference between axillary clearance and SLNB patients was found (Rietman et al. 2003). In two studies no SLNB patients reported numbness or paraesthesia (Haid et al. 2002a, Schrenk et al. 2000). Numbness was more common in patients who received mastectomy than in patients who had breast-conserving surgery, regardless of type of axillary surgery (Swenson et al. 2002).

Pain

Pain severity was measured using the European Organisation for Research and Treatment of Cancer quality of life questionnaire QLQ-C30 pain subscale, the McGill Pain Questionnaire or visual analogue scales. Pain was reported either by more axillary clearance patients than SLNB patients, or was more severe in axillary clearance patients in six studies (Veronesi et al. 2003, Blanchard et al. 2003, Haid et al. 2002a, Haid et al. 2002b, Peintinger et al. 2003, Swenson et al. 2002) but no significant difference was found in one study (Rietman et al. 2003). In one study no SLNB patients reported pain (Schrenk et al. 2000).

Stiffness

In one study two axillary clearance patients reported stiffness compared to no SLNB patients but the difference was not statistically significant (Schrenk et al. 2000) (see Appendix J, Tables J8 and J12).

Activities of daily living and return to normal activity

More axillary clearance patients experienced difficulties with everyday tasks at home or at work than SLNB patients in two studies (Haid et al. 2002a, Schijven et al. 2003) but no significant difference was found between the two groups in three studies (Rietman et al.

2003, Schrenk et al. 2000, Peintinger et al. 2003). In another study, SLNB patients returned to normal activity significantly faster than axillary clearance patients, with more than two-thirds of SLNB patients returning in 3 days or less (Burak et al. 2002).

Quality of life

Quality of life was assessed in two studies. Using the European Organisation for Research and Treatment of Cancer quality of life questionnaires QLQ-C30 and QLQ-BR23, one study found no significant differences between axillary clearance patients and SLNB patients up to 12 months postoperatively, except in the pain subscale of the QLQ-30. SLNB patients also experienced a significant improvement in global quality of life over time (Peintinger et al. 2003). In a second study, SLNB patients experienced a decrease in quality of life compared to axillary clearance patients, despite experiencing fewer sensory morbidities (Haid et al. 2002a).

Cosmesis

In one study SLNB patients were more pleased with the aesthetic appearance of the axillary scar than axillary clearance patients (Veronesi et al. 2003) (for details see Appendix J, Tables J8 and J13).

Recurrence and survival

Recurrence

After treatment cancer can recur at the primary tumour site (local recurrence), in the axilla (regional or axillary recurrence) or elsewhere in the body (systemic recurrence). SLNB patients may be at risk for regional recurrence if their biopsy result was negative but positive nodes were unintentionally left in the axilla (i.e. their result was a false negative). Axillary recurrence is thus an important outcome of SLNB.

Comparative studies

In the one randomised controlled trial (Veronesi et al. 2003) patients with SLNB were compared with patients who had received SLNB followed by axillary clearance. There were no axillary recurrences in either group after median 46 months. The two groups did not differ significantly in the total number of breast cancer related events. The event rate per thousand patients per year was higher in the axillary clearance group (see Table 22).

Table 22 Recurrence in the randomised controlled trial of SLNB versus SLNB+AC

After 46 months n/N (%)	SLNB		SLNB + AC		p-value
Axillary recurrence	0/259	(0%)	0/257	(0%)	
Local recurrence	1/259	(0.4%)	1/257	(0.4%)	
Systemic recurrence	6/259	(2.3%)	10/257	(3.9%)	
De novo tumours	3/259	(1.2%)	2/257	(0.8%)	
Total breast cancer events	10/25 events		15/25 events		log-rank p=0.26
Total events	13/34 events		21/34 events		log-rank p=0.13
Event rate/1000/year	10.1 (95%CI: 4.9 – 18.5)		16.4 (95%CI: 9.2 – 26.9)		

Notes: SLNB – sentinel lymph node biopsy; AC – axillary clearance
Source: Veronesi et al. 2003.

In one Level III-3 historically controlled study (Haid et al. 2002a), there was no regional lymph node recurrence in either group, but length of follow-up was not stated.

Case series and case reports

Recurrences reported in case series are summarised in Table 23, which includes two comparative studies that did not report recurrence data for patients receiving axillary clearance. Case reports are discussed below.

Table 23 Cancer recurrence and survival in the included case series (SLNB patients only)

Study n/N (%)	Mean follow-up (months)	Axillary recurrence		Local recurrence	Systemic recurrence	*De novo* tumours	Survival	
Badgwell et al. 2003*	32	A: 0/159	(0%)	1/159	4/159	NR	NR	
		B: 1/63	(1.6%)	3/63	2/63	NR		
Balch et al. 2003	24	0/32	(0%)	0/32	2/32	NR	28/32**	(87.5%)
Bauer et al. 2002	28	0/332	(0%)	NR	NR	NR	NR	
Blanchard et al. 2003	29	1/685	(0.15%)	6/685	8/685	NR	677/685	(98.8%)
Borgstein et al. 1998	11	0/16	(0%)	NR	NR	NR	NR	
Chung et al. 2002	26	3/207	(1.4%)	0/207	3/207	NR	206/207	(99.5%)
Cox et al. 2000a	20	0/809	(0%)	NR	NR	NR	NR	
Estourgie et al. 2003a	21	1/599	(0.16%)	NR	NR	NR	NR	
Fant et al. 2003	30	0/31	(0%)	NR	0/31	NR	29/31	(93.5%)
Giuliano et al. 2000	39	0/67	(0%)	0/67	0/67	3/67	66/67	(98.5%)
Grube et al. 2002	44	0/?	(0%)	NR	NR	NR	NR	
Guenther et al. 2003	32	0/46	(0%)	NR	1/46	NR	NR	
Hansen et al. 2002	39	0/238	(0%)	4/238	4/238	8/238†	235/238	(98.7%)
Henry-Tillman et al. 2002	NR	0/?	(0%)	NR	NR	NR	NR	
Jakub et al. 2002	18	0/16	(0%)	1/16	4/16	NR	NR	
Liang et al. 2001	13.5	0/144	(0%)	NR	0/144	NR	NR	
Meijer et al. 2002	47	1/100	(1%)	1/100	3/100	NR	98/100	(98%)
Mirzaei et al. 2003	NR	0/128	(0%)	0/128	0/128	NR	NR	
Pelosi et al. 2002	NR	0/154	(0%)	0/154	0/154	NR	NR	
Ponzone et al. 2003	15	0/212	(0%)	0/212	0/212	NR	NR	
Reitsamer et al. 2003c	22	0/116	(0%)	0/116	NR	NR	NR	
Roka et al. 2002	20	2/383	(0.5%)	0/383	1/383	NR	382/383	(99.7%)
Roumen et al. 2001	24	1/100	(1%)	1/100	1/100‡	NR	99/100	(99%)
Schrenk et al. 2001	22	0/83	(0%)	0/83	0/83	NR	83/83	(100%)
Simmons et al. 2003	8	1/112	(0.9%)	NR	NR	NR	NR	
Takei et al. 2002	21	0/354	(0%)	1/354	2/354	NR	352/354	(99.4%)
Tanis et al. 2002b	19	0/38	(0%)	0/38	3/38	NR	NR	
Veronesi et al. 2001a	NR	0/187	(0%)	1/187	1/187	NR	186/187	(99.4%)
Zervos et al. 2001	19	0/266	(0%)	2/266	NR	NR	NR	

Note: SLNB – sentinel lymph node biopsy; NR – not reported; ? – unknown; * internal comparison between patients who were sentinel node (SN) negative and did not receive AC (A) and those who were SN positive and did receive AC (B); ** all patients received neoadjuvant chemotherapy; † 1/8 developed tumour in contralateral breast; ‡ the same patient developed axillary recurrence and then distant metastases (pulmonary, bone, brain).

Axillary recurrence after SLNB was reported in 11 patients in the included case series (see Table 23) and in four case reports (Agnese et al. 2003, Cserni 2000, Loza et al. 2002,

Salmon et al. 2002, Yen et al. 2003). Recurrences occurred between 9 months and 41 months after SLNB. The axillary recurrence rate did not exceed 1% in patients who were node negative at the time of SLNB. In two studies axillary recurrence was reported in patients who were sentinel node positive and received axillary clearance following SLNB (Badgwell et al. 2003, Cserni 2000).

Local recurrences were reported in 21 patients and systemic recurrences (distant metastases) in 39 patients, however, not all studies clearly reported these outcomes (whereas all clearly reported axillary recurrence). Two studies (Giuliano et al. 2000, Hansen et al. 2002) reported *de novo* tumours including one patient who developed cancer in the contralateral breast (Hansen et al. 2002).

Survival

Comparative studies

Survival was reported in two studies. There was no significant difference in overall survival between SLNB patients and SLNB+AC patients in the randomised trial. Two patients in the SLNB group died (one from metastatic breast cancer) and six patients in the axillary clearance group died (two from metastatic breast cancer) (p=0.15) (Veronesi et al. 2003). In one Level III-2 concurrently controlled study six SLNB patients and two SLNB+AC patients died from metastatic breast cancer (Blanchard et al. 2003).

Case series

Overall survival (based on mortality from all causes) reported in case series is shown in Table 23. After at least 24 months, survival was greater than 98% in all but two of 12 studies. Of the 26 deaths reported, all but five were from metastatic cancer (i.e. related to the breast cancer) (see Appendix J, Table J14).

Patient preference

No studies providing information about the choices made by women with breast cancer about SLNB were identified.

Trials in progress

Three large multicentre randomised clinical trials are ongoing; one in Australia – SNAC – and two in the United States – NSABP-B32 and ACOSOG-Z0011. A fourth large United Kingdom multicentre trial – ALMANAC – has concluded. A number of additional single-centre trials (some large) are also ongoing.

The first results of the ALMANAC trial (variable follow-up from 1 month to 18 months) were published in abstract form, and presented at the 2004 Annual Meeting of the American Society of Clinical Oncology. Mansel et al. (2004) reported that on an intention-to-treat basis, the relative risks for sensory loss and lymphoedema at 3 months in the SLNB group (515 patients) relative to the conventional axillary treatment (516 patients) were 0.39 and 0.28 respectively. Quality of life scores did not differ between the two groups at baseline but at 3 months follow-up overall quality of life and self-rated arm morbidity was significantly better in the group who underwent SLNB. Hospital stay,

axillary operative time and drain usage were significantly reduced in the group who underwent SLNB ($p<0.001$) and time to normal activities was also significantly reduced in the SLNB group ($p=0.002$). Mansel and colleagues (2004) concluded that SLNB is associated with less arm morbidity, a better quality of life and is cost effective compared to conventional axillary treatment. For more details on ongoing trials, see Appendix K.

Summary of results

The results of the review of the safety and effectiveness of SLNB are summarised in Table 24.

Table 24 Summary of results of safety and effectiveness of SLNB review

Result	Comparative studies N=18 included studies	Case series/case reports N=63 included studies
Levels of evidence	Level II – 1* Level III-2 – 14 Level III-2/3 – 1 Level III-3 – 2	Consecutive case series – 14 Consecutive not stated – 37 Case reports – 12
Wound infection, seroma, haematoma	*Level III-2 evidence* (5 studies) Fewer wound infections, wound inflammation, seromas, aspiration of fluid collection in SLNB	(15 studies) Seroma: 1.2%, 2%, 7.4% of patients Axillary lymphocoele: 8% and 11% of patients Axillary abscess: 2% of patients Wound infection: 0% and 1.2% of patients Haematoma: 0.3% of patients Cellulitis: 0.4% of patients No complications: 8 studies
Anaphylactic and allergic reaction to blue dye	*Level III-2 evidence* (1 study) No difference in proportion of patients reporting dye reaction (compared SLNB to SLNB+AC)	(13 case studies and 15 case reports) No reactions in 7 studies Isosulphan blue: 0% to 1.6% patients (med. 1%) Patent blue: 0% to 0.8% patients (med. 0%) Methylene blue: 0% in 2 studies 24 case reports in 15 studies – isosulphan blue in 10 and patent blue in 5, no case reports of allergic reaction to methylene blue
Skin discolouration or necrosis from blue dye	Reported in 11 studies (*Level IV evidence)*	
Internal mammary artery injury	Reported in 10 studies (*Level IV evidence)*	
Pleural injuries and pneumothorax	Reported in 10 studies (*Level IV evidence)*	
Length of hospital stay	*Level III-2 and III-3 evidence* (2 studies) Shorter for SLNB than AC	
Placement of drains	*Level III-2 and III-3 evidence* (4 studies) Required by more AC patients or for longer in AC patients than SLNB patients	
Lymphoedema	*Level III-2 and III-3 evidence* Patients reporting lymphoedema or arm swelling (6 studies): more AC than SLNB patients Changes in arm circumference (4 studies): no clear difference between AC and SLNB	
Range of motion limitation	*Level III-2 and III-3 evidence* (8 studies) Less limitation for SLNB or in fewer SLNB than AC patients	
Sensory morbidities	*Level III-2, III-2/3 and III-3 evidence* More sensory morbidities in AC than SLNB patients (2 studies) Numbness or paraesthesia in more AC patients than SLNB patients (6 studies) More pain, or more severe pain in AC patients than in SLNB patients (6 studies) No difference in numbness or pain (1 study)	
Activities of daily living and quality of life	*Level III-2 and III-3 evidence* (7 studies) No clear effect on activities of daily living (2 studies SLNB better, 3 studies no difference) No difference in quality of life in one study, and SLNB worse (1 study) Cosmesis better SLNB than AC (1 study)	
Recurrence	*Level II evidence* No axillary recurrences in either SLNB or SLNB+AC groups after 46 months	(29 studies) No axillary recurrence in 21 studies Axillary recurrence did not exceed 1% in node-negative patients
Survival	*Level II evidence* No difference in overall survival between SLNB and SLNB+AC 1 death from metastatic cancer in SLNB and 2 in SLNB+AC	(12 studies) Overall survival (all cause mortality) greater than 98% after 24 months in 10/12 studies 21/26 deaths from metastatic cancer

Note: * only for recurrence and survival; SLNB – sentinel lymph node biopsy; AC – axillary clearance.

What are the economic considerations?

From the literature

Two studies performed a cost comparison. In one study, cumulative charges for SLNB procedures were compared to non-SLNB procedures (which may not have been axillary clearance). Unadjusted for covariates, cumulative charges for SLNB procedures were approximately 91% of charges for non-SLNB procedures: '… if nothing else mattered … SLNB neither raises nor necessarily lowers the cost of breast cancer treatment' (Chirikos et al. 2001, p. 629). However, when adjusted for covariates, cumulative charges were approximately 11% higher for SLNB procedures. In a second study, inpatient charges for SLNB and axillary clearance were compared. No significant differences in the mean hospital related charges between the SLNB and axillary clearance groups were identified, as higher operating room charges for axillary clearance were balanced by higher pathologic examination and intraoperative frozen-section charges for SLNB (Gemignani et al. 2000). Node negative SLNB patients were found to have lower mean hospital charges than either all SLNB patients (node negative and positive) or axillary clearance patients, whereas node positive SLNB patients who required axillary clearance (either immediately or in a subsequent surgery) were also found to have higher mean hospital charges than all SLNB patients or axillary clearance patients.

Cost data were also reported in two case series. In one, per-patient costs increased with use of SLNB (Cox et al. 2001a), but in the second SLNB resulted in a 15% reduction in costs (Flett et al. 1998) (see Tables 25 and 26).

Table 25 Mean direct costs by procedure

	Without SN	With SN
Lumpectomy	US$3171	US$3872
Mastectomy	US$4836	US$5528
Readmission and completion axillary clearance	US$2591	US$2820
Intraoperative completion axillary clearance	US$456	–

Note: SN – sentinel node
Source: Cox et al. 2001

Table 26 Costs of overall breast procedure

	SLNB plus AC if SN+	Axillary clearance
Total operating costs	£32 659	£42 106
Pathology	£7 210	£4 760
Combined cost	£39 869	£46 866
Total saving	**£6 997**	**–**

Note: SLNB – sentinel lymph node biopsy; AC – axillary clearance; SN – sentinel node
Source: Flett et al. 1998

Economic model

The following assumptions were made:

- Mapping (localisation) failure rate estimated to be 5% at present (source: this systematic review).
- For T1 tumours, 20% of patients will have a positive sentinel lymph node; and for T2 tumours, 30% will have a positive sentinel lymph node (source: Cox et al. 2001).
- Approximately 50% of tumours will be T1 and 50% T2.
- Theatre costs will be similar for SLNB and axillary clearance.
- The cost of gamma probes has been amortised over 5 years with each probe used on an average of 165 patients per year.
- If a gamma probe is used, it is assumed that prior lymphoscintigraphy has been performed.
- The SLNB procedure itself has been costed at a low of $288.20 (30332; the present interim arrangement) and a high of $720.40 (30035; Level 1 axillary clearance).
- Hospital stay has been estimated as the total stay for the primary surgery since it is not possible to separate out the length of stay needed for SLNB and/or axillary clearance from that required due to the primary tumour.
- Recurrence and survival outcomes are similar for SLNB and axillary clearance (source: this systematic review (for recurrence)).
- The risk difference between SLNB and axillary clearance for lymphoedema/arm swelling is 23.8% in favour of SLNB, but this has been discounted to 17% since just under 30% of SLNB patients will also need axillary clearance (source: this systematic review).

Analyses have been done from a health system perspective. For recurrence and survival a cost minimisation analysis has been done, since recurrence and survival have been assumed to be similar for SLNB and axillary clearance. For avoidance of lymphoedema, a cost-effectiveness analysis was done, using a risk difference of 17% in favour of SLNB compared to axillary clearance.

Unit costs

Table 27 Unit costs as at February 2005

AUS $	SN (negative)	SN+AC if SN+ (AC same surgery)	SN+AC if SN+ (AC subsequent surgery)	SN (mapping failure) – convert to AC	AC
Detection					
Lymphoscintigraphy (if done)	334.60 to 459.60	334.60 to 459.60	334.60 to 459.60	334.60 to 459.60	NA
Dye	60.00	60.00	60.00	60.00	NA
Gamma probe (if used)	20.00	20.00	20.00	20.00	NA
Subtotal (1)	***60.00 to 539.60***	***60.00 to 539.60***	***60.00 to 919.60***	***60.00 to 539.60***	**–**
Operating costs					
SLNB (costed as 30332 to 30035)	288.20 to 720.40	50% of 288.20 to 720.40 = 144.10 to 360.20	288.20 to 720.40	50% of 288.20 to 720.40 = 144.10 to 360.20	NA
AC (30035 or 30036)	NA	720.40 to 864.55	720.40 to 864.55	720.40 to 864.55	720.40 to 864.55
Anaesthetic costs	750.00	750.00	1000.00	750.00	750.00
Subtotal (2)	***1038.20 to 1470.40***	***1614.50 to 1974.75***	***2008.60 to 2584.95***	***1614.50 to 1974.75***	***1470.40 to 1614.50***
Pathology					
Intra-operative (frozen section (72855) or imprint cytology)	185.60 (if done) **and**	185.60	185.60 (if done)	NA	NA
Postoperative (H&E or IHC) – 72825	181.45	181.45	181.45 x 2 = 362.90*	181.45	181.45
Subtotal (3)	***181.45 to 367.05***	***367.05***	***362.90 to 548.50***	***181.45***	***181.45***
Hospital stay (days assumed)	(1–3)	(2–4)	(3–7) (i.e. 1–3 + 2–4)	(2–4)	(2–4)
$800 per day**	800.00 to 2400.00	1600 to 3200	2400 to 5600	1600 to 3200	1600 to 3200
Subtotal (4)	***800.00 to 2400.00***	***1600.00 to 3200.00***	***2400.00 to 5600.00***	***1600.00 to 3200.00***	***1600.00 to 3200.00***
Total (1–4)	**2079.65 to 4777.05**	**3641.55 to 6081.40**	**4831.50 to 9273.05**	**3455.95 to 5895.80**	**3251.85 to 4996.00**

Notes: * first and second surgery; ** private system; SN – sentinel node; AC – axillary clearance; SLNB – sentinel lymph node biopsy; H&E – haematoxylin and eosin; IHC – immunohistochemistry

Unit costs are shown as a range of possible values reflecting the upper and lower boundaries of the cost for each scenario depending on the combination of lymphoscintigraphy, dye and or gamma probe used preoperatively, the item number of SLNB intraoperative and/or postoperative histology was used, and the length of hospital stay in a particular instance. For example, for the SN negative scenario (column 1) the upper limit of unit costs results from the combination of the use of lymphoscintigraphy, dye and radioisotope (detected with the gamma probe), SLNB costed with item number 30035 (i.e. Level I axillary clearance), intraoperative and postoperative histology and a hospital stay of 3 days.

Sentinel node unit costs

Table 28 Sentinel node negative

AUS$	Low	High
Detection	60.00	539.60
Operating costs	1038.00	1470.40
Pathology	181.45	367.05
Hospital stay	800.00	2400.00
Total	**2079.65**	**4777.05**

Table 29 Sentinel node positive (axillary clearance same surgery)

AUS$	Low	High
Detection	60.00	539.60
Operating costs	1614.50	1974.75
Pathology	367.05	367.05
Hospital stay	1600.00	3200.00
Total	**3641.55**	**6081.40**

Table 30 Sentinel node positive (axillary clearance subsequent surgery)

AUS$	Low	High
Detection	60.00	539.60
Operating costs	2008.60	2584.95
Pathology	362.90	548.50
Hospital stay	2400.00	5600.00
Total	**4831.50**	**9273.05**

Table 31 Sentinel node localisation failure (immediate conversion to axillary clearance)

AUS$	Low	High
Detection	60.00	539.60
Operating costs	1614.50	1974.75
Pathology	181.45	181.45
Hospital stay	1600.00	3200.00
Total	**3455.95**	**5895.80**

Table 32 Axillary clearance (alone) unit costs

AUS$	Low	High
Detection	NA	NA
Operating costs	1470.40	1614.55
Pathology	181.45	181.45
Hospital stay	1600.00	3200.00
Total	**3251.85**	**4996.00**

Note: NA – not applicable

Table 33 Breakdown of costs per 100 procedures

	1	2	3	4	5
	SN negative	**SN (AC same surgery OR**	**SN (AC subsequent surgery)**	**SN mapping failure (then AC)**	**Total (when AC is same surgery)**
5% mapping failure	–	–	–	5.00	(columns 1+2+4)
Node negative					
50% T1 (80% of 95)	38.00	–	–	–	
50% T2 (70% of 95)	33.25	–	–	–	
Subtotal	***71.25***	**–**	**–**	**–**	
Node positive					
50% T1 (20% of 95)	–	9.50	9.50	–	
50% T2 (30% of 95)	–	14.25	14.25	–	
Subtotal	**–**	***23.75***	***23.75***	**–**	
Total	**71.25**	**23.75**	**23.75**	**5.00**	**100.00**
Unit cost – range	2079.65 to 4777.05	3641.55 to 6276.10	4831.50 to 9251.65	3455.95 to 6090.50	
Total	**148,175.06 to 340,364.81**	**86,486.81 to 144,433.25**	**114,748.12 to 220,234.93**	**17,279.75 to 29,479.00**	**251,941.62 to 514,277.06**

Notes: SN – sentinel node; AC – axillary clearance

Thus, for every 100 sentinel node procedures attempted, 71.25 will involve sentinel node only and 28.75 will also require axillary clearance (either in the same or subsequent surgery), including 5 localisation failures.

Table 34 Sentinel node (axillary clearance same surgery) – 100 procedures

AUS$		**SN**		**AC**
	Low	**High**	**Low**	**High**
SN negative	148,175.06	340,364.81	–	–
SN positive	86,486.81	144,433.25	–	–
SN mapping failure	17,279.75	29,479.00	–	–
Total	**251,941.62**	**514,277.06**	**325,185.00**	**499,600.00**

Notes: SN – sentinel node; AC – axillary clearance

Table 35 Sentinel node (axillary clearance subsequent surgery) – 100 procedures

AUS$		**SN**		**AC**
	Low	**High**	**Low**	**High**
SN negative	148,175.06	340,364.81	–	–
SN positive	114,748.12	220,234.93	–	–
SN mapping failure	17,279.75	29,479.00	–	–
Total	**280,202.93**	**590,078.74**	**325,185.00**	**499,600.00**

Notes: SN – sentinel node; AC – axillary clearance

The cost per 100 procedures for SLNB (plus axillary clearance in the same surgery when required) ranges from $251,942 to $514,277 compared to a range of $325,185 to $499,600 for axillary clearance alone.

The cost per 100 procedures for sentinel node (plus axillary clearance in a subsequent surgery when required) ranges from $280,203 to $590,079 compared to a range of $325,185 to $499,600 for axillary clearance alone.

Avoidance of lymphoedema cost effectiveness calculations

For every 100 sentinel nodes attempted, 28.75 of these will also require axillary clearance (23.75 for positive nodes and 5 for localisation failures).

In this review we found that the risk difference for avoidance of lymphoedema was 23.8% between sentinel node and axillary clearance, in favour of sentinel node. However, as shown in the tables above, this risk difference needs to be discounted by the proportion of women undergoing sentinel node who subsequently also need axillary clearance (i.e. 28.75%). Thus a risk difference of 23.8% minus (28.75% of 23.8%) equals 17% has been used in the economic analysis in Tables 36 and 37.

Table 36 Sentinel node (axillary clearance same surgery); per 100 procedures

	Low	High
SLNB	251,941.62	514,277.06
AC	325,185.00	499,600.00
Difference	**– 73,243.38**	**14,677.06**
ICER	**NA**	**14,677.06 / 17 = $863.36**

Notes: SLNB – sentinel lymph node biopsy; AC – axillary clearance; ICER – Incremental cost effectiveness ratio; NA – not applicable.

Table 37 Sentinel node (axillary clearance subsequent surgery); per 100 procedures

	Low	High
SLNB	280,202.93	590,078.74
AC	325,185.00	499,600.00
Difference	**–44,982.07**	**89,419.24**
ICER	**NA**	**90,478.74 / 17 = $5322.28**

Notes: SLNB – sentinel lymph node biopsy; AC – axillary clearance; ICER – Incremental cost effectiveness ratio; NA – not applicable.

The incremental cost effectiveness ratio for the highest range is $863 for SLNB (with axillary clearance in the same surgery) and $5322 (with axillary clearance in a subsequent surgery). The incremental cost effectiveness ratio was not calculated for the low end of ranges since SLNB is cheaper than axillary clearance in these cases.

Thus SLNB costs less than axillary clearance and is more effective at the low end of the costing range.

At the high end of the costing range SLNB (with axillary clearance in the same surgery, when required) costs $8.63 for one case of lymphoedema avoided and $53.20 when axillary clearance (if required) is performed in a subsequent surgery.

6. Discussion

Study limitations

Limited conclusions can be drawn from this systematic review of SLNB. Although the very large number of diagnostic accuracy studies available allowed meta-analysis and subgroup analyses to be undertaken, less than one-third of the included studies were consecutive in their selection of patients. Significant heterogeneity was seen between patients in individual studies and between different studies included to assess diagnostic accuracy. Few studies compared SLNB with axillary clearance. There was one published randomised controlled trial included, although Level II evidence was only applicable for the recurrence and survival outcomes, not the safety and efficacy outcomes.[11] The remainder of comparative evidence came from studies in which significant selection bias was likely. As it was anticipated that safety evidence from comparative studies would be sparse, evidence from case series and case reports was included. Many factors influence the validity of these study types, and they represent poor quality evidence, serving to indicate safety concerns rather than to enable a judgment of the relative safety of SLNB compared to axillary clearance.

Diagnostic accuracy of sentinel lymph node biopsy

SLNB was found to have a mapping failure rate of 5.9% (i.e. a mean localisation rate of 94.1%) and 95.3% of patients received the correct staging of their axillary lymph nodes (i.e. a mean false negative rate of 4.7%). These results were well within the targets set for the ALMANAC trial (Clarke et al. 2001).

While the localisation rate is not as important as the false negative rate in determining the overall diagnostic accuracy of SLNB, it does influence the number of women exposed to unnecessary morbidities, such as lymphoedema, and increases overall costs, since it is standard practice to perform an axillary clearance whenever a sentinel node cannot be located. In SLNB, a false negative result occurs when the excised node(s) are not true sentinel nodes. These false negatives can only be determined by analysing the axillary lymph nodes dissected as part of a subsequent axillary clearance. They probably arise from a combination of the function of the lymphatic system of the breast in the presence of a tumour and/or metastases, and differences in operator experience with the sentinel node technique. In contrast, a false negative rate in axillary clearance is usually due to pathology failure since Level I, Level II and sometimes Level III axillary nodes are excised and subject to pathological analysis. Since a large number of nodes must be examined in axillary clearance this may be a result of less intensive pathological assessment. One of the possible advantages of SLNB is that with fewer nodes to examine a more thorough histological analysis can be performed and as a result there will be less chance of pathology failures.

[11] The groups being compared were a convenience sample of the first 100 patients to undergo sentinel lymph node biopsy without axillary clearance compared with the first 100 patients to undergo axillary clearance.

Despite these differences, when comparing the diagnostic accuracy of SLNB and axillary clearance the false negative rate associated with each procedure does give an indication of how many patients are likely to receive inadequate treatment as a result of the understaging of their disease. Assuming a false negative rate of 2% to 3% for axillary clearance (Boova et al. 1982, Rosen et al. 1983, van Lancker et al. 1995), SLNB appears to have in the order of a two times higher false negative rate at around 5%. However, the important outcome in making this comparison is whether there is an impact on survival. The available evidence suggests that axillary recurrence rates in SLNB may be comparable to axillary clearance, but at present there is insufficient evidence to compare the survival outcomes of SLNB and axillary clearance and this will only be available when the ongoing randomised controlled trials are completed. In the meantime, it is highly recommended that patients undergoing SLNB alone be examined at regular intervals to observe the axilla for signs of regional recurrence.

In the absence of long-term survival data, it is reasonable to compare SLNB and axillary clearance in terms of short-term outcomes, such lymphoedema and other morbidities, and the impact this may have on quality of life or activities of daily living. While it was apparent that lymphoedema is more commonly associated with axillary clearance, data about activities of daily living and quality of life were relatively sparse and inconsistent. axillary clearance was also associated with more wound complications and sensory morbidities than SLNB. However, the advantages of SLNB as a minimally invasive technique could be nullified if too many nodes that are radioactive or blue are removed, and care should be taken to only remove those thought to be sentinel nodes.

It is difficult to determine what weight to give to the avoidance of morbidities associated with axillary clearance given that at present diagnostic accuracy does not appear to be completely equivalent. Women's own preferences would help make this determination, however, no relevant evidence on this issue could be identified.

Improving the diagnostic accuracy of sentinel lymph node biopsy

Although there appears to be a learning curve associated with SLNB this could not be directly assessed from the data available in the included studies. However, sensitivity analyses, comparing diagnostic accuracy over time and in larger series of patients, provide some proxy indications of the impact of cumulative world experience with SLNB and increasing experience of surgical teams. Localisation rates improved over time suggesting that as experience with the SLNB technique has grown worldwide the procedure has become more refined and mapping failures less likely to occur. However, false negative rates became slightly worse over the same period, suggesting that there are still factors associated with either the SLNB technique or patient selection, which may be impacting on its diagnostic accuracy.

Ideally, a standard test protocol for SLNB should be identified that minimises the chance of identifying sentinel nodes, which are not the true sentinel node. To optimise the test protocol, it must be specified to maximise the localisation rate without compromising the false negative rate. Aspects of the test protocol believed to increase the false negative rate should be avoided where possible, and patients in whom it is more likely that a false negative will result from SLNB should be identified.

Dye or radioisotope?

It was clear from the subgroup analysis that use of blue dye alone resulted in poorer localisation and false negative rates; whereas a combination of radioisotope and dye improved diagnostic accuracy. It is not entirely clear why diagnostic accuracy would be worse with blue dye, however, it seems likely that a learning curve effect is overlying the diagnostic accuracy results (Guenther 1999, Kollias et al. 2000, Morrow et al. 1999, Noguchi et al. 1999, Euhus et al. 2002, Nwariaku et al. 1998, McMasters et al. 2001b). It is possibly more difficult to locate a sentinel node visually than with the assistance of a gamma-probe, particularly early in the learning curve. It is logical that diagnostic accuracy would be improved if two methods of mapping the node were used rather than one. Again, the differences in concordance between radioisotope and dye evident in the included studies may be a function of the surgeon's experience with the technique being used (Kumar et al. 2003).

However, if blue dye is used, consideration must be given to the possibility of anaphylactic reaction. Anaphylactic reaction may be fatal, and although rarely reported in the included studies (less than 1% of SLNB patients and no deaths) when dye is used, adequate resuscitation measures must be available, especially if the procedure is performed as an outpatient procedure. Patients should also be made aware of the remote possibility of a severe reaction.

Injection site

Localisation rates were also poorer when the peritumoural injection site was used compared to the subareolar site, both for blue dye and for radioisotope. Although the peritumoural site is the most commonly used, it is technically more difficult than either dermal or subareolar injection sites, requiring the accurate placement of a number of injections around the tumour. For this reason it is not suitable for multifocal tumours and ultrasound or stereotaxic guidance may be needed for nonpalpable tumours or excisional biopsy cavities (Bauer et al. 2002, Layeeque et al. 2003, Kern et al. 1999, Klimberg et al. 1999). The function of the lymphatic system in the deep breast parenchyma may also account for the poorer localisation rates using the peritumoural site (Tuttle et al. 2002). If tracer flow is impeded to the sentinel lymph node or if radioisotope shine-through obscures detection then a mapping failure would be more likely to occur, particularly if the operator lacks experience with SLNB.

It is possible that there is an interaction effect between use of dye or radioisotope and the site of injection. Unfortunately, the available evidence did not allow this issue to be examined.

Patient characteristics

A number of issues appeared to increase the chance that the lymph node identified was not the true sentinel node. It appeared that patients who had previously had an excisional biopsy, those who had clinically positive lymph nodes, and those who had received neoadjuvant chemotherapy were all more likely to have a false negative result on SLNB. All of these factors appear to disrupt the normal functioning of the lymphatic system and the take-up of dye or radioisotope (Liberman et al. 1999, Moffat et al. 1999, Ponzone et al. 2003, Nason et al. 2000, Vigario et al. 2003).

Though not subject to subgroup analysis, age appears to have an impact on localisation rate, with women over 50 years more likely to have a mapping failure than younger

women (Birdwell et al. 2001, Chua et al. 2003, McMasters et al. 2000a, Motomura et al. 1999a, Motomura et al. 2002b, Kollias et al. 2000, Noguchi et al. 2000a, Tanis et al. 2002b, Koizumi et al. 2003, Morrow et al. 1999, Bergkvist et al. 2001, Nason et al. 2000, Cox et al. 2002). Anatomical changes in older women, in particular increased fatty tissue in the breast, may cause decreased lymphatic flow and lead to increased localisation failures (Cox et al. 2002). However, no significant differences in localisation rates were reported in other studies comparing women of different ages (Krag et al. 2001, Tsugawa et al. 2000, Ozmen et al. 2002, Brenot-Rossi et al. 2003, Patel et al. 2003, Nos et al. 2001).

Issues to be resolved

Given the available evidence a number of issues remain unresolved at this time. Some of these issues will be addressed by the findings of the ongoing randomised trials, however, for some others additional research may be required.

While it was clear that a combination of radioisotope and dye provided the best diagnostic accuracy, it was not clear whether radioisotope alone would produce similar results to the combination of radioisotope and dye. Furthermore, the role of the learning curve in mapping success with blue dye is still unclear, though it seems likely that some of the heterogeneity seen in the meta-analysis of localisation rates could be explained by differences in surgical experience with blue dye. This has important implications for practice, since the availability of equipment and tracer types may influence the choice of radioisotope/dye combinations. For example, radioisotope may not be commonly used in Japan because government regulations limit the use of radioisotopes and gamma-probes are expensive (Ikeda et al. 2003). In Australia, smaller or more remote hospitals may not have nuclear medicine facilities or may not be able to afford the hand-held gamma probes used for intraoperative mapping of radioisotopes, and instead may have to rely on use of blue dye for mapping (Kollias & Gill 2001).

The place of subareolar injections in SLNB requires further research. The vast majority of studies included in this review used the peritumoural injection site, however, this appears to result in poorer diagnostic accuracy. Subareolar injections may also have some technical benefits (in that ultrasonic or stereotaxic imaging is not required for nonpalpable lesions and less skill is required to inject them) and be more suitable for some patients (especially those with multifocal tumours). The ongoing randomised trials will not address this question as the peritumoural site has been used in the NSABP B-32, ALMANAC and SNAC trials.

The diagnostic accuracy of the histological methods used in SLNB also appears to be under-researched and the value of intraoperative pathology or the addition of IHC to permanent histology is unclear.

The evidence available in many studies may have confounded the safety and effectiveness of SLNB compared to axillary clearance by including in the axillary clearance group patients who had received confirmatory axillary clearance after SLNB. As a result it was difficult to quantify the additive effect of SLNB on the results of axillary clearance and to compare SLNB and axillary clearance directly. If the results of the current ongoing randomised trials are compared this will provide some information relevant to this question as the ALMANAC trial compares SLNB to axillary clearance without prior SLNB, whereas, the NSABP B-32, ACOSOG Z0011 and SNAC trials compare SLNB and SLNB+AC.

7. Conclusions

SLNB appears to be an effective alternative to, but not a replacement for, axillary clearance for determining the metastatic status of axillary lymph nodes. Overall, 94% of patients can be successfully mapped with SLNB with a 5% false negative rate. This leads to a reduction in lymphoedema and associated symptoms for around 70% of patients (those accurately staged as node-negative) compared with axillary clearance. However, the impact of the 5% false negative rate on recurrence and survival outcomes remains unclear at present. Ongoing randomised trials (which are currently nearing the end of the recruitment phase) should provide additional useful information. However, accurate assessment of outcomes, such as survival, requires long-term follow-up, which often lags behind current clinical requirements for guidance.

It was clear from the subgroup analysis that use of blue dye alone resulted in poorer localisation and false negative rates, whereas a combination of radioisotope and dye improved diagnostic accuracy. Localisation rates were also poorer when the peritumoural injection site was used compared to the subareolar site, both for blue dye and for radioisotope. Although it is apparent there is a learning curve for the SLNB procedure, the impact of surgeon and team experience/skill on localisation rates could not be assessed directly. However, localisation rate was found to have improved every year since SLNB was introduced, though heterogeneity between studies remained high. Patient characteristics such as previous excisional biopsy, clinically positive lymph nodes and treatment with neoadjuvant chemotherapy were associated with an increased false negative rate.

SLNB was associated with fewer morbidities than axillary clearance (i.e. wound infections and a range of sensory morbidities such as pain, numbness and paraesthesia). However, some SLNB patients also reported a range of morbidities associated with use of blue dye (anaphylactic and allergic reactions and skin discolouration or necrosis). Some patients having extra-axillary node dissection after SLNB also reported internal mammary artery injuries, and pleural injuries or pneumothorax.

There was a 23.8% risk difference in avoidance of lymphoedema for SLNB patients compared with axillary clearance patients; however, this only applies to the 70% to 80% of patients who are node negative (as node positive patients will receive axillary clearance). Data regarding quality of life or impact on activities of daily living were relatively sparse and inconsistent. No relevant studies regarding women's preferences for SLNB or axillary clearance were located.

There were insufficient data to determine the relative survival of SLNB and axillary clearance patients. However, in the majority of case series overall survival was greater than 98% after 24 months. Axillary recurrence appeared similar in axillary clearance and SLNB and was very low (less than 1% in node-negative patients).

Overall, the costs of SLNB (plus axillary clearance when required) are very similar to axillary clearance alone using recurrence and survival (cost-minimisation analysis) and avoidance of lymphoedema (cost-effectiveness analysis) as measures of effectiveness.

8. Recommendation(s)

Sentinel node biopsy appears to be safe and effective in identifying sentinel lymph nodes resulting in reduction of complications due to axillary lymph node dissection, in particular lymphoedema. Longer-term outcomes are uncertain. MSAC recommends that interim funding for sentinel node biopsy should be provided pending the outcome of trials already in progress and should be reviewed in 5 years.

– The Minister for Health and Ageing endorsed this recommendation on 4 July 2005 –

Appendix A MSAC terms of reference and membership

MSAC's terms of reference are to:

- advise the Minister for Health and Ageing on the strength of evidence pertaining to new and emerging medical technologies and procedures in relation to their safety, effectiveness and cost-effectiveness and under what circumstances public funding should be supported
- advise the Minister for Health and Ageing on which new medical technologies and procedures should be funded on an interim basis to allow data to be assembled to determine their safety, effectiveness and cost-effectiveness
- advise the Minister for Health and Ageing on references related either to new and/or existing medical technologies and procedures
- undertake health technology assessment work referred by the Australian Health Ministers' Advisory Council (AHMAC) and report its findings to AHMAC.

Membership of MSAC comprises a mix of clinical expertise covering pathology, nuclear medicine, surgery, specialist medicine and general practice, plus clinical epidemiology and clinical trials, health economics, consumers, and health administration and planning:

Member	Expertise or affiliation
Dr Stephen Blamey (Chair)	general surgery
Associate Professor John Atherton	cardiology
Professor Syd Bell	pathology
Dr Michael Cleary	emergency medicine
Dr Paul Craft	clinical epidemiology and oncology
Dr Gerry FitzGerald	Australian Health Ministers' Advisory Council representative
Dr Kwun Fong	thoracic medicine
Dr Debra Graves	medical administrator
Professor Jane Hall	health economics
Professor John Horvath	Chief Medical Officer, Department of Health and Ageing
Dr Terri Jackson	health economics
Professor Brendon Kearney	health administration and planning
Associate Professor Donald Perry-Keene	endocrinology
Dr Ray Kirk	health research
Dr Michael Kitchener	nuclear medicine
Professor Alan Lopez	medical statistics and population health
Dr Ewa Piejko	general practice
Ms Sheila Rimmer	consumer health issues
Ms Samantha Robertson	Acting Assistant Secretary
Professor Jeffrey Robinson	obstetrics and gynaecology
Professor Michael Solomon	colorectal surgery, clinical epidemiology
Professor Ken Thomson	radiology
Dr Douglas Travis	urology

Appendix B Advisory panel committee

Advisory Panel for MSAC application Reference 1065 Sentinel Lymph Node Biopsy in Breast Cancer

Professor Bruce Barraclough, MBBS FRACS FACS DDU Professor/Director Cancer Services Northern Sydney Health	Member of MSAC General Surgeon
Dr Ewa Piejko, MBBS, FRACGP, DRANZCOG General Practitioner, Melbourne	Member of MSAC General Practitioner
Dr Paul Craft, MBBS MPH FRACP Director, Medical Oncology Unit The Canberra Hospital, Woden, ACT	Member of MSAC Clinical Epidemiologist and Oncologist
Associate Professor John Collins, MBBS FRACS FACS Head Breast Unit Royal Melbourne Hospital Chairman, Breast Section Royal Australasian College of Surgeons	Nominated by the Royal Australasian College of Surgeons
Mrs Avis Macphee, AAIMS (retired) Consumer Representative Consumer's Health Forum	Nominated by the Consumer's Health Forum
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Appendix C Studies included in the review

Table C.1 Included studies

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Acosta et al. 2003	IV (case series)	South America	Safety and efficacy	X	Localisation rates	X	X	54	None
Agnese et al. 2003	IV (case report)	USA	X	Recurrence	X	X	X	1	NA
Ahrendt et al. 2002*	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	174	None
Albo et al. 2001	IV (case series)	USA	Safety and efficacy	X	X	X	X	639	NA
Allen et al. 2001	IV (case series)	New Zealand	X	X	Localisation rates	False negative rates	X	36	None
Altiyollar et al. 2000	IV (case series)	Turkey	Safety and efficacy	X	Localisation rates	False negative rates	X	60	None
Aras et al. 2002	IV (case series)	Turkey	X	X	Localisation rates	X	X	30	None
Badgwell et al. 2003	IV (case series)	USA	X	Recurrence	X	X	X	222	NA
Baichev et al. 2001	IV (case series)	Bulgaria	X	X	X	False negative rates	X	238	Deliiski et al. 1999
Baitchev et al. 2002	IV (case series)	Bulgaria	X	X	Localisation rates	False negative rates	X	87	None
Balch et al. 2003	IV (case series)	USA	Safety and efficacy	Recurrence	Localisation rates	False negative rates	X	122	None
Barnwell et al. 1998	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	42	Sabel et al. 2001
Baron et al. 2002	III-2	USA	Safety and efficacy	X	X	X	X	283	NA
Barranger et al. 2003	IV (case series)	France	X	X	Localisation rates	False negative rates	X	32	None
Bass et al. 1999b	IV (case series)	USA	X	X	X	False negative rates	X	186	Albertini et al. 1996 Bass et al. 1999a Cox et al. 1998a
Bauer et al. 2002	IV (case series)	USA	X	Recurrence	Localisation rates	X	X	332	Bedrosian et al. 2000 Reynolds et al. 1999
Beitsch et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	85	None
Bembenek et al. 1999*	IV (case series)	Germany	X	X	Localisation rates	X	X	146	None
Bergkvist et al. 2001	IV (case series)	Sweden	X	X	Localisation rates	False negative rates	X	498	Frisell et al. 2001
Birdwell et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	155	None
Blanchard et al. 2003	III-2	USA	Safety and efficacy	Recurrence	X	X	X	1253	NA
Blessing et al. 2002	IV (case series)	USA	Safety and efficacy	X	Localisation rates	X	X	199	None
Bobin et al. 1999	IV (case series)	France	X	X	Localisation rates	False negative rates	X	100	None
Borgstein et al. 1998	IV (case series)	The Netherlands	X	Recurrence	X	X	X	130	NA
Borgstein et al. 2000	IV (case series)	The Netherlands	Safety and efficacy	X	Localisation rates	X	X	217	Borgstein et al. 1997 Borgstein et al. 1998 Pijpers et al. 1997
Bourgeois et al. 2003b	IV (case series)	Belgium	X	X	Localisation rates	X	X	181	None
Bourgeois et al. 2003a	IV (case series)	Belgium	X	X	X	False negative rates	X	393	None
Brady 2002	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	14	None
Branagan et al. 2002*	IV (case series)	UK	X	X	Localisation rates	X	X	52	None

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Brenot-Rossi et al. 2003	IV (case series)	France	X	X	Localisation rates	X	X	332	None
Breslin et al. 2000	IV (case series)	USA	X	X	Localisation rates	X	X	51	Cohen et al. 2000
Burak et al. 1999	IV (case series)	USA	X	X	X	False negative rates	X	50	None
Burak et al. 2002	III-2	USA	Safety and efficacy	X	X	X	X	96	NA
Byrd et al. 2001*	IV (case series)	USA	X	X	Localisation rates	X	X	220	None
Canavese et al. 2000a	IV (case series)	Italy	X	X	X	False negative rates	X	55	None
Canavese et al. 2001	IV (case series)	Italy	X	X	X	False negative rates	X	212	Canavese et al. 1998 Canavese et al. 2000b
Carcoforo et al. 2002	IV (case series)	Italy	Safety and efficacy	X	X	X	X	143	NA
Casalegno et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	102	Sandrucci & Mussa 1998
Chirikos et al. 2001	III-3	USA	X	X	X	X	Cost comparison	811	NA
Choi et al. 2003	IV (case series)	USA	Safety and efficacy	X	Localisation rates	X	X	81	None
Chua et al. 2001	IV (case series)	Australia	X	X	Localisation rates	X	X	167	None
Chua et al. 2003	IV (case series)	Canada	X	X	Localisation rates	X	X	547	Smillie et al. 2001
Chung et al. 2001a	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	41	None
Chung et al. 2001b	IV (case series)	Hong Kong	X	X	Localisation rates	False negative rates	X	30	None
Chung et al. 2002	IV (case series)	USA	X	Recurrence	X	X	X	206	NA
Cimmino et al. 2001	IV (case reports)	USA	Safety and efficacy	X	X	X	X	5	NA
Classe et al. 2003	IV (case series)	France	Safety and efficacy	X	Localisation rates	X	X	200	None
Cohen et al. 2000	IV (case series)	USA	X	X	X	False negative rates	X	38	Breslin et al. 2000
Cox et al. 2000a	IV (case series)	USA	Safety and efficacy	Recurrence	X	X	X	1356	NA
Cox et al. 2002	IV (case series)	USA	X	X	Localisation rates	X	X	1356	Bass et al. 1999c Bass et al. 2001 Cox et al. 1998b Cox et al. 1998c Cox et al. 2000a Cox et al. 2000b Reintgen et al. 1997 Kamath et al. 2001
Crivellaro et al. 2003	IV (case report)	Italy	Safety and efficacy	X	X	X	X	1	NA
Crossin et al. 1998	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	50	None
Cserni 2000a	IV (case report)	Hungary	X	Recurrence	X	X	X	1	NA
Cserni 2002	IV (case series)	Hungary	X	X	Localisation rates	X	X	201	Cserni 1999 Cserni et al. 2000a Cserni 2001a Cserni 2001b Cserni et al. 2002
Cserni et al. 2000b	IV (case series)	Hungary	X	X	X	False negative rates	X	130	Cserni 1999 Cserni et al. 2000a

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
									Cserni 2001b
Czerniecki et al. 1999	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	44	None
Dale & Williams 1998	IV (case series)	USA	Safety and efficacy	X	Localisation rates	False negative rates	X	28	None
de Kanter et al. 2000*	IV (case series)	The Netherlands	X	X	Localisation rates	False negative rates	X	241	None
de Rubeis et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	21	None
d'Eredita et al. 2003*	IV (case series)	Italy	X	X	Localisation rates	X	X	155	d'Eredita et al. 2001 d'Eredita et al. 2002
Derossis et al. 2003*	IV (case series)	USA	X	X	Localisation rates	X	X	2495	Boolbol et al. 2001 Cody et al. 1999 Cody et al. 2001 Derossis et al. 2001 Hill et al. 1999 Linehan et al. 1999a Linehan et al. 1999b Martin et al. 2001a Martin et al. 2001b McCarter et al. 2001a McCarter et al. 2001b O'Hea et al. 1998 Olson et al. 2000 Weiser et al. 2000 Yeung et al. 2001
Donahue 2001	IV (case series)	USA	X	X	Localisation rates	X	X	42	None
Doting et al. 2000	IV (case series)	The Netherlands	X	X	X	False negative rates	X	136	None
Dowlatshahi et al. 1999	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	54	None
Dunnwald et al. 1999	IV (case series)	USA	X	X	Localisation rates	X	X	93	None
Dupont et al. 2001	IV (case series)	USA	Safety and efficacy	X	X	X	X	1470	NA
Efron et al. 2002	IV (case report)	USA	Safety and efficacy	X	X	X	X	1	NA
Estourgie et al. 2003b*	IV (case series)	The Netherlands	X	Recurrence	Localisation rates	X	X	599	Nieweg et al. 2003 Tanis et al. 2001a Tanis et al. 2002b Tanis et al. 2002a Valdes Olmos et al. 2000 Valdes Olmos et al. 2001
Estourgie et al. 2003a	IV (case series)	The Netherlands	Safety and efficacy	X	X	X	X	150	NA
Euhus et al. 2002	IV (case series)	USA	X	X	Localisation rates	X	X	153	None
Fant et al. 2003	IV (case series)	USA	X	Recurrence	X	X	X	31	NA
Feezor et al. 2002	IV (case series)	USA	X	X	Localisation rates	X	X	118	None
Feggi et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	60	Carcoforo et al. 1999
Feggi et al. 2001	IV (case series)	Italy	Safety and efficacy	X	Localisation rates	X	X	73	None
Feldman et al. 1999*	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	75	None
Fenaroli et al. 2000	IV (case series)	Italy	X	X	Localisation rates	X	X	14	None

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Fernandez et al. 2001	IV (case series)	Spain	X	X	Localisation rates	False negative rates	X	76	None
Fernandez et al. 2002	IV (case series)	Spain	X	X	Localisation rates	False negative rates	X	110	None
Fialdini et al. 2000	IV (case series)	Italy	X	X	Localisation rates	X	X	25	None
Fleming et al. 2003	IV (case series)	Ireland	X	X	Localisation rates	False negative rates	X	125	Manecksha et al. 2001
Flett et al. 1998	IV (case series)	UK	X	X	Localisation rates	X	X	68	None
Formisano et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	42	None
Fraile et al. 2000	IV (case series)	Spain	X	X	Localisation rates	False negative rates	X	132	None
Galatius et al. 2003	IV (case reports)	Denmark	Safety and efficacy	X	X	X	X	3	NA
Galimberti et al. 2002	IV (case series)	Italy	Safety and efficacy	X	X	X	X	182	NA
Galli et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	46	None
Gemignani et al. 2000	III-2	USA	X	X	X	X	Cost comparison	100	NA
Giménez et al. 2001	IV (case reports)	Spain	Safety and efficacy	X	X	X	X	2	NA
Giuliano et al. 1997	IV (case series)	USA	Safety and efficacy	X	X	X	X	110	NA
Giuliano et al. 2000	III-2	USA	Safety and efficacy	Recurrence	X	X	X	133	NA
Golshan et al. 2003	III-2	USA	Safety and efficacy	X	X	X	X	125	NA
Gray et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	43	None
Grube et al. 2002	IV (case series)	USA	X	Recurrence	X	X	X	105	NA
Gucciardo et al. 2000*	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	50	None
Guenther 1999	IV (case series)	USA	X	X	Localisation rates	X	X	260	Guenther et al. 2000
Guenther et al. 1997	IV (case series)	USA	Safety and efficacy	X	X	False negative rates	X	145	None
Guenther et al. 2003	IV (case series)	USA	X	Recurrence	X	X	X	46	NA
Gulec et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	165	None
Haid et al. 2001	IV (case series)	Austria	X	X	X	False negative rates	X	33	None
Haid et al. 2002a	III-3	Austria	Safety and efficacy	Recurrence	X	X	X	140	NA
Haid et al. 2002b	III-2	Austria	Safety and efficacy	X	X	X	X	151	NA
Haigh et al. 2000[12]	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	283	Bilchik et al. 1998 DiFronzo et al. 2000 Giuliano et al. 1994 Giulianoet al. 1995 Giulianoet al. 1997 Grube et al. 2002 Turner et al. 1997
Hansen et al. 2002[13]	IV (case series)	USA	Safety and efficacy	Recurrence	Localisation rates	X	X	238	Giulianoet al. 2000

[12] Slight overlap of approximately 3 months with Hansen et al. 2002 (but only for localisation data).

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Henry-Tillman et al. 2002	IV (case series)	USA	X	Recurrence	X	X	X	247	NA
Hoar & Stonelake 2003	IV (case series)	UK	X	X	Localisation rates	False negative rates	X	66	None
Hodgson et al. 2001	IV (case series)	Canada	X	X	Localisation rates	False negative rates	X	47	None
Hung et al. 2002	IV (case series)	Hong Kong	X	X	Localisation rates	False negative rates	X	50	None
Ilum et al. 2000	IV (case series)	Denmark	Safety and efficacy	X	Localisation rates	False negative rates	X	159	None
Imoto & Hasebe 1999	IV (case series)	Japan	Safety and efficacy	X	Localisation rates	False negative rates	X	86	None
Imoto et al. 2000	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	58	None
Intra et al. 2003b	IV (case series)	Italy	X	X	Localisation rates	X	X	223	None
Intra et al. 2003a	IV (case series)	Italy	X	X	Localisation rates	X	X	41	None
Ishida et al. 2002*	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	44	None
Jaderborg et al. 1999	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	91	None
Jakub et al. 2002	IV (case series)	USA	X	Recurrence	X	X	X	409	NA
Jansen et al. 2000	IV (case series)	The Netherlands	Safety and efficacy	X	X	X	X	113	NA
Jastrzebski et al. 2002	IV (case series)	Poland	X	X	Localisation rates	X	X	123	None
Jianjun et al. 2001	IV (case series)	China	X	X	Localisation rates	False negative rates	X	94	None
Jinno et al. 2002	IV (case series)	Japan	X	X	Localisation rates	X	X	184	Ikeda et al. 2000
Johnson et al. 2000	IV (case series)	USA	Safety and efficacy	X	X	X	X	80	NA
Johnson et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	96	None
Kapteijn et al. 1998	IV (case series)	The Netherlands	Safety and efficacy	X	X	False negative rates	X	30	None
Kataoka et al. 2000	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	70	None
Kern 1999	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	40	Kern 2001
Kern 2002	IV (case series)	USA	X	X	Localisation rates	X	X	185	Kern 2001
Kim et al. 2001	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	23	None
Kitapci et al. 2001	IV (case series)	Turkey	X	X	Localisation rates	False negative rates	X	14	None
Klimberg et al. 1999[14]	IV (case series)	USA	X	X	Localisation rates	X	X	68	None
Koizumi et al. 2003	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	60	None
Koller et al. 1998	IV (case series)	Israel	Safety and efficacy	X	Localisation rates	False negative rates	X	98	None

[13] Slight overlap of approximately 3 months with Haigh et al. 2000 (but only for localisation data).

[14] Slight overlap with Smith et al. 2000.

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Krag et al. 2001	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	145	Krag et al. 1993
Kuerer et al. 2001a	IV (case report)	USA	Safety and efficacy	X	X	X	X	1	NA
Kuerer et al. 2001b	IV (case report)	USA	Safety and efficacy	X	X	X	X	1	NA
Kumar et al. 2003	IV (case series)	USA	X	X	Localisation rates	X	X	362	None
Lauridsen et al. 2000	IV (case series)	Denmark	X	X	Localisation rates	False negative rates	X	258	None
Laurie et al. 2002	IV (case reports)	USA	Safety and efficacy	X	X	X	X	2	NA
Layeeque et al. 2003	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	40	None
Leidenius et al. 2003b	IV (case series)	Finland	X	X	Localisation rates	X	X	395	None
Leidenius et al. 2003a	III-2	Finland	Safety and efficacy	X	X	X	X	85	NA
Liang et al. 2001	IV (case series)	USA	X	Recurrence	X	X	X	227	NA
Liang et al. 2003	IV (case series)	New Zealand	X	X	Localisation rates	X	X	20	None
Liberman & Cody 2001	IV (case series)	USA	X	X	Localisation rates	X	X	197	None
Liberman et al. 1999	IV (case series)	USA	X	X	Localisation rates	X	X	33	None
Liu et al. 2000a	IV (case series)	Taiwan	X	X	Localisation rates	False negative rates	X	218	Hsieh et al. 2000
Liu et al. 2000b	IV (case series)	China	X	X	Localisation rates	False negative rates	X	33	None
Liu et al. 2000c	IV (case series)	USA	X	X	Localisation rates	X	X	38	None
Liu et al. 2003	IV (case series)	Taiwan	X	X	Localisation rates	X	X	38	None
Llatjos et al. 2002	IV (case series)	Spain	X	X	X	False negative rates	X	76	None
Lloyd et al. 2002	IV (case series)	USA (Michigan)	X	X	Localisation rates	X	X	107	None
Loza et al. 2002	IV (case report)	USA	X	Recurrence	X	X	X	1	NA
Luini et al. 2002	IV (case series)	Italy	Safety and efficacy	X	Localisation rates	X	X	115	None
Lyew et al. 2000	IV (case report)	USA	Safety and efficacy	X	X	X	X	1	NA
Macmillan et al. 2001	IV (case series)	UK	X	X	Localisation rates	X	X	200	None
Mahajna et al. 2003	IV (case series)	Israel	X	X	Localisation rates	False negative rates	X	100	None
Mann et al. 2000*	IV (case series)	Australia	X	X	Localisation rates	X	X	62	None
Mariotti et al. 2002	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	76	Buonomo et al. 2001
Mateos et al. 2001	IV (case series)	Spain	X	X	Localisation rates	False negative rates	X	80	None
McIntosh et al. 2001	IV (case series)	UK	X	X	X	False negative rates	X	27	None
Meijer et al. 2002	IV (case series)	The Netherlands	Safety and efficacy	Recurrence	X	X	X	100	NA
Meyer-Rochow et al. 2003	IV (case series)	New Zealand	X	X	Localisation rates	False negative rates	X	104	None
Miller et al. 2002	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	35	None
Minato et al. 2003	IV (case series)	Japan	X	X	Localisation rates	X	X	35	None
Miner et al. 1998*	IV (case series)	USA	X	X	X	False negative rates	X	42	None
Miner et al. 1999*	IV (case series)	USA	Safety and efficacy	X	Localisation rates	X	X	82	None

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Mirzaei et al. 2003	IV (case series)	Austria	X	Recurrence	Localisation rates	X	X	128	None
Moffat et al. 1999	IV (case series)	USA	Safety and efficacy	X	Localisation rates	False negative rates	X	70	Gulec et al. 1998
Mokbel & Mostafa 2001	IV (case series)	UK	Safety and efficacy	X	Localisation rates	False negative rates	X	35	None
Molland et al. 2000	IV (case series)	Australia	X	X	Localisation rates	X	X	103	None
Montgomery et al. 2002	IV (case series)	USA	Safety and efficacy	X	X	X	X	2392	NA
Morrow et al. 1999	IV (case series)	USA	X	X	X	False negative rates	X	139	None
Mostafa & Carpenter 2001	IV (case series)	UK	Safety and efficacy	X	X	X	X	80	NA
Motomura et al. 1999a	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	172	Motomura et al. 1999b
Motomura et al. 2002a	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	154	Motomura et al. 2002b Motomura et al. 2003
Motta et al. 2000*	IV (case series)	Italy	X	X	Localisation rates	X	X	54	None
Mullan et al. 2001	IV (case reports)	UK	Safety and efficacy	X	X	X	X	2	NA
Nahrig et al. 2000	IV (case series)	Germany	X	X	Localisation rates	False negative rates	X	40	Kowolik et al. 2000
Nano et al. 2002	IV (case series)	Australia	X	X	Localisation rates	False negative rates	X	328	Kollias et al. 1999 Kollias et al. 2000 Sutton et al. 2002
Nason et al. 2000	IV (case series)	USA	X	X	X	False negative rates	X	82	Eary et al. 1999 Morgan et al. 1999
Noguchi et al. 1999[15]	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	72	None
Noguchi et al. 2000a	IV (case series)	Japan	X	X	Localisation rates	X	X	674	Noguchi et al. 2000b Motomura et al. 2001
Nos et al. 2001	IV (case series)	France	X	X	Localisation rates	False negative rates	X	324	Nos et al. 2001 Fréneaux et al. 2002
Nwariaku et al. 1998	IV (case series)	USA	X	X	X	False negative rates	X	119	None
Offodile et al. 1998	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	41	None
Ozmen et al. 2002	IV (case series)	Turkey	X	X	Localisation rates	False negative rates	X	122	None
Paganelli et al. 2002a	IV (case series)	Italy	X	X	Localisation rates	X	X	892	de Cicco et al. 1998b Paganelli et al. 1998 Veronesi et al. 2001a Viale et al. 2001 Zurrida et al. 2000 Zurrida et al. 2001
Paganelli et al. 2002b	IV (case series)	Italy	Safety and efficacy	X	X	X	X	100	NA
Patel et al. 2003	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	125	Julian et al. 2001 Julian et al. 2002

[15] Slight overlap with Tsugawa et al. 2000.

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Peintinger et al. 2003	III-2	Austria	Safety and efficacy	X	X	X	X	56	NA
Peley et al. 2001	IV (case series)	Hungary	X	X	Localisation rates	False negative rates	X	68	None
Pelosi et al. 2002	IV (case series)	Italy	X	Recurrence	X	X	X	201	NA
Pelosi et al. 2003	IV (case series)	Italy	X	X	Localisation rates	X	X	148	Pelosi et al. 2002
Pijpers et al. 1997	IV (case series)	The Netherlands	Safety and efficacy	X	X	X	X	37	NA
Pizzocaro et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	83	None
Ponzone et al. 2003	IV (case series)	Italy	X	Recurrence	Localisation rates	X	X	212	None
Povoski et al. 2002*	IV (case series)	USA	X	X	Localisation rates	X	X	165	None
Quan et al. 2002*	IV (case series)	Canada	X	X	Localisation rates	False negative rates	X	152	None
Quiney et al. 2003	IV (case report)	UK	Safety and efficacy	X	X	X	X	1	NA
Rahusen et al. 2000a	IV (case series)	The Netherlands	X	X	Localisation rates	X	X	115	None
Rahusen et al. 2003	IV (case series)	The Netherlands	Safety and efficacy	X	Localisation rates	X	X	67	None
Ratanawichitrasin et al. 1998	IV (case series)	USA	Safety and efficacy	X	Localisation rates	False negative rates	X	40	None
Ratanawichitrasin et al. 1999	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	55	None
Reitsamer et al. 2003a	IV (case series)	Austria	X	X	Localisation rates	False negative rates	X	30	None
Reitsamer et al. 2003c	IV (case series)	Austria	X	Recurrence	X	X	X	116	NA
Reitsamer et al. 2003b	IV (case series)	Austria	X		Localisation rates	X	X	154	None
Rettenbacher et al. 2000	IV (case series)	Austria	X	X	Localisation rates	X	X	45	None
Rietman et al. 2003	III-2	The Netherlands	Safety and efficacy	X	X	X	X	204	NA
Rink et al. 2001	IV (case series)	Germany	X	X	Localisation rates	False negative rates	X	155	Heuser et al. 2001
Rodier et al. 2000	IV (case series)	France	Safety and efficacy	X	Localisation rates	False negative rates	X	73	Rodier et al. 1996 Rodier & Janser 1997
Roka et al. 2002	IV (case series)	Austria	X	Recurrence	X	X	X	383	NA
Rönka et al. 2002	IV (case series)	Finland	Safety and efficacy	X	X	X	X	170	NA
Roumen et al. 1997	IV (case series)	The Netherlands	X	X	Localisation rates	False negative rates	X	83	None
Roumen et al. 2001	IV (case series)	The Netherlands	X	Recurrence	X	X	X	100	NA
Rubio et al. 1998b	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	55	Rubio et al. 1998a
Rufino et al. 2003	IV (case series)	South America	X	X	Localisation rates	False negative rates	X	25	None
Sabel et al. 2003	IV (case series)	USA	Safety and efficacy	X	Localisation rates	X	X	25	None
Sacchini et al. 2001	IV (case series)	USA	Safety and efficacy	X	X	X	X	142	NA
Sachdev et al. 2002	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	25	None
Sadiq et al. 2001	IV (case report)	USA	Safety and efficacy	X	X	X	X	2	NA
Salmon et al. 2002	IV (case report)	France	X	Recurrence	X	X	X	1	NA
Salvat et al. 1999	IV (case report)	France	Safety and efficacy	X	X	X	X	1	NA
Sardi et al. 2002	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	58	Rehman et al. 1999

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Sato et al. 2001a*	IV (case series)	Japan	X	X	X	False negative rates	X	206	Sato et al. 2000 Sato et al. 2001b Ishikawa et al. 2002
Sato et al. 2003	IV (case series)	Japan	X	X	Localisation rates	X	X	186	None
Schijven et al. 2003	III-2	The Netherlands	Safety and efficacy	X	X	X	X	393	NA
Schneebaum et al. 1998	IV (case series)	Israel	X	X	Localisation rates	False negative rates	X	30	None
Schrenk et al. 2000	III-2	Austria	Safety and efficacy	X	X	X	X	70	NA
Schrenk et al. 2001	IV (case series)	Austria	Safety and efficacy	Recurrence	X	X	X	247	NA
Schrenk et al. 2002a	IV (case series)	Austria	X	X	X	False negative rates	X	48	Schrenk & Wayand 2001
Schrenk et al. 2002b*	IV (case series)	Austria	X	X	Localisation rates	X	X	284	Schrenk et al. 2001
Schrenk et al. 2003	IV (case series)	Austria	X	X	Localisation rates	False negative rates	X	21	None
Schwartz et al. 2003	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	21	None
Sener et al. 2001	III-2/3	USA	Safety and efficacy	X	X	X	X	492	NA
Shenoy et al. 2002	IV (case series)	UK	X	X	Localisation rates	X	X	100	None
Shimazu et al. 2002*	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	155	None
Shiver et al. 2002	IV (case series)	USA	X	X	Localisation rates	X	X	132	None
Shivers et al. 2002	IV (case series)	USA	X	X	X	False negative rates	X	426	None
Simmons et al. 2003	IV (case series)	USA	X	Recurrence	Localisation rates	X	X	113	Simmons et al. 2001
Smillie et al. 2001	IV (case series)	Canada	X	X	X	False negative rates	X	158	Chua et al. 2003
Smith et al. 2000[16]	IV (case series)	USA	X	X	Localisation rates	X	X	38	None
Snider et al. 1998	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	80	Jannink et al. 1998
Solarzano et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	117	None
Spanu et al. 2001*	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	101	None
Sprung et al. 2003	IV (case report)	Israel	Safety and efficacy	X	X	X	X	1	NA
Stearns et al. 2002	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	34	None
Stefanutto et al. 2002	IV (case report)	USA	Safety and efficacy	X	X	X	X	1	NA
Stitzenberg et al. 2002*	IV (case series)	USA	X	X	Localisation rates	False negative rates	X	78	None
Stradling et al. 2002	IV (case series)	USA	Safety and efficacy	X	Localisation rates	X	X	24	None
Swenson et al. 2002	III-2	USA	Safety and efficacy	X	X	X	X	247	NA
Tafra et al. 2001b	IV (case series)	USA	X	X	Localisation rates	X	X	968	Tafra et al. 2001a
Takei et al. 2002	IV (case series)	Japan	X	Recurrence	X	X	X	354	NA
Tanis et al. 2002a	IV (case series)	The Netherlands	Safety and efficacy	Recurrence	X	X	X	549	NA

[16] Slight overlap with Klimberg et al. 1999.

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Tausch et al. 2002	IV (case series)	Austria	X	X	Localisation rates	X	X	1637	Gallowitsch et al. 2002 Pichler-Gebhard et al. 2002
Tavares et al. 2001	IV (case series)	South America	X	X	Localisation rates	False negative rates	X	100	None
Temple et al. 2002	III-2	USA	Safety and efficacy	X	X	X	X	233	NA
Tousimis et al. 2003	IV (case series)	USA	X	X	X	False negative rates	X	70	None
Travagli et al. 2003	IV (case series)	France	X	X	Localisation rates	X	X	165	None
Tsugawa et al. 2000[17]	IV (case series)	Japan	Safety and efficacy	X	X	False negative rates	X	48	Noguchi et al. 2000c
Tuthill et al. 2001	IV (case series)	USA	X	X	Localisation rates	X	X	119	None
Tuttle et al. 2002	IV (case series)	USA	X	X	Localisation rates	X	X	158	None
Ugur et al. 2003*	IV (case series)	Turkey	Safety and efficacy	X	Localisation rates	False negative rates	X	28	None
Upponi et al. 2002	IV (case series)	UK	X	X	Localisation rates	X	X	62	None
Vaggelli et al. 2000	IV (case series)	Italy	X	X	Localisation rates	False negative rates	X	35	None
van Berlo et al. 2003*	IV (case series)	The Netherlands	Safety and efficacy	Recurrence	Localisation rates	False negative rates	X	162	None
van der Ent et al. 2001	IV (case series)	The Netherlands	Safety and efficacy	X	Localisation rates	False negative rates	X	256	van der Ent et al. 1999
Vargas et al. 2002a	IV (case series)	USA	X	X	Localisation rates	X	X	73	None
Vargas et al. 2002b	IV (case series)	USA	X	X	X	False negative rates	X	70	None
Vargas et al. 2003	IV (case series)	USA	X	X	Localisation rates	X	X	110	None
Veronesi et al. 1999	IV (case series)	Italy	X	X	X	False negative rates	X	376	de Cicco et al. 1998a Galimberti et al. 1998 Galimberti et al. 2000 Veronesi et al. 1997 Veronesi et al. 2001b Viale et al. 1999 Zurrida et al. 2000 Zurrida et al. 2001
Veronesi et al. 2001a	IV (case series)	Italy	X	Recurrence	X	X	X	373	NA
Veronesi et al. 2003	II	Italy	Safety and efficacy	Recurrence	X	False negative rates	X	516	None
Vigario et al. 2003	IV (case series)	South America	X	X	Localisation rates	False negative rates	X	83	Piato et al. 2003
Villa et al. 2000	IV (case series)	Italy	X	X	Localisation rates	X	X	284	Mariani et al. 2000
Walker et al. 2002	IV (case series)	UK	Safety and efficacy	X	Localisation rates	False negative rates	X	122	None
Watanabe et al. 2001	IV (case series)	Japan	X	X	Localisation rates	False negative rates	X	87	None
Wear et al. 2003	IV (case report)	USA	Safety and efficacy	X	X	X	X	1	NA
Weerts et al. 2002	IV (case series)	Belgium	X	X	Localisation rates	False negative rates	X	60	None
Winchester et al. 1999	IV (case series)	USA	X	X	Localisation rates	X	X	180	None

[17] Slight overlap with Noguchi et al. 1999.

Author	Level of evidence	Location	Safety and efficacy	Recurrence	Localisation rates	False negative rates	Cost comparison	N	Incorporated studies
Wong et al. 2002a	IV (case series)	USA (Kentucky)	X	X	Localisation rates	False negative rates	X	3324	Chao et al. 2003 McMasters et al. 2000a McMasters et al. 2000b McMasters et al. 2001a McMasters et al. 2001b Martin et al. 2000 Wong et al. 2001a Wong et al. 2001b Wong et al. 2001c Wong et al. 2001d Wong et al. 2002b Wong et al. 2002c
Xavier et al. 2001	IV (case series)	South America	X	X	Localisation rates	False negative rates	X	58	None
Xu et al. 2002	IV (case series)	China	X	X	Localisation rates	False negative rates	X	42	None
Yang et al. 2001	IV (case series)	Korea	X	X	Localisation rates	False negative rates	X	18	None
Yen et al. 2003	IV (case report)	USA	X	Recurrence	X	X	X	1	NA
Yong et al. 2003	IV (case series)	Singapore	Safety and efficacy	X	Localisation rates	False negative rates	X	312	None
Yu et al. 2002	IV (case series)	Taiwan	Safety and efficacy	X	Localisation rates	False negative rates	X	218	None
Zavagno et al. 2000	IV (case series)	Italy	X	X	X	False negative rates	X	126	None
Zavagno et al. 2002a	IV (case series)	Italy	X	X	Localisation rates	X	X	384	None
Zavagno et al. 2002b	IV (case series)	Italy	X	X	Localisation rates	X	X	50	None
Zervos et al. 2001	IV (case series)	USA	X	Recurrence	Localisation rates	X	X	509	Zervos & Burak 2000
Zerwes et al. 2002	IV (case series)	South America	X	X	Localisation rates	X	X	29	None
Zgajnar et al. 2003	IV (case series)	Slovenia	X	X	Localisation rates	X	X	17	None
Zhang et al. 2003	IV (case series)	China	Safety and efficacy	X	Localisation rates	False negative rates	X	95	None

Appendix D Excluded studies and reasons for exclusion

Lymphoscintigraphy only:

1) Krynyckyi B, Kim CK, Mosci K, Fedorciw B, Zhang Z, Lipszyc H et al. Areolar-cutaneous 'junction' injections to augment sentinel node count activity. *Clinical Nuclear Medicine* 2003; 28(2):97–107.
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Data not suitable for analysis:

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Pathology only:

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Not sentinel node biopsy:

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Appendix E Concordance and subgroup analyses

Table E.1 Radioisotope/dye concordance

Data set	Cases mapped by			Concordance *	
	Dye only	Radioisotope only	Dye and radioisotope		
Allen et al. 2001	1	2	31	31/34	91.2%
Barnwell et al. 1998	1	29	8	8/38	21.1%
Bauer et al. 2002	Gp 1: 1 Gp 2: 6 Total: 7	Gp 1: 9 Gp 2: 18 Total: 27	Gp 1: 69 Gp 2: 217 Total: 152	Gp 1: 69/79 Gp 2: 217/241 Total: 286/320	87.3% 90.0% 89.4%
Beitsch et al. 2001	1	3	79	79/83	95.2%
Borgstein et al. 2000	2	10	200	200/212	94.3%
Byrd et al. 2001	21	45	128	128/194	66.0%
Donahue 2001	0	1	41	41/42	97.6%
Doting et al. 2000	37	68	119	119/136	87.5%
Hodgson et al. 2001	NS	NS	44	44/46	95.7%
Hung et al. 2002	5	40	89	89/134	66.4%**
Kern 2002	NS	NS	174	174/184	94.5%
Klimberg et al. 1999	3	4	62	62/69	89.9%
Kumar et al. 2003	1	3	39	39/42	92.9%
Leidenius et al. 2003a	6	111	246	246/363	67.8%
Liberman et al. 1999	2	6	22	22/30	73.3%
Mahajna et al. 2003	NS	NS	61	61/88	69.3%
Mann et al. 2000	5	7	32	32/44	72.7%
Pelosi et al. 2003	Gp 1: 7 Gp 2: 3	Gp 1: 1 Gp 2: 1	Gp 1: 92 Gp 2: 45	Gp 1: 92/100 Gp 2: 45/50	92.0% 90.0%
Rahusen et al. 2000b	0	6	100	100/106	94.3%
Rahusen et al. 2003	0	6	58	58/64	90.6%
Reitsamer et al. 2003c	0	4	151	151/155	97.4%
Sardi et al. 2002	12	50	51	51/113	45.1%**
Schneebaum et al. 1998	0	2	26	26/28	92.9%
Shimazu et al. 2002	3	16	70	70/89	78.7%
Simmons et al. 2003	NS	NS	94	94/99	94.9%
Smith et al. 2000	Gp 1: 2 Gp 2: 1	Gp 1: 4 Gp 2: 2	Gp 1: 12 Gp 2: 16	Gp 1: 12/18 Gp 2: 16/19	66.7%† 84.2%‡
Solorzano et al. 2001	28	46	192	192/266	72.2%**
Tuttle et al. 2002	NS	NS	151	151/159	95.0%
Ugur et al. 2003	2	5	15	15/22	68.2%
Vargas et al. 2002a	8	5	56	56/71	78.9%
Zavagno et al. 2002b	3	4	40	40/47	85.1%
Zervos et al. 2001	2	19	107	107/128	83.6%§
Zgajnar et al. 2003	1	1	13	13/15	86.7%

Notes: NS – not stated; Gp – group; * concordance = number successfully mapped by both (i.e. column 3) divided by total successfully mapped multiplied by 100; ** results on a nodal basis; † peritumoural injection site; ‡ subareolar injection; § true positives patients only.

Table E.2 Results of multiple comparison tests in random-effects subgroup analyses

Subgroup	Group 1	Group 2	Localisation rates		False negative rates	
			difference* (95%PI)	p-value‡	difference** (95%PI)	p-value‡
Type of tracer	All radioisotope, all dye	Radioisotope only	1.6 (-0.2, 3.5)	0.08	-1.6 (-3.5, 0.2)	0.084
	All radioisotope, all dye	Dye only	8.5 (5.1, 12.2)	<0.001	-2.9 (-5.3, -0.8)	0.005
	Radioisotope only	Dye only	6.9 (3.2, 10.8)	<0.001	-1.4 (-3.8, 1.0)	0.25
Radioisotope injection location	Peritumoral	Subareolar or periareolar	-4.4 (-6.2, -2.3)	<0.001	-1.3 (-7.5, 2.3)	0.70
	Peritumoral	Intradermal, subdermal or subcutaneous	-2.4 (-4.3, -0.5)	0.020	-1.7 (-4.5, 0.6)	0.17
	Subareolar or periareolar	Intradermal, subdermal or subcutaneous	2.0 (-0.3, 4.0)	0.070	-0.4 (-5.0, 6.1)	0.76
Timing of radioisotope injection	Same day as SLNB	Day before SLNB	0.7 (1.3, 2.7)	0.46	2.0 (0.0, 4.1)	0.046
Type of dye	Patent blue	Isosulfan	-1.4 (-3.7, 0.8)	0.18	1.4 (-0.4, 3.3)	0.13
	Patent blue	Methylene	-0.9 (-4.9, 4.9)	0.63	-0.6 (-8.0, 3.5)	0.99
	Isosulfan	Methylene	0.5 (-2.9, 6.0)	0.95	-2.0 (-9.3, 2.1)	0.53
Dye injection location	Peritumoral	Subareolar or periareolar	-3.4 (-5.6, -0.6)	0.026	1.3 (-4.2, 4.1)	0.41
	Peritumoral	Intradermal, subdermal or subcutaneous	-2.0 (-4.2, 0.5)	0.11	-0.8 (-3.6, 1.5)	0.58
	Subareolar or periareolar	Intradermal, subdermal or subcutaneous	1.4 (-1.7, 4.4)	0.34	-2.1 (-5.9, 3.6)	0.32
Histology	Permanent histology	Permanent histology plus IHC	-	-	0.4 (-1.3, 2.2)	0.61
Biopsy method	FNA, CB or no biopsy	Excisional biopsy only	5.8 (-1.4, 17.0)	0.18	-8.1 (-20.9, 1.1)	0.094
Tumour palpability	Palpable only	Impalpable only	-3.8 (-9.4, 1.5)	0.15	4.0 (-4.4, 8.5)	0.19
Clinical axillary status	Negative	Negative and positive	4.7 (2.0, 8.0)	0.001	-2.3 (-4.8, -0.0)	0.046
Neoadjuvant chemotherapy	No neoadjuvant chemotherapy	All neoadjuvant chemotherapy	3.1 (-3.0, 11.2)	0.42	-9.0 (-17.9, -2.2)	0.026

Notes: PI – posterior interval; IHC – immunohistochemistry; SLNB – sentinel lymph node biopsy; FNA – fine needle aspiration; CB – core biopsy; IHC – immunohistochemistry; * difference in localisation rates, Group 1 minus Group 2; ** difference in false negative rates, Group 1 minus Group 2; ‡ Probability that the mean in Group 1 is equal to the mean in Group 2.

Abbreviations

AC	axillary clearance
ACOSOG	American College of Surgeons Oncology Group
AIHW	Australian Institute of Health and Welfare
ALMANAC	Axillary Lymphatic Mapping Against Nodal Axillary Clearanc
ASERNIP-S	Australian Safety and Efficacy Register of New Interventional Procedures – Surgical
H&E	haematoxylin and eosin
IHC	immunohistochemistry
MBS	Medical Benefits Scheme
mRNA	messenger ribonucleic acid – a specific form of RNA
NHMRC	National Health and Medical Research Council
NSABP	National Surgical Adjuvant Breast and Bowel Project
RNA	ribosome nucleic acid
RT-PCR	reverse transcriptase – polymer chain reaction
SLNB	sentinel lymph node biopsy
SNAC	Sentinel Node Axillary Clearance
^{99m}Tc	technetium
nm	nanometres

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